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Lymph Node Staging by CT Texture Analysis in Patients with Sigmoid Cancer

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ABSTRACT

Objective: Accurate radiological staging of colon cancer is essential for appropriately selecting patients who might benefit from neoadjuvant chemotherapy. Lymph node staging and the detection of metastatic lymph nodes form an integral part of the local staging. This study aimed to determine the efficacy of computed tomography texture analysis (CTTA) in characterizing lymph nodes in patients with sigmoid cancers.

Materials and Methods: Forty-five patients diagnosed with sigmoid adenocarcinoma, who underwent computed tomography (CT) scans, were included in this retrospective study. Based on post-surgery histopathological results, 25 patients were classified as stage N1-2, and 20 patients were classified as stage N0. CTTA was conducted on 51 metastatic lymph nodes from the 25 N1-2 patients and 30 benign lymph nodes from the 20 N0 patients. Histogram analysis was employed to calculate texture features, and the texture features of both groups were statistically compared. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of the parameters.

Results: The maximum of the histogram, 99th percentile of the histogram, and entropy values were significantly higher in the metastatic lymph nodes. Conversely, skewness, uniformity, and kurtosis values were significantly higher in benign lymph nodes ($p<0.05$). ROC analysis for uniformity and skewness revealed area under the curve (AUC) values of 0.904 and 0.909, respectively.

Conclusion: In patients with sigmoid cancer, CTTA can serve as a useful tool for lymph node staging.

Keywords: Sigmoid cancer, CT, texture analysis, lymph node, staging.

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INTRODUCTION

Colorectal cancer ranks as the third most common cancer type in men and the second in women.[1] Radical surgery stands as the sole curative treatment option. However, even when undergoing radical resection, the prognosis for locally advanced colon cancer remains unfavorable. The integration of surgery with other treatment modalities may improve outcomes. Several advanced gastrointestinal malignancies, such as rectal cancer, exhibit favorable responses to preoperative (neoadjuvant) treatment. Initial studies on locally advanced colon cancer have also indicated positive outcomes with neoadjuvant chemotherapy.[2,3] The onset of lymph node metastases characterizes locally advanced

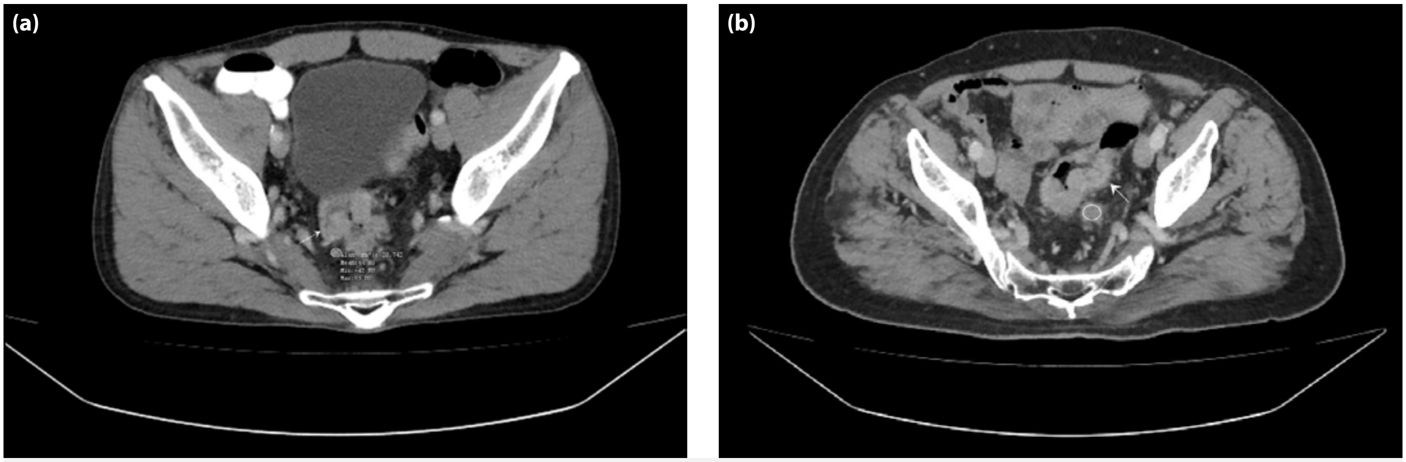

Figure 1. (a) Sigmoid cancer (indicated by the arrow) in a histopathologically determined T3N0 patient, showcasing a benign lymph node and the ROI drawing. **(b)** Sigmoid cancer (indicated by the arrow) in a histopathologically determined T3N2 patient, highlighting a metastatic lymph node and the ROI drawing.

colon cancer, underscoring the significance of accurate staging. Utilizing computed tomography (CT), one can assess the entire chest, pelvis, and abdomen in a single examination, facilitating the evaluation of both distant metastases and local staging.

Research has revealed that lymph nodes with a short axis measurement exceeding 8 mm are highly indicative of metastatic lymph nodes.[4,5] Conversely, numerous metastatic lymph nodes possess a diameter of less than 5 mm, and some benign lymph nodes exceed 5 mm in diameter.[6,7] Consequently, size alone does not serve as an optimal criterion to distinguish between benign and metastatic lymph nodes.

In contemporary clinical practice, radiological images are procured digitally. Texture analysis within a digital image pertains to the distribution of gray level values among pixels. Computed tomography texture analysis (CTTA) is a quantitative analytical method that provides more detailed data on the region of interest (ROI) than can be obtained through visual inspection alone. Microscopic biological changes can lead to tissue heterogeneity, and texture analysis can assess this tumor heterogeneity. Tumor heterogeneity is associated with necrosis, high cell density, and bleeding. The histogram is among the commonly used texture parameters.[8] A gray-level intensity histogram, utilizing all pixel values, provides first-order statistical information about an image. This information included the standard deviation of the histogram, mean gray level intensity, minimum, median, and maximum intensity values, percentile values of the histogram, variance, range, skewness, kurtosis, entropy, and uniformity values.[9] Entropy refers to the irregularity of the value distribution. Kurtosis describes the peakedness of the histogram, while skewness indicates the asymmetry of the histogram curve. Uniformity describes the gray level distribution, signifying how close the gray tones of an image are to a uniform distribution.

Recently, techniques like texture analysis have garnered significant attention, with applications in distinguishing pathological statuses in different tissues.[9,10] and assessing post-treatment changes.[11]

Lymph nodes are another area where texture analysis is gaining interest. This method has been employed to identify cervical and mediastinal malignant lymph nodes.[12,13] However, a texture analysis study of metastatic lymph nodes in sigmoid cancers has not been reported to date. The objective of this research is to assess the efficacy of CTTA in characterizing lymph nodes associated with sigmoid cancers.

MATERIALS AND METHODS

The ethics committee approved this retrospective study (Date: 25. 05. 2023, Number: 2023/07-44). We examined patients diagnosed with sigmoid adenocarcinoma after colonoscopy between 2013 and 2020 who had undergone CT imaging. Patients with distant metastases were excluded from the study as they were inoperable and, therefore, lacked pathological data (n=12). The final study cohort included 45 patients who underwent surgery. Pathological data from the surgical resection for all patients were sourced from the hospital database. Of the cohort, 25 patients were diagnosed with stages N1-2, while 20 patients had stage N0. Fifty-one metastatic lymph nodes, each larger than 5 mm, were selected from the 25 N1-2 patients, and 30 benign lymph nodes, each exceeding 5 mm, were chosen from the mesosigmoid fat tissue of the 20 N0 patients. Texture analysis was conducted on both benign and metastatic lymph nodes and then compared.

Table 1. Statistical analysis of histogram parameters between benign and metastatic lymph nodes (Student's t-test)

Texture features	Group statistics		p
	Benign (n=30) Mean±SD	Metastasis (n=51) Mean±SD	
Mean of histogram	1081.02±32.01	1086.4±16.23	0.319
Median of histogram	1085.63±29.91	1086.79±16.37	0.822
Maximum of histogram	**1113.47±24.47**	**1128.12±23.69**	**0.010**
Skewness of histogram	**-1.01±0.55**	**-0.12±0.39**	**<0.001**
25th percentile of histogram	1071.23±35.95	1074.58±15.96	0.565
75th percentile of histogram	1095.92±26.31	1098.25±17.22	0.631
90th percentile of histogram	1104.26±24.82	1107.88±18.005	0.451
95th percentile of histogram	1108.32±25.16	1113.78±19.43	0.277
97th percentile of histogram	1110.55±24.61	1118.11±20.57	0.142
99th percentile of histogram	**1113.14±24.32**	**1125.27±22.48**	**0.026**
Entropy of histogram	**4.83±0.45**	**5.22±0.48**	**0.001**
Uniformity of histogram	**0.48±0.10**	**0.31±0.07**	**<0.001**

SD: Standard deviation

CT Examination

CT examination employed a GE Optima 128 detector. The CT settings were as follows: 120 kVp, 250 mAs, and a 1:1 pitch. Patients were administered approximately 80 mL of the non-ionic contrast agent, Iohexol 350 (GE Healthcare). Axial abdominal images were uploaded to an iMac computer. Histogram analysis was carried out using the OsiriX V.4.9 imaging software. The ROI was delineated based on the lymph node's long axis, encompassing the entire lymph node. Two radiologists, with 7 and 15 years of experience in abdominal radiology respectively, drew the ROIs (Fig. 1). We derived values for mean, minimum, median, maximum, standard deviation, variance, covariance, histogram range, skewness, kurtosis, entropy, and uniformity by using the gray-level intensities of the pixels. The entire image analysis algorithm was processed using the internal Matrix Laboratory (MATLAB) software (version R2009b; MathWorks, MA).

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 25.0. The normality of the distribution was assessed with the Kolmogorov-Smirnov test and the quantile-quantile (Q–Q) plot. For numerical data that did not follow a normal distribution, the Mann-Whitney U test was employed. Data were presented as the median, first quartile, and third quartile values for the Mann-Whitney U analysis. For numerical data that adhered to a normal distribution, the Student's t-test was applied. The data were presented as the mean±standard deviation for the Student's t-test. Statistical significance was defined as p<0.05. The potential validity of parameters was assessed using the Receiver Operating Characteristic (ROC) analysis. The Youden index was used to identify the cut-off value. Interobserver agreement between the two radiologists' measurements was determined using the intraclass correlation coefficient (ICC) and concordance correlation coefficient (CCC). ICC values were interpreted as: poor (0–0.4), moderate (0.41–0.6), good (0.61–0.8), and excellent agreement (0.81–1). CCC interpretations were: values close to +1 indicate a high correlation between the two radiologists' measurements, values close to -1 indicate severe discordance, and values near 0 zero show no concordance. Post-hoc power was calculated using the ClinCalc calculator (clincalc.com/stats/Power.aspx).

RESULTS

Patient Profiles

The age range of the sigmoid cancer patients spanned from 31 to 88 years. The patient group consisted of 26 males and 19 females. The N0 group comprised 12 males and 8 females, while the N+ group included 14 males and 11 females. The mean ages for N0 and N+ patients were 61.21±10.32 and 63±12.21 years, respectively. There were no significant differences in gender (p=0.812) or age (p=0.787) between the N0 and N+ groups.

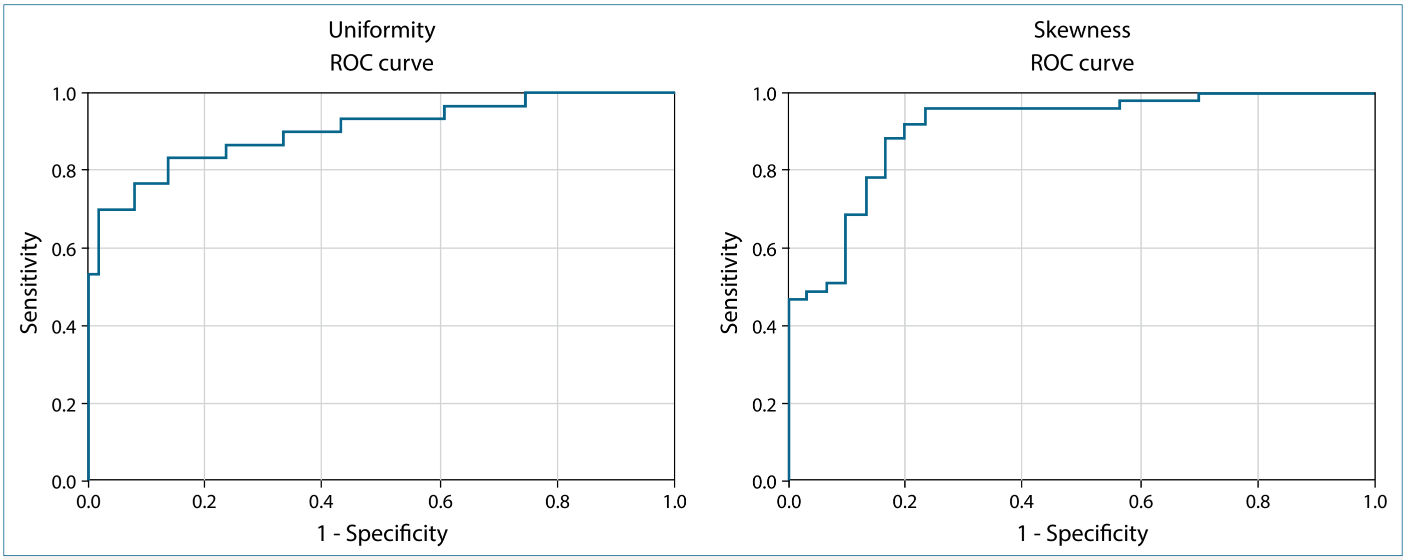

Figure 2. ROC analysis for uniformity (AUC: 0.904) and skewness (AUC: 0.909).

Table 2. Statistical analysis of histogram parameters between benign and metastatic lymph nodes (Mann-Whitney U test)

Texture features	Group statistics		p
	Benign (n=30) Median (1st quartile-3rd quartile)	Metastasis (n=51) Median (1st quartile-3rd quartile)	
Standard deviation of histogram	20.63 (11.87–27.62)	18.17 (12.93–21.51)	0.241
Minimum of histogram	1027.00 (978.75–1066.50)	1045.00 (1031.00–1057.00)	0.115
Variance of histogram	425.96 (141.49–763.01)	330.43 (167.33–462.87)	0.241
Covariance of histogram	425.96 (141.49–763.01)	330.43 (167.33–462.87)	0.241
Range of histogram	95.00 (62.50–123.50)	88.00 (58.00–106.00)	0.601
Kurtosis of histogram	3.67 (3.06–5.37)	2.93 (2.58–3.49)	<0.001
1st percentile of histogram	1027.00 (980.95–1066.87)	1047.24 (1034.10–1060.80)	0.073
3rd percentile of histogram	1036.64 (991.03–1072.14)	1053.36 (1038.12–1065.69)	0.067
5th percentile of histogram	1046.05 (999.31–1076.06)	1055.00 (1041.70–1070.00)	0.169
10th percentile of histogram	1058.10 (1018.35–1083.10)	1062.00 (1051.20–1077.80)	0.366

Interobserver Agreement

The textural features derived from the independent ROIs drawn by the two radiologists demonstrated excellent interobserver agreement (ICC range: 0.854 to 0.945 and CCC range: 0.822 to 0.963). Therefore, measurements from only one of the radiologists were utilized for statistical evaluation.

Texture Analysis

The post-hoc power value for each parameter was 90% or higher. The maximum of the histogram, 99th percentile of the histogram, and entropy values were significantly elevated in the metastatic nodes, while skewness, kurtosis, and uniformity values were notably higher in benign lymph nodes ($p<0.05$). Other texture features showed no significant differences (Table 1, 2). A ROC analysis was conducted for the maximum of the histogram, 99th percentile of the histogram, entropy, skewness, kurtosis, and uniformity values. The Area Under the Curve (AUC) value and rates of sensitivity and specificity were determined within 95% confidence intervals (CI).

ROC analysis indicated that the AUC value for uniformity was 0.904 (Fig. 2). When the cut-off value was set at 0.388, benign and metastatic lymph nodes could be differentiated with a sen-

Table 3. Diagnostic performance of histogram features in differentiating benign and metastatic lymph nodes

Feature	AUC	Sensitivity (%)	Specificity (%)	95% CI	Cut-off value	p
Maximum of histogram	0.660	68.6	63.3	0.534–0.786	>1115.500	0.010
Kurtosis of histogram	0.742	70	70.6	0.628–0.856	<3.197	<0.001
Skewness of histogram	0.909	88.2	83.3	0.842–0.976	<-0.535	<0.001
99th percentile of histogram	0.637	64.7	63.3	0.508–0.766	>1115.520	0.026
Entropy of histogram	0.707	62.7	60	0.595–0.820	>5.031	0.001
Uniformity of histogram	0.904	83.3	86.3	0.831–0.977	<0.388	<0.001

AUC: Area under the curve; CI: Confidence interval.

sitivity of 83.3% and specificity of 86.3%. ROC analysis indicated that the AUC value for skewness was 0.909 (Fig. 2). With a cut-off value at -0.535, benign and metastatic lymph nodes could be differentiated with a sensitivity of 88.2% and specificity of 83.3%. The AUC values, as well as sensitivity and specificity values for the other significant parameters, were determined (Table 3).

DISCUSSION

Lymph node metastases in colon cancer are poor prognostic factors and increase the risk of recurrence. Accurate radiological staging of sigmoid cancer is vital for selecting patients with lymph node metastasis who are at a high risk of recurrence and may benefit from neoadjuvant chemotherapy. Our study suggests that texture analysis can be a valuable tool in lymph node staging in sigmoid cancer.

Using size alone is not a reliable criterion for detecting lymph node metastasis. Hence, besides size, morphological criteria like the presence of irregular borders, heterogeneous signal intensities, and rounded shapes should be considered for nodal assessment.[14] Morphological criteria should be evaluated with magnetic resonance imaging (MRI). However, the high cost and extended image acquisition time are disadvantages of MRI. Moreover, MRI is contraindicated for patients with conditions like metallic implants, claustrophobia, pacemakers, contrast allergy, and so on, making it unsuitable for everyone.

Texture analysis is a cutting-edge technique in image analysis that quantitatively assesses the gray-level intensities of pixels, which can then be evaluated statistically. We noticed a statistically significant difference in six histogram data points. The ROC analysis of skewness and uniformity values yielded high sensitivity and specificity rates. The results of our study show that texture analysis may be utilized to differentiate between benign and metastatic lymph nodes, proving valuable in the N staging of sigmoid cancer.

Using ultrasonographic texture analysis, Kim et al.[15] reported on the nodal metastasis status of papillary thyroid microcarcinomas. These authors indicated that papillary thyroid microcarcinomas with metastatic lymph nodes had significantly higher entropy than tumors without lymph node metastases. In other studies, texture analysis was reported to be useful in distinguishing between metastatic and benign lymph nodes in suspected lung cancer cases[12] and showed potential in predicting metastatic lymph nodes in lung cancer.[16] Kuno demonstrated that CT texture analysis may be effective in predicting nodal metastases in the head and neck for patients with squamous cell carcinoma.[4,5] Texture features derived from T2-weighted imaging of rectal tumors could be used as markers of tumor response to neoadjuvant chemoradiotherapy and prognosis,[17] while histogram parameters obtained from apparent diffusion coefficient (ADC) maps could be linked to extramural invasion in rectal cancers.[18] Texture features of rectal cancer derived from T2-weighted imaging in another study indicated that the entropy values of the N1-2 group were higher than those of the N0 group; therefore, texture analyses could be useful in determining the status of lymph node metastasis.[19] We observed that the entropy values of metastatic lymph nodes were significantly higher than those of benign lymph nodes. Yang et al.[20] reported that, according to T2-weighted imaging (T2WI) histogram analysis of rectal tumors, the N0 group had significantly higher energy, kurtosis, and skewness and lower entropy than the N-positive group. Our study, conducted with histogram features of the lymph nodes on CT images, also showed significantly higher kurtosis and skewness values in the benign lymph nodes.

The current study has several limitations: the number of cases was relatively low, and the research was conducted on patients from a single center. The histopathology results corresponding one-to-one with the selected metastatic lymph nodes on the CT were unknown. Texture analysis was not performed on lymph nodes smaller than 5 mm. For texture extraction, only a single slice was used. Using texture analysis with 3-dimensional volume images can provide a more accurate reflection of the entire lymph node volume and improve the precision of estimates.

CONCLUSION

Overall, our findings suggest that precise radiological staging of lymph nodes may better determine which patients should undergo neoadjuvant chemotherapy. CTTA can be useful for nodal characterization and for N staging in patients with sigmoid cancer.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: The Fırat University Clinical Research Ethics Committee granted approval for this study (date: 25.05.2023, number: 2023/07- 44).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept – MY, MB; Design – MY, MB; Supervision – MY, MB; Resource – MY, MB; Materials – MY, MB; Data Collection and/or Processing – MY, MB; Analysis and/or Interpretation – MY, MB; Literature Search – MY, MB; Writing – MY, MB; Critical Reviews – MY, MB.

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

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