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Histogram Analysis of Computed Tomography Images for Quantitative Assessment of Gastric Cancer Invasiveness

Mide Kanseri İnvazifliğinin Kantitatif Değerlendirmesinde Bilgisayarlı Tomografi Histogram Analizi

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ABSTRACT

Introduction: To explore the role of computed tomography (CT) texture analysis in predicting T-stage of gastric cancers (GC).

Methods: Preoperative enhanced CT images of 110 patients (men: 84, women: 26) with GC were reviewed retrospectively. Regions of interest were manually drawn along the margin of the lesion on the section where it appeared largest on the portal venous CT images, which yielded texture parameters (1, 10, 50, 90, and 99% percentiles; minimum, mean, and maximum norm; variance; skewness, and kurtosis). Correlations between texture parameters and pathological stage were analysed with Spearman's correlation test. The distributions of all variables were checked with the aid of the Kolmogorov-Smirnov test. The Independent-Samples t-test and the Mann-Whitney U test were used (as appropriate) to compare quantitative data. The chi-squared test was employed to compare qualitative data. The diagnostic performance of CT texture parameters in differentiating different stages was evaluated using receiver operating characteristic analysis.

Results: The T4 variance was significantly greater than that of the T1-to-T3 group ($p<0.05$). The T4 skewness was significantly lower than that of the T1-to-T3 group ($p<0.05$) but the T4 kurtosis significantly higher ($p<0.05$).

Conclusion: The histogram parameters of CT-TA, especially skewness and kurtosis derived from portal, venous phase CT images, may serve as biomarkers stratifying the risk of serosal invasion (stage-T4) by locally advanced GC. Thus, histogram analysis can be used preoperatively to evaluate serosal invasion.

Keywords: Gastric cancer, T-staging, CT, histogram analysis

ÖZ

Amaç: Mide kanserlerinin (MK) T-evresini tahmin etmede bilgisayarlı tomografi (BT) doku analizinin rolünü keşfetmektir.

Yöntemler: MK'li 110 hastanın (erkek: 84, kadın: 26) ameliyat öncesi geliştirilmiş BT görüntüleri retrospektif olarak incelendi. İlgi bölgeleri, doku parametreleri (1, 10, 50, 90 ve %99 persentiller; minimum, ortalama ve maksimum norm; varyans; çarpıklık ve basıklık). Doku parametreleri ile patolojik evre arasındaki ilişkiler Spearman korelasyon testi ile analiz edildi. Tüm değişkenlerin dağılımları Kolmogorov-Smirnov testi yardımıyla kontrol edildi. Niceliksel verileri karşılaştırmak için Independent-Samples t-test ve Mann-Whitney U testi (uygun şekilde) kullanıldı. Nitel verileri karşılaştırmak için ki-kare testi kullanılmıştır. Farklı aşamaları ayırt etmede CT doku parametrelerinin tanısal performansı, alıcı işletim karakteristiği analizi kullanılarak değerlendirildi.

Bulgular: T4 varyansı, T1-T3 grubuna göre anlamlı derecede daha yüksekti ($p<0,05$). T4 çarpıklığı, T1-T3 grubuna göre anlamlı derecede düşüktü ($p<0,05$), ancak T4 basıklığı anlamlı derecede yüksekti ($p<0,05$).

Sonuç: BT doku analizi histogram parametreleri, özellikle portal, venöz faz BT görüntülerinden türetilen çarpıklık ve basıklık, lokal olarak ilerlemiş mide tümörlerinde serozal invazyon riskini (evre-T4) katmanlandıran biyobelirteçler olarak hizmet edebilir. Bu nedenle, histogram analizi, serozal invazyonu değerlendirmek için preoperatif olarak kullanılabilir.

Anahtar Kelimeler: Mide tümörü, T-evreleme, BT, histogram analizi

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Introduction

Although the incidence of, and mortality from, gastric cancer (GC) have decreased recently, GC remains the fifth most common cancer and the third leading cause of cancer deaths worldwide (1). Treatment options are limited beacuse many patients exhibit locally advanced cancer at diagnosis (stages T4a, 4b, and N1,2,3). New diagnostic options for locally advanced GC and identification of patient subgroups who can benefit from personalised treatments have become prime research topics (2-4). Multidetector computed tomography (MDCT) is often the primary method used for preoperative GC staging and shows promise in terms of detecting intra-tumour heterogeneity and, thus, variations in differentiation, angiogenesis, and the extracellular matrix (5). Textural analysis (TA) is a new non-invasive technique that can be applied to various images such as those of radiography, ultrasound, MDCT, magnetic resonance imaging, and positron emission tomography; TA assesses spatial changes in tumoural gray level densities (5). TA has attracted particular attention in the context of malignant tumour imaging, and may be used to estimate tumour stage, grade, treatment response, and prognosis (6-9). The diagnostic accuracy of MDCT in terms of T-staging improves from early to advanced stages, but remains unsatisfactory because it is difficult to evaluate all gastric wall layers, particularly the minor curvature (10). However, to the best of our knowledge, no previous report has explored whether TA can detect stage T4 locally advanced GC. Therefore, we retrospectively analysed whether first-order histogram analysis of the preoperative computed tomography "CT" textural features of locally advanced GC patients could be used to predict stage T4 disease.

Methods

Ethics

This single-centre retrospective study adhered to all relevant tenets of the Helsinki Declaration and the Good Clinical Practice Guidelines and was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Medical Ethics Committee (approval number: 1750, date: 15.03.2019). All patients were included after their informed consent was obtained.

We retrieved images taken from January 2017 to December 2019 from our archiving system.

Patients

A total of 148 consecutive patients who underwent radical gastrectomy with standard D1+/D2 lymph node dissection to treat locally advanced GC between January 2017 and December 2019 in our hospital were retrospectively analysed. The inclusion criteria were: the availablility of contrast-enhanced CT images taken in our institution within 4 weeks before surgery and histologically confirmed GC. We excluded patients who were very weak because they lacked adequate adipose tissue in the perigastric region in which regions of interest (ROIs) were drawn for TA (n=21), and also those whose images afforded only poor tumour visualisation because of inadequate distension or peristalsis (n=17) We finally included 110 GC patients who underwent CT.

CT image acquisition

CT was performed using a 128-detector scanner (Philips Ingenuity, the Netherlands) or a 64-detector scanner (Aquilion, Canon Medical Systems, Japan). The usual MDCT scan parameters were: 1) 120 kVp; 2) 80-500 mA; 3) slice thickness 2 mm; 4) pitch 0.797-1.5; 5) field-of-view 50x50 cm; 6) rotation time 0.5-0.75 s; 7) window level 400 (200-600); 8) window width 40 (30-60); 9) matrix 512x512; and, 10) reconstruction interval 0.4 mm for 128-detector CT and 0.5 mm for 64-detector CT. A nonionic intravenous contrast agent (2 mL/kg iopromide (maximum: 150 mL); Ultravist 370: Bayer, Berlin, Germany) was delivered via an automatic injector (Optivantage) (Mallinckrodt, 2010); the volume varied by patient weight. Patient drank 1000-1500 mL of water and was injected with a hypotonic agent (20 mg of scopolamine) to distend the stomach before CT scanning.

Image preprocessing

All CT images were labelled, anonymised, and recorded in Digital Imaging and Communication in Medicine format. Pixel gaps were resized and synchronised to a 1x1 mm^2 in-plane resolution using free 3D-Slicer software (ver. 4.10.2). To minimise the effects of differences between the two CT devices, image normalisation and grey level discretisation were performed by assigning a gray level range between 1 and 2 kbits/pixel (termed K-values); the MaZda software (see below) analysed only images with K-values of 6. All images were normalised using the $\pm$ 3-sigma technique (11,12).

Texture analysis

Preoperative CT images were retrieved from our archive and loaded onto an independent workstation for TA in random order. CT-TA was performed with the aid of MaZda software (ver. 4.6, P.M. Szczypiński, Institute of Electronics, Technical University of Lodz), which is free for research purposes (12). The first line of each region of interest (ROI) was drawn parallel to the gastric wall via the consensus of two radiologists (Aytül Hande Yardımcı and İpek Sel with 12 and 4 years of experience respectively, blinded to histopathological data). When expanding the ROI, the radiologists were careful to avoid large vessels and adjacent organs. In the section exhibiting the greatest portion of the tumour, a line was drawn to the outer tumour boundary. Three-fold dilatation was then performed using MaZda, and the area of perigastric area invasion within the ROI expanded toward that area. All tumour masses were evaluated separately (Figure 1a-c). The software automatically calculated all pixel attenuations within the ROI and generated 275 feature variables including first-, second-, and higher-order statistics for each patient (http://www.Eletel.p.lodz.pl/programy/MaZda). We used only the histogram features (1, 10, 50, 90, and 99% percentiles; minimum, mean, and maximum norm; variance; skewness, and kurtosis). All images were from the portal venous phase. The cases were divided in to two groups by tumour T-stage [T 4 (a, b) and T1-to-3]; calculations were performed separately for each group.

Statistical Analysis

The descriptive statistics include the mean, median, standard deviation, minimum, maximum, and percentage. The distributions of all variables

were checked with the aid of the Kolmogorov-Smirnov test. The Independent-samples t-test and the Mann-Whitney U test were used (as appropriate) to compare quantitative data. The chi-squared test was employed to compare qualitative data. Receiver operator curve analysis was performed to assess whether various features were of diagnostic utility. SPSS ver. 26.0 software was used for all statistical analyses.

Surgical resection

All GC resections was performed according to the Japanese Gastric Cancer Society guidelines (13). Radical gastrectomy and standard D1/D2 lymph node dissection were performed by surgeons expert in gastrointestinal system procedures; all cases had pathologically confirmed GC.

Pathological analysis and the reference standard

Specimens were evaluated by reference to edition 8 of the Tumour, Node, Metastasis staging system by two pathologists with 5 and 10 years of experience.

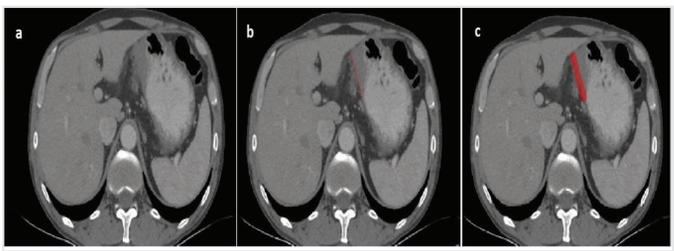

Figure 1. In picture (a), the single largest segment showing the perigastric tumor extension was selected and the tumor margins were determined, then a line showing the largest portion of the tumor (b) was drawn using Mazda software. Then, using the program, three-fold dilatation was performed sequentially (c) and a standard perigastric area to be analyzed within the ROI boundaries was provided

ROI: Regions of interest

Results

Patient data

A total of 110 patients with histopathologically proven GC were enrolled, of whom 10 had stage T1, 9 T2, 28 T3, and 63 T4 a,b disease. Eighty-four (76.4%) patients were male and 26 (23.6%) female. Histologically, 50 tumours were tubular adenocarcinomas; four papillary adenocarcinomas; three mucinous adenocarcinomas; 13 poorly cohesive carcinomas (including signet ring cell carcinomas and other variants); and 40 mixed adenocarcinomas (tubular, papillary, mucinous, medullary and poorly cohesive GCs).

Histogram analysis

Neither age nor gender differed significantly between the T1-to-T3 and T4 groups (both $p>0.05$). Stage T4 tumours were significantly larger in size than stage T1-to-T3 tumours ($p<0.05$). In the T4 group, the min, max, and mean norms; and the 1, 10, and 50% percentiles were significantly lower than in the T1-to-T3 group (all $p<0.05$). Neither the 90 nor 99% percentiles differed between the two groups (both $p>0.05$). The T4 variance was significantly greater than that of the T1-to-T3 group ($p<0.05$). The T4 skewness was significantly lower than that of the T1-to-T3 group ($p<0.05$) but the T4 kurtosis significantly higher ($p<0.05$) (Table 1, 2). The mean AUCs and classification accuracies with 95% confidence intervals are listed in Table 3.

Discussion

Locally advanced GC is defined as stage T4 disease in which the tumour perforates the serosa (T4a) or invades adjacent structures (T4b), and often has a poor prognosis because of the presence of peritoneal seeding, liver metastasis, and/or distant lymph node involvement (14). CT-TA has recently been considered a promising tool; CT-TA evaluates gray level

Table 1. Tumor size, age, gender distribution and histogram analysis findings among the T4 and T1,2,3 groups of the patients are summarized

		Grade T1-T2-T3		Grade T4		p
		Mean ± SD/(n, %)	Median	Mean ± SD/(n, %)	Median	
Age		62.7±11.2	64.5	60.5±10.2	60.0	0.289[t]
Gender	Female	14 (29.2%)	-	12 (19.4%)	-	0.230[χ2]
	Male	34 (70.8%)	-	50 (80.6%)	-	
Tumor size		4.88±2.21	4.50	6.89±3.35	6.00	0.001[m]
Minimum norm		32,663±225	32,607	32,148±4,028	32,677	0.001[m]
Maximum norm		32,957±199	32,922	32,402±4,040	32,905	0.012[m]
Mean		32,811±210	32,765	32,425±2,854	32,789	0.001[m]
Percentile 01%		32,717±215	32,673	32,170±4,032	32,694	0.002[m]
Percentile 10%		32,743±216	32,695	32,209±4,030	32,737	0.001[m]
Percentile 50%		32,819±209	32,779	32,285±4,034	32,798	0.001[m]
Percentile 90%		32,868±205	32,826	32,320±4,034	32,834	0.105[m]
Percentile 99%		32895±207	32,845	32,341±4,035	32,855	0.273[m]
Variance		3,196±1,739	2,876	3,240±2,744	1,911	0.031[m]
Skewnes		-0.26±0.38	-0.22	-0.64±0.43	-0.55	0.001[m]
Kurtosis		-0.78±1.09	-1.14	0.03±1.14	-0.26	0.001[m]

[t]: t-test, [m]: Mann-Whitney U test, $\chi 2$: chi-square test, SD: standard deviation

Table 2. Stage T4 tumors were significantly larger in size than stage T1-to-T3 tumors (p<0.05) in the left graphics on Table 2. All histogram parameters between stages 4 and stages 1-3 are listed in Table 2 and the right graphics

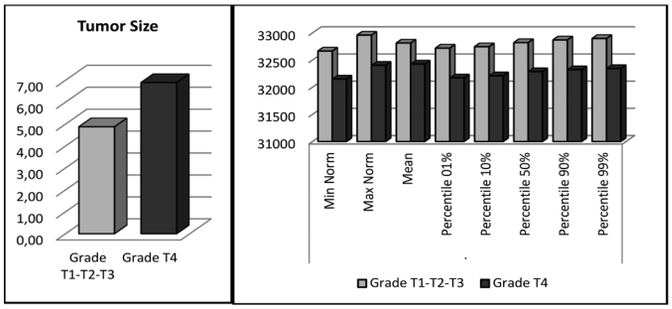

Table 3. The mean AUCs and classification accuracies with 95% confidence intervals are listed in Table 3

	AUC	95% CI	p
Skewnes	0.798	0.711-0.885	**0.000**
Kurtosis	0.776	0.684-0.868	**0.000**
Minimum norm	0.743	0.645-0.841	**0.000**
Mean	0.715	0.614-0.817	**0.000**
Percentile 10%	0.718	0.617-0.819	**0.000**
Percentile 50%	0.715	0.614-0.816	**0.000**
Tumor size	0.681	0.582-0.779	**0.001**
Percentile 01%	0.669	0.564-0.774	**0.002**
Maximum norm	0.640	0.535-0.746	**0.012**
Variance	0.620	0.513-0.727	**0.031**
Percentile 90%	0.590	0.482-0.699	0.105
Percentile 99%	0.561	0.451-0.671	0.273

Receiver operating characteristic curve.
AUC: Area under the curve, CI: confidence interval

distributions and spatial intratumoural heterogeneities (15). Earlier studies suggested that CT-TA might usefully evaluate GC clinical stage, pathological grade, and prognosis (16,17). However, CT-TA has not previously been used to detect serosal invasion (stage-T4) GC. We found significant differences in tumour size; the minimum, maximum, and mean norms; the 1, 10, and 50% percentiles; variance; skewness; and kurtosis between the T4 and T1-to-T3 stages. Skewness derived from portal venous phase images most accurately (AUC: 0.798) distinguished T4 from T1-to-T3 disease. CT attenuation reflects tumour enhancement (18); higher attenuation probably reflects the higher vascularity of more aggressive tumours.

We found that lower skewness and higher kurtosis were significantly associated with T4 status and serosal invasion. Higher skewness and lower kurtosis were significantly associated with the presence of a K-ras mutation in non-small cell lung cancer patients in the study of Weiss et al. (19). Feng et al. (20) showed that volumetric CT textural features, particularly entropy, could potentially serve as biomarkers for risk stratification of small intestinal/gastrointestinal stromal tumours. Here, we performed first-order histogram analysis of single slices; thus, not entire tumours. Previous studies found that CT-TA predicted GC histopathological characteristics (16-20). Liu et al. (17) reported that the invasiveness of tumours of different grades depended principally on the extent of neovascularisation, reflected by attenuation of contrast-enhanced CT.

Study Limitations

Our work had several limitations. First, this was a retrospective single-centre study, with an inevitable patient selection bias. Second, we did not evaluate arterial phase data; this would aid determination of gastric wall invasion depth, especially early in disease progression.

Thirdly, when the perigastric area invasion of the tumor was evaluated after 3-fold dilatation using the MaZda program, both the perigastric and the area towards the tumor fell within the limits of the analysis. Considering different tumor types, this creates a limitation since it is analyzed in the tumor with the perigastric area, and in the next studies, the analysis by removing the tumor margin will give more successful results in evaluating the actual perigastric area invasion.

Finally, in weak patients, the absence of perigastric adipose tissue rendered it difficult to draw ROIs and perform CT-TA; we excluded such patients.

Conclusion

The histogram parameters of CT-TA, especially skewness and kurtosis derived from portal, venous phase CT images, may serve as biomarkers stratifying the risk of serosal invasion (stage-T4) by locally advanced GC. Thus, histogram analysis can be used preoperatively to evaluate serosal invasion.

Ethics Committee Approval: This single-centre retrospective study adhered to all relevant tenets of the Helsinki Declaration and the Good Clinical Practice Guidelines and was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Medical Ethics Committee (approval number: 1750, date: 15.03.2019).

Informed Consent: All patients were included after their informed consent was obtained.

Peer-review: Externally peer-reviewed.

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