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*Retrospective Study*

**Quantitative parameters in novel spectral computed tomography: Assessment of Ki-67 expression in patients with gastric adenocarcinoma**

Mao LT *et al.* Assessment of Ki-67 expression with spectral CT

## Abstract

### BACKGROUND

The level of Ki-67 expression has served as prognostic factor in gastric cancer. The quantitative parameters based on the novel dual-layer spectral detector computed tomography (DLSRCT) in discriminating the expression of Ki-67 status are unclear.

### AIM

To investigate the diagnostic ability of DLSRCT-derived parameters for Ki-67 expression status of gastric carcinoma (GC).

### METHODS

Dual-phase enhanced abdominal DLSRCT was performed preoperatively for 108 patients with gastric adenocarcinoma. Primary tumors monoenergetic CT attenuation value at 40-100 kilo electron volt (keV), the slope of the spectral curve ( $\lambda_{HU}$ ), iodine concentration (IC), normalized IC (nIC), effective atomic number ( $Z^{eff}$ ) and normalized  $Z^{eff}$  ( $nZ^{eff}$ ) in the arterial phase (AP) and venous phase (VP) were retrospectively compared between patients with low and high Ki-67 expression of gastric adenocarcinoma. Spearman correlation coefficient was used to analyze the association between the above parameters and Ki-67 expression status. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic efficacy of the statistically significant parameters between two groups.

### RESULTS

Thirty-seven and 71 patients were classified as low and high Ki-67 expression respectively.  $CT_{40 \text{ keV-VP}}$ ,  $CT_{70 \text{ keV-VP}}$ ,  $CT_{100 \text{ keV-VP}}$ , and  $Z^{eff}$ -related parameters were significantly higher, but IC-related parameters were lower in the group with low Ki-67 status than the group with high Ki-67 status, and other analyzed parameters had no statistical difference between two groups. Spearman correlation analysis showed that  $CT_{40 \text{ keV-VP}}$ ,  $CT_{70 \text{ keV-VP}}$ ,  $CT_{100 \text{ keV-VP}}$ ,  $Z^{eff}$ , and  $nZ^{eff}$  exhibited negative correlations with Ki-

67 status, whereas IC and nIC positively correlated with it. The results of ROC analysis demonstrated that the multi-variable model of spectral parameters performed excellent ability for identifying the Ki-67 status [area under the curve (AUC) = 0.967; sensitivity 95.77%; specificity 91.89%]. Nevertheless, the differentiating capabilities of single-variable model were moderate (AUC value from 0.630 to 0.835). Besides, the  $nZ_{VP}^{eff}$  and  $nIC_{VP}$  (AUC 0.835 and 0.805) showed better performance than  $CT_{40\text{ keV-VP}}$ ,  $CT_{70\text{ keV-VP}}$  and  $CT_{100\text{ keV-VP}}$  (AUC 0.630, 0.631 and 0.662) in discriminating the Ki-67 status.

## CONCLUSION

Quantitative spectral parameters are feasible to distinguish low and high Ki-67 expression of gastric adenocarcinoma.  $Z^{eff}$  and IC may be a useful noninvasive method for evaluating the Ki-67 expression.

**Key Words:** Spectral computer tomography; Quantitative parameters; Gastric carcinoma; Iodine concentration; Effective atomic number; Ki-67 expression

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**Core Tip:** This is a retrospective study to preoperatively distinguish the expression of Ki-67 index based on the parameters of spectral computer tomography (CT) in patients with gastric adenocarcinoma. The CT attenuation of virtual monoenergetic images in venous phase and effective atomic number were negatively related to the expression of Ki-67, while iodine concentration exhibited positive associations with it. Multi-variable model of spectral parameters exhibited a better diagnostic efficiency than other single-variable model of spectral parameter in discriminating low and high Ki-67 expression of gastric adenocarcinoma.

## **INTRODUCTION**

Gastric carcinoma (GC) is the fifth commonest malignancy and the fourth most predominant cause of cancer-related mortality in the world according to the Global Cancer Statistics 2020<sup>[1]</sup>. Though the global age-standardized rates of incidence and mortality presented a slight decrease from 1990 to 2019, China had a high incidence-mortality ratio (0.845) and five-year prevalence (27.6/100000)<sup>[2]</sup>. A large number of GC cases are discovered at the advanced stage and have a relatively poor prognosis, with an overall survival rate of 25% worldwide<sup>[3]</sup>. The high proportion of tumor metastasis, intratumor heterogeneity and chemotherapeutic resistance leads to unfavorable survival outcomes in patients with GC. Conventionally, the tumor-node-metastasis (TNM) stage, histologic classification and differentiation are the major prognostic indicators for GC<sup>[4]</sup>. In addition, some oncogenic protein markers, such as antigen Ki-67, have been associated with the prognosis of GC patients<sup>[5]</sup>.

Cell proliferation is a distinguishing feature of cancer. The Ki-67 protein, a nucleus-associated antigen, which is a convenient and reproducible biomarker for this process, is expressed during the cell proliferation cycle including G1, S, G2, and mitosis phases<sup>[6]</sup>. Some studies have demonstrated that Ki-67 proliferation index could be a potential indicator to predict the prognosis and identify high-risk cases in GC, and was relevant to TNM stage, tumor differentiation grade, invasion depth and distant metastasis<sup>[5,7,8]</sup>. Additionally, Ki-67 index was associated with chemotherapy efficacy in the advanced GC, because cytotoxic chemotherapeutic drugs are effective against tumor cells that have entered the cell division cycle. Thus, identifying the Ki-67 status noninvasively would be beneficial for predicting the prognosis and chemotherapeutic response in the patients with GC.

Recently, a novel dual-layer spectral detector CT (DLSPECT), which utilizes a detector-based dual-energy separation technology to acquire low- and high-energy data synchronously with two layers of detectors, makes for beam-hardening rectification, material decomposition, and image de-noising<sup>[9,10]</sup>. This system applies projection-space decomposition could generate various spectral basis images (SBIs) except for the

conventional polyenergetic images, including material-specific images [iodine concentration (IC) images, virtual non-contrast images, effective atomic number ( $Z^{\text{eff}}$ ) images] and energy-specific images (virtual monoenergetic images, VMIs). These spectral images are widely used for enhancing image contrast, improving lesion detection, characterizing materials, reducing artifact, and lowering radiation dosage<sup>[9-12]</sup>. Some studies have investigated the gastric lesions based on the IC derived from dual-energy spectral CT, such as distinguishing between malignant and benign gastric mucosal lesions<sup>[13]</sup>, diagnosing GC and its histological type<sup>[14]</sup>, and detecting serosal invasion of GC<sup>[15]</sup>. The latest study demonstrated that virtual monochromatic CT values were related to proliferative activity of tumor cells<sup>[16]</sup>. The  $Z^{\text{eff}}$  was correlated with Ki-67 expression in laryngeal squamous cell carcinoma<sup>[17]</sup>, and could predict the vascular density of diseased lesions<sup>[18]</sup>. However, only a few studies have applied the quantitative parameters [IC and normalized IC (nIC)] from spectral CT to evaluate the Ki-67 expression status in patients with gastric adenocarcinoma, but not including the CT attenuation value and  $Z^{\text{eff}}$  derived from the novel DLSDCT. Thus, the aim of this study is to explore the clinical usefulness of the quantitative parameters of novel DLSDCT in assessing the Ki-67 expression status of patients with gastric adenocarcinoma.

## **MATERIALS AND METHODS**

### ***Patients***

This retrospective study was approved by Institutional Review Board of our hospital, with a waiver for written informed consent. From May 2021 to June 2022, 135 patients diagnosed as gastric adenocarcinoma through endoscopic biopsy and underwent non-contrast and contrast-enhanced CT scans on a DLSDCT scanner (IQon Spectral CT, Philips Healthcare, Best, The Netherlands). 28 cases were excluded for the following factors: (1) Transferred to another hospital for further treatment ( $n = 4$ ); (2) Accepted or required neo-adjuvant chemotherapy prior to surgery ( $n = 12$ ); (3) Poor image quality or the lesion is ambiguous on the image ( $n = 7$ ); or (4) Lack of the Ki-67 index

immunohistologic result ( $n = 4$ ). Finally, 108 patients were analyzed in our study. The detailed procedure of patient selection is shown in Figure 1.

### *Spectral CT imaging protocol*

The interval between the DLSRCT examination and surgery was less than one week. Before CT examination, patients were required to be fast for 6-8 h and drank 800-1000 mL of water. The scan ranged from the diaphragm to the symphysis pubis in a supine position and cranio-caudal direction. Nonionic contrast agent (Ultravist, Byer HealthCare) (370 mg/mL, 80 mL) was injected intravenously at a flow rate of 2.5 mL/s, with an automated injector (Stellant, Medrad, Byer HealthCare), following 30 mL of normal saline flushing at the same flow rate. Using bolus-tracking technique, the arterial phase (AP) scan was triggered at a threshold of 200 hounsfield unit (HU) and an additional delay of 6 s. The venous phase (VP) images were respectively collected at 35 s after injecting the contrast agent.

CT scan parameters were as follows: Tube voltage 120 kVp, automatic tube current 37-84 mAs, detector collimation 64 mm  $\times$  0.625 mm, reconstruction matrix 512  $\times$  512. Conventional and SBI were reconstructed using the iDose 4 algorithm (Philips Healthcare). All CT images were reconstructed with a slice thickness of 1 mm and an increment of 1 mm, using a standard kernel. All image data were transferred to a workstation (IntelliSpace Portal, version 10.1, Philips Healthcare) for post-processing and analysis.

### *Image analysis*

The image analysis was conducted by two gastrointestinal radiologists (reader 1 and reader 2, with 10 and 26 years of experience, respectively), who were blind to pathological results. The two-dimensional region-of-interest (ROI) was drawn on lesion manually, according to following principles: (1) Polygon ROIs covered the enhanced areas of the lesions as much as possible; (2) Be careful to avoid the areas of necrosis, calcification, and vessels; (3) All lesions were measured on three consecutive axial layers

by the same evaluator, and average values were calculated; and (4) The size, form, and position of the ROIs were maintained consistently between two phases images, by applying the copy-and-paste function of the workstation. A circular ROI was placed in the abdominal aorta parallel with lesion. The intraclass correlation coefficient (ICC) between the two radiologists was calculated. The final results of all ROIs were measured by the radiologist with 10 years' experience.

The following quantitative spectral parameters were automatically calculated through the post-processing software: The CT attenuation values of monochromatic images [40 kilo electron volt (kev), 70 kev and 100 kev], IC, and the  $Z^{eff}$ . Additionally, three related parameters were measured in our study: (1) The nIC was computed as  $nIC = IC_{lesion}/IC_{aorta}$ , where  $IC_{lesion}$  and  $IC_{aorta}$  are the ICs of the lesions and abdominal aorta, which help to minimize individual variation; (2) The normalized  $Z^{eff}$  ( $nZ^{eff}$ ) was counted similarly to nIC,  $nZ^{eff} = Z^{eff}_{lesion}/Z^{eff}_{aorta}$ ; and (3) The slope of the spectral curve ( $\lambda_{HU}$ ) was calculated as the CT attenuation values,  $\lambda_{HU} = (CT_{40\text{ kev}} - CT_{70\text{ kev}})/30$ , where  $CT_{40\text{ kev}}$  and  $CT_{70\text{ kev}}$  are the attenuation of the tumors at 40 kev and 70 kev monochromatic images, respectively<sup>[19]</sup>. Two phases (AP and VP) of CT attenuation value, IC, nIC,  $Z^{eff}$ ,  $nZ^{eff}$ , and  $\lambda_{HU}$  were measured.

### ***Histopathology evaluation***

A pathologist with 22 years of experience (Yu Zhang) conducted the pathologic analysis. The TNM staging was identified on the basis of the American Joint Committee on Cancer (AJCC) 8<sup>th</sup> manual of gastric cancer<sup>[20]</sup>. The Ki-67 proliferation index was evaluated according to the normal immunohistochemistry process and evaluated by the pathologist blindly. The Ki-67 polyclonal antibody used (Roche #) was produced by ShangHai Rebiosci Biotech Co.,Ltd. The specimens were analyzed in a high power field ( $\times 400$ ). The pathologist selected five fields of view randomly and each region was observed. Then she selected one hundred cells in each field and counted the number and intensity of positively stained cells. Finally, an average number of five fields were



recorded. The Ki-67 indexes were categorized as low expression (< 50% positive cells) or high expression ( $\geq$  50% positive cells), according to relevant reports<sup>[7,21]</sup>.

### ***Statistical analysis***

Statistical analysis was performed using MedCalc Statistical Software version 19.4.1 (MedCalc Software, Ostend, Belgium; <https://www.medcalc.org>; 2020). Continuous variables were displayed as the mean  $\pm$  standard deviation (SD), and categorical variables as proportions. ICC analyses were performed with the data of 20 patients to evaluate the reliability of spectral parameters measurement. An ICC > 0.75 was considered good.

The Shapiro-Wilk test was applied to test the normality of data distributions. The student's *t*-test was employed to analyze the differences in clinical demographics and imaging parameters between low and high Ki-67 expressing status. Spearman correlation coefficient was used to assess the correlation between the quantitative imaging parameters and the Ki-67 expression status.

Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic efficacy in classifying Ki-67 statuses. Area under the curve (AUC) and their 95% confidence intervals (CIs) were determined utilizing unstratified bootstrap replicates 10000 times. The optimal cutoff value is determined according to the Youden index. The difference between ROC curves were evaluated by pairwise comparison test. A two-sided *P* value of less than 0.05 was regarded statistically significant.

## **RESULTS**

### ***Patient demographics and histopathological findings***

A total of 108 patients (mean age 61.9 years, range 34-85 years) were analyzed in this study, consisting of 46 females and 62 males. The gastric tumors were located in the antrum in 48 cases (44.4%), in the corpus in 24 cases (22.2%), in the fundus in 11 cases (10.1%), in the antrum and corpus in 9 cases (8.3%), in the gastric angle in 9 cases (8.3%), and in the cardia in 7 case (6.4%).

Referring to the pathologic TNM staging of GC (AJCC 8<sup>th</sup> edition), 27 patients had gastric cancer of less than stage pT2, 32 patients had stage pT3 gastric cancer, and 49 patients had stage T4 gastric cancer. 26 patients had no regional lymph node metastasis, whereas 24 patients had less than three lymph nodes invaded (pN1), 30 patients had 3-6 regional lymph nodes invaded (pN2), and 28 patients had seven or more regional lymph nodes invaded (pN3). The immunohistochemical staining results revealed that 37 cases were categorized as low expression of the Ki-67 indexes, while 71 cases were categorized as high expression. According to World Health Organization grading criteria, 29 (26.8%) and 79 (73.1%) tumors were respectively classified as moderately and poorly differentiated adenocarcinoma.

#### ***Reliability of measurements***

The ICC values for  $Z_{\text{lesion}}^{\text{eff}}$ ,  $Z_{\text{aorta}}^{\text{eff}}$ ,  $IC_{\text{lesion}}$ ,  $IC_{\text{aorta}}$ ,  $CT_{40 \text{ kev}}$ ,  $CT_{70 \text{ kev}}$ ,  $CT_{100 \text{ kev}}$  in AP and VP were all more than 0.85, and the specific values are shown in Table 1.

#### ***Correlation between spectral parameters and Ki-67 status***

$Z^{\text{eff}}$  and  $nZ^{\text{eff}}$  in AP and VP present a moderate negative correlation with Ki-67 status ( $P < 0.001$ ), whereas the IC and nIC in AP and VP were moderately positive-correlated with Ki-67 status ( $P < 0.001$ ). The  $CT_{40 \text{ kev-VP}}$ ,  $CT_{70 \text{ kev-VP}}$  and  $CT_{100 \text{ kev-VP}}$  were weakly negative-correlated with Ki-67 status (all  $P < 0.05$ ). However, the  $CT_{40 \text{ kev-AP}}$ ,  $CT_{70 \text{ kev-AP}}$ ,  $CT_{100 \text{ kev-AP}}$  and  $\lambda_{\text{HU-AP}}$  and  $\lambda_{\text{HU-VP}}$  were not correlated with Ki-67 expression (all  $P > 0.05$ ). The correlation coefficients and 95% CIs were shown in Table 2.

#### ***Comparison of spectral parameters between different Ki-67 status***

Table 3 and Figure 2 displayed the results of quantitative analysis. Compared with high Ki-67 status, the low Ki-67 status had higher  $Z_{\text{AP}}^{\text{eff}}$ ,  $Z_{\text{VP}}^{\text{eff}}$ ,  $nZ_{\text{AP}}^{\text{eff}}$ ,  $nZ_{\text{VP}}^{\text{eff}}$ ,  $CT_{40 \text{ kev-VP}}$ ,  $CT_{70 \text{ kev-VP}}$  and  $CT_{100 \text{ kev-VP}}$ , and had lower  $IC_{\text{AP}}$ ,  $IC_{\text{VP}}$ ,  $nIC_{\text{AP}}$  and  $nIC_{\text{VP}}$ . Although the  $CT_{40 \text{ kev-AP}}$ ,  $CT_{70 \text{ kev-AP}}$  and  $CT_{100 \text{ kev-AP}}$  of low Ki-67 status were little higher than that of high Ki-67 status, it was not statistically significant. Similarly, there were no significant

differences found in the  $\lambda_{\text{HU}}$  of AP and VP between two groups. Figures 3 and 4 shows the spectral parameter images of two cases with high and low Ki-67 expression respectively.

### *Diagnostic performance*

Table 4 summarize the results of ROC analysis for evaluating the diagnostic performance of twelve significant spectral parameters in discriminating the Ki-67 status. For diagnosing the high Ki-67 Labeling index, the  $Z^{\text{eff}}$ ,  $nZ^{\text{eff}}$ , IC and  $n\text{IC}$  in AP and VP performed moderate efficiency (AUC value, ranged from 0.747 to 0.835), and there were no significant difference among the AUC values of these parameters. Nevertheless, the  $\text{CT}_{40 \text{ kev-VP}}$ ,  $\text{CT}_{70 \text{ kev-VP}}$ , and  $\text{CT}_{100 \text{ kev-VP}}$  showed general differentiating capabilities (AUC value, 0.630, 0.631, 0.662 respectively) in differentiating low- from high-level Ki-67 expression in GC, and the AUC values of these parameters had no statistical differences. Comparing the AUC values of CT attenuation with that of the  $Z^{\text{eff}}$ - and IC-related parameters, the AUC value of  $nZ^{\text{eff}}_{\text{AP}}$  was higher than  $\text{CT}_{40 \text{ kev-VP}}$  (0.796 vs 0.630,  $P = 0.047$ ), and the AUC values of  $nZ^{\text{eff}}_{\text{VP}}$  and  $n\text{IC}_{\text{VP}}$  were higher than  $\text{CT}_{40 \text{ kev-VP}}$ ,  $\text{CT}_{70 \text{ kev-VP}}$  and  $\text{CT}_{100 \text{ kev-VP}}$  ( $P = 0.02, 0.01, 0.009$  and  $0.03, 0.01, 0.02$  respectively). Besides, the multi-variable model ( $\text{CT}_{70 \text{ kev-VP}}$ ,  $nZ^{\text{eff}}_{\text{AP}}$ ,  $nZ^{\text{eff}}_{\text{VP}}$ ,  $n\text{IC}_{\text{AP}}$ ,  $n\text{IC}_{\text{VP}}$ ) were selected for most powerful parameters by multivariate logistic regression, and the model performed excellent efficiency (AUC = 0.967; sensitivity 95.77%; specificity 91.89%) in discriminating high expression of Ki-67 index of GC.

### **DISCUSSION**

The recently developed DLSDCT could quantitatively map the IC and  $Z^{\text{eff}}$  of the tissue in enhanced images, and offer CT attenuation values on a wide range of VMIs. In this study, we explored the association between quantitative parameters derived from DLSDCT and the Ki-67 labeling index of gastric adenocarcinoma. Our results revealed that the  $\text{CT}_{40 \text{ kev-VP}}$ ,  $\text{CT}_{70 \text{ kev-VP}}$ ,  $\text{CT}_{100 \text{ kev-VP}}$ , and  $Z^{\text{eff}}$ -related parameters were significantly higher, but IC-related parameters were lower in the group with low Ki-67 status.

Additionally, the  $CT_{40\text{ keV-VP}}$ ,  $CT_{70\text{ keV-VP}}$ ,  $CT_{100\text{ keV-VP}}$ , and  $Z^{\text{eff}}$ -related parameters exhibited negative correlations with Ki-67 status, whereas IC-related parameters positively correlated with it. These results were partially in agreement with previous reports that used different spectral CT systems, which demonstrated that IC and nIC were positively associated with Ki-67 status, and the values of nIC were higher in poorly differentiated gastric adenocarcinomas significantly<sup>[22,23]</sup>.

We found a negative correlation between  $Z^{\text{eff}}$  and Ki-67 labeling index, which is seemingly at variance with a previous study that  $Z^{\text{eff}}$  was positively correlated with Ki-67 expression in the laryngeal squamous cell carcinoma<sup>[17]</sup> and invasive breast cancer<sup>[24]</sup>.  $Z^{\text{eff}}$  reflects the total atomic numbers of complex or mixture of materials, has a close relationship with fundamental properties of the elements<sup>[25]</sup>. Previous research indicated that the evaluation of  $Z^{\text{eff}}$  could be able to distinguish the different tissues showing similar attenuative properties at given energy<sup>[26]</sup>. On account of the concentrations of elements (Cl, K, Ca, Ti, Mn, Fe, Co, Cu, and Zn) are lower in the stomach cancerous tissue than normal tissue<sup>[25]</sup>, gastric cancer tissue exhibits a lower  $Z^{\text{eff}}$  than its healthy counterpart<sup>[27]</sup>. It is known that deficiency or excess of certain essential trace metals is relevant to carcinogenesis of the specific organs<sup>[27,28]</sup>. The abnormal levels of these elements lead to the discrepancy of toxicity and proliferation activity of cancer cells. We hypothesis that  $Z^{\text{eff}}$  difference between high and low-Ki-67 status is more due to abnormal metal concentration than tumor heterogeneity and angiogenesis, especially in case of using  $nZ^{\text{eff}}$ , which eliminate individual differences in hemodynamics.

The blood vessels of tumors are supplied by tumor angiogenesis and invasion of vessels around the tumor. The degree of tumor angiogenesis is strongly linked to tumor growth, progression, and metastasis<sup>[29,30]</sup>. Wang *et al*<sup>[31]</sup> found that the degree of CT enhancement is correlated with tumor angiogenesis and the malignancy of the tumor. Compared to CT contrast enhancement, IC can quantitatively indicate the degree of tumor neovascularization and reflect the deposition of iodine in the tissue objectively<sup>[32]</sup>. In this study, we detected significantly higher IC and nIC values in the

AP and VP of the high-expression Ki-67 group, indicating a richer blood supply in these tumors. Compared to IC, the normalized parameter nIC minimize hemodynamic variations between individuals, which could be more comparable among different groups. These findings are consistent with the fact that the high proliferative activity is accompanied by abundant angiogenesis.

In our study, we found no statistical difference in the CT attenuation values at 40-100 keV (at 30 keV interval) in AP between low- and high-expression Ki-67 groups. Likewise, the  $\lambda_{HU}$  of AP and VP between the two groups showed no significant differences, which was different from the result reported by Cheng *et al*<sup>[22]</sup>, who found that the  $\lambda_{HU}$  values had significantly difference among the low, medium and high level Ki-67 groups both in VP and delayed phase, and had positive correlation with Ki-67 grade. We deemed that the discrepancy might be attributable to the grouping method of Ki-67 index and the constituent ratio of differentiation degree of the analyzed cases was distinct from our study. It is necessary to further explore the usefulness of  $\lambda_{HU}$  values.

When evaluating the diagnostic performance of spectral parameters in discriminating the Ki-67 status, the results from ROC analysis demonstrated that the multi-variable model of spectral parameters performed excellent capacity, with high sensitivity and specificity. In contrast, the single-variable model of  $Z^{eff}$ - and IC-related parameters demonstrated moderate efficiency, and 40-100 keV (at 30 keV interval) in VP showed general efficiency. Therefore, the parameters derived from DLSDCT were feasible for the prediction of Ki-67 expression in the gastric adenocarcinoma, which is of great significance in predicting prognosis and guiding treatment for the patients with GC.

There were several limitations in our study. First, this is a retrospective study that case grouping is not random, hence, an unconscious selection bias may exist. Second, a relatively small number of patients might overstate the consequence of association. Third, the number of cases with different degrees of differentiation was disproportionate, resulting in significance hard to achieve for partially analyzed variables. Fourth, our uniform standard of enhanced scanning protocol with DLSDCT

may be different from other centers, thus, the results acquired from other vendors or different scanning parameters may not be directly concluded from our results. It demands further studies to confirm and outspread our preliminary results.

## **CONCLUSION**

Quantitative spectral parameters are feasible to distinguish low and high Ki-67 expression of gastric adenocarcinoma. Multi-variable model of spectral parameters exhibited a better diagnostic efficiency than single-variable model of spectral parameter in discriminating low and high Ki-67 expression of gastric adenocarcinoma.  $Z^{eff}$  and IC derived from DLSDCT may be a useful noninvasive method for evaluating the Ki-67 proliferation index for gastric adenocarcinoma.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

The level of Ki-67 expression is a valuable prognostic factor in gastric cancer. However, the quantitative parameters based on the novel dual-layer spectral detector computed tomography (DLSDCT) in discriminating the expression of Ki-67 status are unclear.

### ***Research motivation***

The relationship between the Ki-67 expression in gastric carcinoma (GC) and part spectral parameters [including the effective atomic number ( $Z^{eff}$ ) and the monoenergetic CT attenuation] is unclear.

### ***Research objectives***

<sup>6</sup> This study aimed to investigate the diagnostic ability of DLSDCT-derived parameters for Ki-67 expression status of GC.

### ***Research methods***



Dual-phase enhanced abdominal CT was performed preoperatively for 108 patients with GC. The monoenergetic CT attenuation value at 40-100 kilo electron volt (keV), the slope of the spectral curve ( $\lambda_{HU}$ ), iodine concentration (IC), normalized IC (nIC),  $Z^{eff}$  and normalized  $Z^{eff}$  ( $nZ^{eff}$ ) in the arterial phase (AP) and venous phase (VP) were retrospectively compared between the group of low and high Ki-67 status. The relationship between the spectral parameters and Ki-67 expression status were analyzed, and the diagnostic efficacy of the statistically significant parameters between two groups were evaluated.

### **Research results**

The low and high Ki-67 expression group is 37 and 71 patients respectively.  $CT_{40\text{ keV-VP}}$ ,  $CT_{70\text{ keV-VP}}$ ,  $CT_{100\text{ keV-VP}}$ , and  $Z^{eff}$ -related parameters were significantly higher, but IC-related parameters were lower in the low Ki-67 group than the high Ki-67 group.  $CT_{40\text{ keV-VP}}$ ,  $CT_{70\text{ keV-VP}}$ ,  $CT_{100\text{ keV-VP}}$ ,  $Z^{eff}$ , and  $nZ^{eff}$  exhibited negative correlations with Ki-67 status, whereas IC and nIC positively correlated with it. The results of receiver operating characteristic analysis showed that the multi-variable model of spectral parameters performed excellent ability for identifying the Ki-67 status [area under the curve (AUC) = 0.967; sensitivity 95.77%; specificity 91.89%]. Nevertheless, the differentiating capabilities of single-variable model were moderate (AUC value from 0.630 to 0.835).

### **Research conclusions**

$Z^{eff}$  and IC may be a useful noninvasive method for evaluating the Ki-67 expression in GC.

### **Research perspectives**

The spectral CT images are prospective to provide the pathological information of Ki-67 expression of GC in the future.

# 3%

SIMILARITY INDEX

### PRIMARY SOURCES

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