

Dual energy CT based iodine density in relation to histological parameters in gastric cancer

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Abstract

Aim: To evaluate whether iodine density (ID) and normalized iodine density (NID) of tumor on rapid kV-switching dual energy CT is associated with histological parameters which influences disease prognosis in gastric cancer

Material and Methods: Twenty patients with gastric adenocarcinoma who had preoperative staging CT imaging dual energy mode in arterial phase were retrospectively included. Patients who had neoadjuvant treatment prior to surgery were excluded. ID and NID values were measured on arterial phase dual energy CT images on a dedicated workstation.

Results: ID and NID of the tumor were significantly lower in poorly differentiated tumors compared with well differentiated tumors ($p=0.019$, $p=0.046$), and also in patients with unfavorable histology compared with unfavorable histology group ($p=0.005$, $p=0.042$). There were no significant ID and NID value differences between patients with and without serosal infiltration, nodal metastasis, lymphovascular and perineural invasion, surgical margin involvement ($p>0.05$).

Conclusion: ID related parameters can be useful for predicting the prognosis of gastric cancer.

Keywords: Iodine density; dual energy CT; gastric cancer; histological parameters

INTRODUCTION

Gastric cancer has the fifth highest incidence among cancers and one of the top leading causes of cancer-related deaths. Early detection of cancer is very important as 5-year-survival rate of stage I tumor is as high as 88-94% whereas stage IIIc tumors survival rate drop down to 18% (1). Multidetector computed tomography (MDCT) is the primary imaging modality used for tumor-node-metastasis (TNM) staging of gastric cancer and optimal treatment choice is decided according to the stage of the tumor (2). Serosal infiltration (T4a) and lymph node metastasis are associated with poorer prognosis. However, the accuracy of CT to detect serosal infiltration were found to be quite variable in studies ranging from 77.8 to 93.5% (3). Moreover, the accuracy was even somewhat worse for lymph node metastasis detection and in a recent meta-analysis, specificity for MDCT to detect lymph node metastasis ranged between 62.5% and 91.9% while sensitivity varied between 50 and 89.9% across various studies (4). The prognosis of gastric

cancer is also closely related with histological parameters. Signet-ring or mucinous type gastric cancer, diffuse type gastric cancer, poor differentiation, lymphovascular and perineural invasion are also associated with poorer prognosis (5,6). Yet, the performance of MDCT to predict disease prognosis preoperatively and noninvasively is not at the desired level. In this regard, dual energy CT (DECT) seems to have potential.

DECT provides simultaneous acquisition of a data set at two different energy levels in a single examination and constituent elements of a given material can be characterized by decomposition algorithms owing to the photoelectric absorption differences of high and low atomic number elements under different photon energies. Iodine is a very ideal element for dual energy applications because of its relatively high atomic number compared to the low atomic number of soft tissues in the body and can be quantified as another surrogate of enhancement apart from attenuation change or subtracted from tissues forming virtual unenhanced images (7).

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Iodine quantification by means of DECT has widely been studied in oncological applications such as tumor characterization and treatment monitoring (8). However, the number of studies with dual energy CT imaging in gastric cancer is limited and focused on benign-malignant gastric lesion differentiation (9), early-advanced gastric cancer differentiation (10), lymph node metastasis prediction (11,12) and serosal infiltration prediction (13,14). The studies regarding the association of histological parameters to iodine density and normalized iodine density are conflicting because although significant differences were detected between different tumor differentiation groups in two studies (15,16), no significant differences were observed in another study (17). Additionally, there was only one study to our knowledge which evaluated NID differences between different histological diagnoses and they did not observe significant differences between groups (18). Therefore, in this study we aimed to evaluate the correlation of iodine content of gastric adenocarcinoma in preoperative staging DECT with postoperative histological parameters in patients who did not take neoadjuvant treatment prior to surgery and present our own experience.

MATERIAL and METHODS

This retrospective study was approved by institutional review board and the requirement for informed consent from patients was waived.

Patient selection

Patients who underwent gastric cancer surgery between December 2015 and September 2019 and had preoperative staging abdominal MDCT obtained in dual energy mode arterial phase and conventional portal venous phase were eligible for inclusion (n=118). Patients who had neoadjuvant treatment prior to surgery (n=90), whose staging CT examination was not performed in dual energy mode (3), who did not have further follow-up in our hospital database (n=2), whose gastric tumor was not visible on staging CT (n=1) and whose gastric lesion did not turn out to be an adenocarcinoma (n=2) were excluded from the study.

Image acquisition

CT examinations were performed on a rapid kV-switching dual-energy 64-detector MDCT scanner (Discovery CT750 HD scanner, General Electric Healthcare, Waukesha, WI, USA). Patients were instructed to fast for 8 hours prior to CT examination and to drink 700-1000 ml of water in 15 minutes to distend the stomach. Arterial phase dual energy CT images covering the whole stomach were acquired at 40 seconds after the contrast injection (scan type, helical, detector coverage, 40 mm, slice thickness, 2.5 mm, interval, 1.25 mm, pitch, 0.984:1, speed, 39.37, and gantry rotation time, 0.7 s, automatic mA modulation (range 260-600 mA), targeted noise index 20). Images were reconstructed with a standard algorithm and application of 30% adaptive statistical iterative reconstruction (ASIR). Portal venous phase was acquired at 70 seconds

with following parameters: scan type, helical, detector coverage, 40 mm, slice thickness, 2.5 mm, interval, 1.25 mm, pitch, 1,375:1 speed, 55, and gantry rotation time, 0.7 s, automatic mA modulation (range 260-600 mA), targeted noise index 17.25. Portal venous phase images covered the entire abdomen and pelvis to detect distant metastases but were not used for analysis.

Intravenous contrast material was administered (Iohexol: Omnipaque 350, General Electronic Healthcare, Princeton NJ, USA) using a standardized weight-based dose injected at 3 cc/s rate for a fixed 30-s injection interval, followed by a 25 cc saline flush.

Image analysis

All image analyses were made on the dedicated workstation by Gemstone Spectral Image (GSI) software (ADW 2.0, General Electric Healthcare, Milwaukee, WI).

Arterial phase images which were acquired in dual energy mode were opened on GSI reformat viewer and iodine density images were generated. An elliptic region of interest (ROI) was placed on the gastric tumor in the slice where it was largest and encompassed the tumor as much as possible avoiding the perigastric fat and necrotic areas when present. ID was measured in mg/ml in the sampled area. All measurements were performed three times and the average values were recorded. To minimize variation between individuals, a circular ROI was also placed on the abdominal aorta at the level of the gastric tumor and iodine density of the aorta was measured for normalization (Fig 1). NID was calculated as the ratio of ID of the tumor to the ID of the aorta ($NID=ID_{tumor}/ID_{aorta}$). All analyses were performed by an abdominal radiologist with 5 years of experience in abdominal radiology.

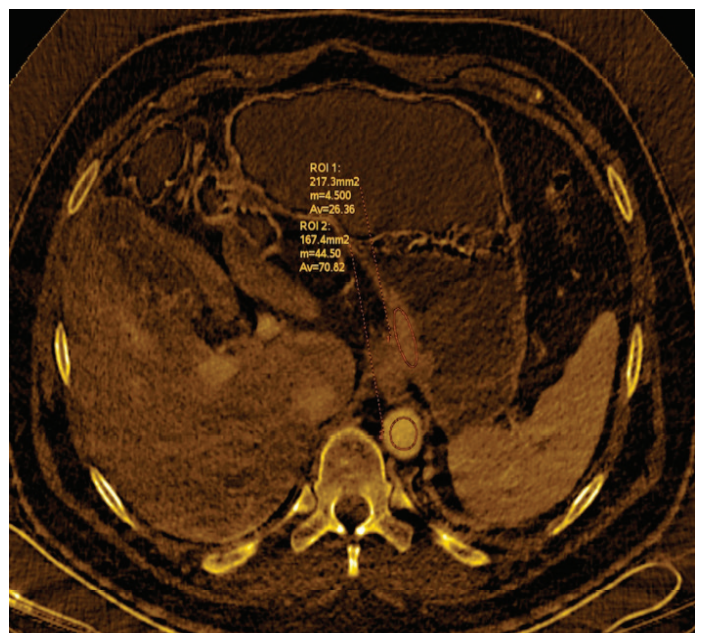


Figure 1. 48-year-old male patient with moderately differentiated tubular adenocarcinoma in gastric cardia. Axial arterial phase iodine density images depict the tumor as irregular wall thickening and the region of interest (ROI) placement onto the tumor and the aorta

Statistical analysis

Statistical analysis was performed on SPSS 22.0 software package. Normality of parameter distribution was assessed using Shapiro Wilk test. Mann-Whitney U and Kruskal Wallis tests were used for comparing ID and NID differences of the tumor between different groups. Data were presented as median (minimum-maximum). The level of statistical significance was set as $p < 0.05$.

RESULTS

There were a total of 20 patients (15 male, 5 female). Mean patient age was 64 ± 14 years (range 36-83). Three tumors were located in cardia, 4 in corpus and 13 in antrum. Median tumor thickness was 16.5 mm (range 7-60). Based on surgical histopathology results, 13 patients had intestinal type gastric adenocarcinoma and 2 patients had tubular adenocarcinoma. These two types were assigned to the group of favorable histology. Diffuse infiltrative type tumors ($n=3$) and mucinous adenocarcinoma ($n=2$) cases were assigned to the group of unfavorable histology. Sixteen tumors did not have serosal infiltration (8 T1, 3 T2, 5 T3) and 4 tumors had serosal infiltration. 8 tumors were node positive and 12 were node negative. None of the patients had distant metastasis. 7 tumors were well-differentiated, 5 were

moderately differentiated and 8 were poorly differentiated. Thirteen were intestinal type adenocarcinoma, 3 were diffuse infiltrative type adenocarcinoma, 2 were mucinous adenocarcinoma and 2 were tubular adenocarcinoma. Ten tumors had lymphovascular invasion and 8 tumors had perineural invasion. Surgical margins were positive for 3 tumors. The median iodine densities of the tumor and the aorta were 2.38 mg/ml (1.42-5.37) and 12.08 mg/ml (7.37-16). The median NID was 0.18 (0.11-0.46). Results of Mann-Whitney U and Kruskal-Wallis tests are shown in table 1. There were no significant differences between IDs and NIDs of the tumors with and without serosal infiltration, nodal metastasis, lymphovascular and perineural invasion, surgical margin involvement ($p > 0.05$). There was a significant ID and NID difference between favorable and unfavorable histology groups ($p=0.005$; $p=0.042$) and unfavorable histology group had lower ID and NID values compared to favorable histology group. There was significant ID and NID difference between well-differentiated and poorly differentiated tumors ($p=0.019$, $p=0.046$) and poorly differentiated tumors had lower ID and NID values compared to well differentiated tumors. However, there were no significant ID and NID differences between moderately-well differentiated tumors and moderately-poorly differentiated tumors ($p=0.63$ and $p=0.69$; $p=1$ and $p=0.56$).

Table 1. Iodine density and normalized iodine density values with regard to histological parameters

Parameter	Status (number)	IDtumor (mg/ml) (median(min-max))	NIDtumor (median(min-max))	p value
Serosal infiltration	Present (4)	1.73 (1.42-2.56)	0.18 (0.12-0.37)	0.148
	Not present (16)	2.44 (1.45-5.37)	0.19(0.11-0.46)	0,68
Nodal metastasis	Present (8)	2.33 (1.42-5.37)	0.20 (0.12-0.46)	1
	Not present (12)	2.38 (1.45-3.45)	0.16 (0.11-0.30))	0.384
Lymphovascular invasion	Present(10)	1.79 (1.42-3.26)	0.16 (0.11-0.37)	0.052
	Not present (10)	2.81 (1.45-5.37)	0.20(0.13-0.46)	0.247
Perineural invasion	Present (8)	2 (1.49-3.26)	0.18(0.11-0.37)	0.427
	Not present (12)	2.54 (1.42-5.37)	0.17(0.13-0.46)	0.851
Surgical margin involvement	Positive (3)	1.86 (1.61-3.44)	0.22 (0.12-0.29)	0.921
	Negative (17)	2.38 (1.42-5.37)	0.17(0.11-0.46)	1
Histological groups	Favourable (15)	2.56 (1.49-5.37)	0.18(0.11-0.46)	0.005*
	Unfavorable (5)	1.61 (1.42-1.86)	0.12(0.12-0.23)	0.042*
Differentiation	Well (7)	3.14 (1.69-5.37)	0.24(0.14-0.46)	0.024*
	Moderate (5)	2.51 (1.67-2.71)	0.18(0.13-0.37)	0.046*
	Poor (8)	1.67 (1.42-3.26)	0.13(0.11-0.46)	

DISCUSSION

The main findings of our study are that ID and NID values obtained by DECT differ significantly between well and poorly differentiated gastric adenocarcinoma and favorable-unfavorable histology groups.

Quantitative imaging biomarkers derived from various imaging modalities like diffusion weighted magnetic resonance imaging (MRI), dynamic contrast enhanced MRI, perfusion CT or MRI have been widely used in an attempt to be able to detect and characterize pathological processes in conjunction to the morphological changes (19). DECT is another recently introduced imaging technique that can provide additional parameters that single energy CT cannot provide such as virtual non-contrast and monochromatic imaging, material density analysis. Virtual noncontrast imaging shows promise for eliminating the need for replacing true unenhanced imaging and can contribute greatly to radiation dose reduction thereby. Virtual mono-energetic imaging provides optimization of the image quality and decrease beam hardening effects. Material density analysis can show material composition of tissues and quantify different materials in the tissues of the body such as iodine, calcium, iron etc (7, 20). Iodine quantification by DECT was found to be accurate in phantom studies (21) and it has widely been used in oncological applications in terms of distinguishing tumor from nontumoral tissue (22), benign and malignant differentiation (23,24), tumor subtype characterization (8) based on iodine content of various tissues.

Of studies performed in patients with gastric cancer, Meng et. al, (9) aimed to differentiate malignant gastric mucosal lesions from gastric inflammation-normal mucosa and showed that gastric cancer had significantly higher ID and NID than normal gastric mucosa in both arterial and portal venous phases but there was no significant ID difference between gastric cancer and gastric inflammation in arterial phase although there were significant difference in portal venous phase. Li et. al, (15) found significantly higher ID and NID values in gastric cancer in both arterial and portal venous phases. Another study by Cheng et. al, (10) evaluated whether early and advanced gastric cancer could be differentiated by iodine content and found that early gastric cancer had significantly lower ID and NID than advanced gastric cancer in portal venous and delayed phases but arterial phase values were not different significantly. As lymph node involvement is an important prognostic indicator, one of the determinants of treatment type and conventional single energy MDCT accuracy of lymph node metastasis evaluation is not satisfactory enough, studies regarding lymph node positivity based on iodine content have also been performed. Pan et. al, (12) found that metastatic lymph nodes significantly had higher NID values in both arterial and portal phases. Similarly, Li et. al, (11) also found that metastatic lymph nodes significantly had higher NID values in both arterial and portal phases and higher ID values in portal venous phase. In the study of Xie et. al, (18) metastatic lymph

nodes had higher NID values in portal venous phase but the differences were not significant in the arterial and delayed phases. This last study was performed on a dual source DECT system unlike other studies which were performed on rapid kV-switching dual energy platform.

For evaluation of the serosal infiltration in patients with gastric cancer, Yang et. al, (13) evaluated perigastric fat tissue iodine content on a dual source platform and found that patients with serosal infiltration had significantly higher ID in the peritumoral fat than patients without serosal infiltration. Küpeli et. al, (14) obtained similar results in another dual energy platform.

With regard to the association with histological parameters, Liang et. al, (16) found significant NID differences between poorly and moderately differentiated adenocarcinoma in both arterial and portal venous phase. However, they did not include well-differentiated tumors in this analysis due to the low number of cases. In our study, we had significant ID and NID differences between well and poorly-differentiated tumors but no significant differences were observed between well-moderately differentiated and poorly-moderately differentiated tumors. Similarly, they also did not find significant NID differences between patients with and without serosal infiltration or lymph node involvement. Xie et. al. (18) had divided the patients into two groups as differentiated and undifferentiated types. Tubular and papillary adenocarcinoma were considered to be differentiated and undifferentiated group consisted of poorly differentiated tumors, signet-ring cell carcinoma and mucinous carcinoma with signet ring cells. They did not detect any NID difference between these groups in all phases. Similarly, we divided the patients into two groups as patients with favourable and unfavourable histology but we had significantly different ID and NID values in the arterial phase. Chen et. al, (17) also did not show any significant NID difference between patients with and without serosal infiltration, lymph node involvement and poorly differentiated-well and moderately differentiated patients. Li et. al, (15) found significantly higher ID and NID values in poorly differentiated tumors than well differentiated ones in both arterial and portal venous phases.

Tumor angiogenesis is defined as the formation of new vessels to supply the tumor and associated with the tumor grade and differentiation (25,26). Iodine content has been proposed as an indirect marker of tumor angiogenesis due to the correlation with angiogenesis-related parameters such as microvessel density (16,17). In these studies ID and NID were higher in poorly differentiated tumors and correlated with tumor microvessel density. Unlike previous studies, we found lower ID and NID values in poorly differentiated tumors compared to well and moderately differentiated tumors.

Our study had some limitations. The study design was retrospective and we had a small sample size. We did not investigate ID analysis in portal venous phase because based on our institutions routine imaging protocol, we only acquire arterial phase images in dual energy mode as

the arterial phase is the primary phase for gastric lesion detection. Due to the small sample size, we did not perform a receiver operating characteristic (ROC) curve analysis to determine a threshold value. We did not evaluate NID of metastatic and nonmetastatic lymph nodes because majority of the patients with or without nodal involvement did not have a grossly visible lymph node on CT imaging and majority of involved nodes had very small size with microscopic metastasis. Finally, the ID values in this study can only be valid for rapid kV-switching DECT platform and other platforms have to have their own specific values. Although there was nonsignificant variability of iodine content across different platforms in a phantom study (21), in vivo studies propose variable iodine content values (27,28). It was proposed that normalization could minimize such variations (29) but further studies are required to confirm this.

CONCLUSION

In conclusion, tumor ID and NID seems to be a promising biomarker for determining gastric cancer prognosis apart from serosal infiltration and nodal metastasis. Further future studies with a larger sample size are required to validate our findings.

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Ethical approval: This retrospective study was approved by institutional review board and the requirement for informed consent from patients was waived.

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