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Review Article

APPLICATION OF SPECTRAL CT IN EVALUATION OF DIAGNOSTIC VALUE IN PREOPERATIVE T STAGING, NODAL INVOLVEMENT AND SEROSAL INVASION IN GASTRIC CANCER

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ABSTRACT

The objective of this study was to investigate the clinical utility of spectral imaging in T staging of gastric carcinoma and feasibility of measuring Iodine concentration of perigastric fat tissue adjacent to the lesion and lymph nodes in diagnosing serosal invasion and nodal involvement respectively.86 pathologically confirmed gastric carcinoma patients (52 males, 34 females; mean age of 59 years) who underwent spectral CT imaging (Discovery CT750 HD; GE Health-care) between July 2017 and December 2017 were selected. Dual phase contrast enhanced scans were performed using Gemstone spectral imaging (GSI) scan mode and the raw data were transmitted and processed in special workstation to obtain a set of polychromatic images corresponding to conventional 140kVp imaging, monochromatic images ranging from 40-140 keV single energy levels, and material decomposition images (iodine-water base pair).Accuracy, sensitivity, and specificity of CT derived T staging of gastric carcinoma compared to pathological staging was calculated for conventional kVp images, 70 keV images, and MPR on 70 keV images and compared. The overall accuracy, sensitivity and specificity of T staging was 79.9%, 66.28% and 83.57% respectively for conventional kVp images (Group A); 83.96%, 74.42% and 86.79% respectively for 70 keV images (Group B); and 86.39%, 77.9% and 88.98% respectively for MPR on 70keV images (Group C). Group C images had significantly higher accuracy compared to Group B images, while sensitivity and specificity was higher but not significantly different. Group B images compared to Group A images had significantly higher accuracy and sensitivity, while specificity was higher but not significantly different. The nIC value of metastatic lymph nodes were also significantly higher than that of non-metastatic lymph nodes during both AP and PVP (0.24±0.02 vs 0.12±0.04 during AP, $p<0.05$; and 0.45±0.03 vs 0.31±0.01 during PVP, $p<0.05$). DEsCT imaging is a relatively newer technology and its full

capabilities have not been completely studied yet. Preliminary studies have shown promising clinical utility and further research is required for detailed radiological evaluation of gastric carcinoma patients.

Keywords: Gastric carcinoma; spectral CT; monochromatic image; iodine concentration; T staging; serosal invasion.

INTRODUCTION

Gastric carcinoma (GC) (1) is the fourth most common cancer worldwide and the second leading cause of cancer-related deaths (2). The GC rates increase progressively with age and most patients are aged between 50 and 70 years at presentation. GC shows a male predominance in its incidence as up to two males are affected for every female. It is particularly common in eastern Asia (Japan, Korea and China) and many parts of South America (3). Early detection is critical for determining GC respectability as surgical resection is the only cure available and is dependent on the GC stage at presentation (4). Accurate preoperative staging is hence essential for optimal surgical management with consideration of preoperative and/or postoperative chemotherapy. The tumor-node metastasis (TNM) classification system is the most commonly used staging system for GC where T describes the size of the primary tumor and whether it has invaded nearby tissues; N describes the involved regional lymph nodes; and M describes distant metastases (5). Although the diagnosis of GC is typically made by endoscopic-guided biopsy, patient therapy and staging are becoming increasingly directed by multidetector CT (MDCT) because of its ability to provide accurate staging of local tumor growth (T), lymph node involvement (N) and distant metastases (M) in a single exam but is stilled marred by inherent limitations (6-8). The most useful aspect of pre-operative staging is differentiation between early gastric carcinoma (EGC) and advanced gastric carcinoma (AGC), which allows for potential endoscopic resection versus more invasive surgical resection and/or neoadjuvant chemotherapy, respectively. Results from previous studies on T staging have shown wide variations (accuracies on T staging ranging from 43-82%) (9-11). Clinically, N staging is as important as T staging in deciding the appropriate surgical treatment and in determining the prognosis of gastric cancer. In EGC the presence or absence of lymph-node metastases determines the feasibility of less invasive treatment, such as endoscopic mucosal resection (12, 13). In AGC, lymph node status is an important prognostic factor as well as helps in planning the optimal extent of lymphadenectomy (14-16). Dual energy spectral CT (DEsCT) is a recently introduced technology incorporating dual-energy mode based on rapidly switching between low- and high–peak kilovoltage (kVp; 80 and 140 kVp, respectively) energies in less than half a millisecond. During the reconstruction process, material-decomposition (MD) basis-pair images are mathematically transformed from high- to low-kVp attenuation measurements. The MD image can then be used to synthesize (i) virtual monochromatic spectral images, which depicts how the imaged object would look if the x-ray source produced only x-ray photons at a single energy (40–140 keV), and (ii) accurate MD images using various base material pairs (eg, water and iodine based) for quantitative iodine and water concentration measurement (20). Research on spectral CT imaging has been extensively going on with promising results on cancer detection and differentiation, however very few studies dealing with preoperative workup of gastric

carcinoma have been published. This study investigates the clinical utility of DEsCT imaging in T staging of gastric carcinoma and detection of serosal invasion and metastatic lymph node.

MATERIALS AND METHODS

This study was approved by our institutional review board and all patients provided written informed consent before imaging. The study recruited patients with suspected gastric cancer undergoing multi-phase CT on a Discovery CT750 HD (HDCT; GE Health-care) with Gemstone spectral imaging mode from July,2017 to December, 2017at the Department of Medical Imaging, First Affiliated Hospital of Southern Medical University, Guangzhou, China. Inclusion criteria were: (i) endoscopically diagnosed or suspected gastric carcinoma patients (ii) CT scan performed within 14 days before gastrectomy (if required); (iii) no preoperative treatment. The 86 gastric cancer cases included 52 men and 34 women with mean age of 59 years (range 33 - 77 years). Patients were considered ineligible if they had any contraindication to iodinated contrast material, such as a previous history of anaphylactic reaction or cardiac, renal or hepatic insufficiency or without adequate histopathologic confirmation. Diagnosis was confirmed by biopsy or surgery.

i) CT scan:

Patients were required to fast for a minimum of 5 h prior to CT examination. They were asked to drink 1000 ml of water 10 min before examination, about 250 ml of which was ingested just before the examination. They also received 20 mg scopolamine intramuscular injection 10 min before the examination to minimize peristaltic bowel movement. Patients were then placed in the supine position. After scout CT, all patients underwent the unenhanced imaging in the conventional helical mode at a tube voltage of 120 kVp. CT scan was performed with a high definition CT scanner (Discovery CT750HD, GE Healthcare, Wisconsin, USA). Patients were then injected with non-ionic contrast medium (Optiray 320; Tyco Healthcare, Canada) through antecubital venous access at a rate of 3–4 mL/s for a total of 90–120 mL (1.5 mL/kg) during the arterial and portal venous phases. The arterial phase imaging delay was determined by the automated image-triggering software (SmartPrep; GE Healthcare), and arterial phase (AP) imaging automatically began 12 s after the trigger attenuation threshold (100 HU) reached the level of the supracoeliac abdominal aorta. Portal venous phase (PVP) imaging began 30 s after the arterial phase imaging. Dual-phase contrast-enhanced scans were performed using the dual-energy spectral CT mode (GSI mode) with a single tube, rapid dual kVp (80 kVp and 140 kVp) switching technique in less than 0.5 msec. Other imaging parameters were as follows: collimation thickness 0.625 mm, acquisition slice thickness 1.25 mm, auto tube current, rotation speed (gantry rotation time) 0.6 s, helical pitch 1.375:1, CT dose index volume (CTDIvol) 21.8 mGy. The scan encompassed the whole stomach region during AP, and the whole abdomen and pelvis during PVP. The CT images were reconstructed by using projection-based material decomposition software and a standard reconstruction kernel. The reconstruction thickness was 1.25 mm, at an interval of 1.25 mm to balance image noise and spatial resolution. The adaptive statistical iterative reconstruction (ASIR) algorithm was applied to suppress image noise on the decomposition images. The percentage of ASIR was 40 %. Three different types of images were reconstructed

from the single spectral CT acquisition for analysis: the conventional polychromatic images corresponding to 140 kVp, material decomposition images and a set of monochromatic images with energy values ranging from 40 to 140 keV with 10-keV increments.

ii) Image Analysis and Interpretation:

The spectral CT images were analyzed with the GSI Viewer software 4.6 (GE Healthcare, Waukesha, Wisconsin). For the monochromatic images, a global assessment of image noise was performed for each energy values by drawing a region of interest (21) in the anterior abdominal wall muscle. Images with lowest noise were found to be at 70 keV energy level and were selected for evaluation. MPR images were also reconstructed for images at 70 kev and were used for assessing the tumor. The above two set of images and a set of conventional polychromatic images were compared with each other on sensitivity, specificity and accuracy for T staging of GC.

Material decomposition images were used to measure iodine concentration (IC, in mg per ml) in perigastric fat tissue adjacent to the tumor, lymph nodes, and aorta both during AP and VP. The ROI were drawn as large as possible to reduce noise and average of three readings was obtained. The IC in the perigastric fat and lymph node were normalized to the iodine concentration in the aorta to derive normalized iodine concentration ($nIC = IC_{lesion}/IC_{aorta}$). The nIC value of perigastric fat adjacent to the lesion during AP and VP was used to differentiate between serosal invasion and non-invasion by the tumor. The nIC value of the lymph node was used to differentiate presence of metastasis to the lymph node or not. The T staging was performed utilizing both AP and VP images for the conventional kvp images, 70 kev images, and MPR on70 kev images implementing the below mentioned criteria. The sensitivity, specificity and accuracy for T staging was calculated for the three set of images compared with pathological result of GC as reference standard. The IC of perigastric fat adjacent to the tumor was measured by drawing ROIs as large as possible and averaged of three repeated tests. It was then normalized to that of IC of aorta to obtain nIC during AP and PVP. Pathologically confirmed T3 tumours or less were grouped as group A and pathologically confirmed T4 were grouped as group B. nIC of group A and group B was compared to each other during AP and PVP. The lymph node with axial diameter greater than 6 mm for perigastric lymph nodes, and greater than 8 mm for extra perigastric lymph nodes were considered as involved. IC of the lymph nodes were measured and normalized to that of IC of aorta. nIC of the lymph nodes were compared between groups of nodal metastases and no nodal metastasis during AP and PVP.

iv) Statistical Analysis:

Overall accuracy, sensitivity and specificity of CT T-staging was performed with conventional kVp images, 70 keV images, and MPR on 70 keV images. The groups were compared using McNemar's test. The nIC values of perigastric fat tissue adjacent to the lesion and lymph nodes during AP and VP were measured and expressed as mean ± SD. Two-sample t test was used to compare the data using SPSS 20.0 with a p value less than 0.05 considered as statistically significant.

RESULTS

The clinical characteristics of the 86 patients are summarized in table 1. Male predominance was observed with 52 males and 34 females (1.53 : 1). The mean age was calculated at 59 years ranging from 33 to 77 years of age. 39 of the tumours were located in the antrum, 28 in the body, and 19 in the fundus. Comparative study of T staging between conventional kVp images (Group A), 70 kev single energy images (Group B), and 70 keV images combined with MPR (Group C)

T staging was performed and compared with histopathologic stage as reference standard to calculate accuracy, sensitivity and specificity. The accuracy of CT for T staging for Group A images was 94.19% for T1, 87.2% for T2, 76.74% for T3, and 76.74% for T4. Similarly, accuracy for Group B images was 96.51% for T1, 89.53% for T2, 81.39% for T3, and 81.39% for T4. Addition of MPR on 70 kev images (Group C) yielded accuracy of 96.51% for T1, 91.86% for T2, 84.88% for T3, and 83.72% for T4. The overall accuracy of CT for T staging of Group A, Group B, and Group C images was 79.9%, 83.96% and 86.39% respectively. Accuracy of Group B images was significantly higher than that of Group A images ($p<0.05$), while accuracy of Group C images was higher but not significantly different to that of Group B images ($p>0.05$).

Gender	
Male	52
Female	34
Age	59 years
Location of tumor	
Antrum	39 (45%)
Body	28 (33%)
Fundus	19 (22%)
Histopathologic T stage	
T1	6 (7%)
T2	16 (19%)
T3	20 (23%)
T4	44 (51%)

Table 1: Clinical characteristics of patient

The sensitivity of CT for T staging for Group A images was 50.0% for T1, 56.25% for T2, 60.0% for T3, and 75.0% for T4. Sensitivity of CT staging for Group B images was 66.67% for T1, 68.75% for T2, 70.0% for T3, and 79.55% for T4. Addition of MPR on 70 kev images (Group C) yielded sensitivity of 66.67% for T1, 75.0% for T2, 75.0% for T3, and 81.82% for T4. The overall sensitivity of CT for T staging of Group A, Group B, and Group C images was 66.28%, 74.42% and 77.9% respectively. Sensitivity of Group B images was significantly higher than that of Group A images ($p<0.05$), while sensitivity of Group C images was higher but not significantly different to that of Group B images ($p>0.05$). The specificity of CT for T staging for Group A images

was 97.5% for T1, 94.29% for T2, 81.82% for T3, and 78.57% for T4. Specificity of CT staging for Group B images was 98.75% for T1, 94.29% for T2, 84.85% for T3, and 83.33% for T4. Addition of MPR reconstruction with 70 kev images (Group C) yielded specificity of 98.75% for T1, 95.71% for T2, 87.88% for T3, and 85.71% for T4. The overall specificity of CT for T staging of Group A, Group B, and Group C images was 83.57%, 86.79% and 88.98% respectively. Specificity of Group C images was higher but not significantly different than group B images ($p>0.05$). also, the specificity of Group B images was higher but not significantly different to that of Group A images ($p>0.05$).

CT Staging	**Histopathologic staging**				**Accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
	T1(n=6)	T2(n=16)	T3(n=20)	T4(n=44)					
Tx	2	-	-	-					
T1	3	2	0	0	94.19	50.0	97.5	60.0	96.3
T2	1	9	1	2	87.2	56.25	94.29	69.23	90.41
T3	0	3	12	9	76.74	60.0	81.82	50.0	87.1
T4	0	2	7	33	76.74	75.0	78.57	78.57	75.0

Table 2.1: Accuracies, sensitivities, specificities, PPV and NPV for T-staging using kVp images

CT Staging	**Histopathologic staging**				**Accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
	T1(n=6)	T2(n=16)	T3(n=20)	T4(n=44)					
Tx	1	-	-	-					
T1	4	1	0	0	96.51	66.67	98.75	80.0	97.53
T2	1	11	1	1	89.53	68.75	94.29	73.33	92.96
T3	0	2	14	8	81.39	70.0	84.85	58.33	90.32
T4	0	2	5	35	81.39	79.55	83.33	83.33	79.55

Table 2.2: Accuracies, sensitivities, specificities, PPV and NPV for T-staging using 70 keV images

nIC value of perigastric fat tissue adjacent to the lesion of Group D was -0.048±0.01 and -0.043±0.02 during AP and PVP respectively and that of group E was -0.025±0.01 and -0.016±0.01 during AP and PVP respectively. Significantly lower nIC values were obtained in Group D compared to that of group E both during AP and PVP (-0.048±0.01 vs -0.025±0.01 during AP, $p<0.05$; -0.043±0.02 vs -0.016±0.01 during PVP, $p<0.05$).The nIC values for group F were 0.24±0.02 and 0.45±0.03 during AP and VP respectively. Similarly, nIC values for group G were 0.12±0.04 and 0.31±0.01 during AP and VP respectively. Significantly higher nIC values were obtained in Group F compared to that of group G both during AP and PVP (0.24±0.02 vs 0.12±0.04 during AP, $p<0.05$; and 0.45±0.03 vs 0.31±0.01 during PVP, $p<0.05$).

DISCUSSION

Although the diagnosis of GC is typically made by endoscopic-guided biopsy, patient therapy and staging are becoming increasingly directed by multidetector CT (MDCT) because of its ability to provide accurate staging of local tumor growth (T), lymph node involvement (N) and distant metastases (M) in a single exam (6-8). DEsCT has been introduced as newer technology in recent years which provide richer information with better image quality (22). Spectral CT is a single detector single source system with capability for rapid switching between low- and high–peak kilovoltage (kVp; 80 and 140 kVp, respectively) energies in less than half a millisecond allowing the reconstruction of conventional polychromatic images corresponding to 140 kVp, monochromatic images with energy ranging from 40 to 140 keV and material-decomposition (MD) images using various base material pairs (e.g., water and iodine based)In this study, 70 kev monochromatic images were selected for its lower image noise as well as higher CNR which provided better lesion detection with improved image quality. The monochromatic images depict how the imaged object would look if the x-ray source produced only x-ray photons at a single energy (40–140 keV) which reduces the beam hardening artefacts and average attenuating effects, as well as allow selection of monochromatic images to optimally balance in terms of contrast and noise. The 40- to 140-keV energy levels greatly extend the ranges of conventional CT using 80 kVp to 140 kVp that have limited average image energies between 60 and 85 kev. X-ray spectrum at lower energy levels have reduced number of photons and image noise is expected to increase as the photon energy decreases. An adaptive iterative reconstruction algorithm (ASIR) has been incorporated into the generation of monochromatic image sets in spectral CT imaging to effectively reduce image noise and fully take advantage of the increased contrast over the low energy range. Recent studies has shown that images around 70 kev has the lowest image noise and has better image quality with higher contrast noise ratio (CNR) (23-26). The overall accuracy for T staging in this study was improved from 79.9% with conventional kVp images to 83.96% with 70 kev monochromatic images. Inclusion of coronal and sagittal multiplanar reformatted (MPR) images with 70 keV monochromatic images improved the overall accuracy further to 86.39% with significant difference to that of conventional kVp images. The accuracy for T1 staging of greater than 95% was higher than previously reported studies, which maybe mostly due to the low number of early tumors in this study. The T3-T4 diagnostic accuracy (84.88% and 83.72% respectively with 70 kev images including MPR) was improved significantly in this study. The use of DEsCT monochromatic images with optimally balanced image noise and CNR, with MPR reconstruction allowed accurate evaluation of tumor invasion of the gastric wall and clear visualization of the perigastric fat plane between the lesion and adjacent organs after choosing an optimal imaging plane resulting in higher accuracy. The overall sensitivity for T staging was also improved with use of 70 keV monochromatic images with MPR (77.9%) than of 70 kev monochromatic images (74.42%) and conventional kVp images (66.28%). The sensitivity of 70 kev images and 70 kev images with MPR were statistically significant compared to conventional kVp images. Sensitivity of CT images of early tumors was lower than that of advanced tumors as early tumors have the tendency of not being visualized and may appear as a subtle mucosal irregularity (27, 28). Similarly, the overall specificity for T

staging of 70 kev images with MPR (88.98%) was statistically significant to that of conventional kVp images (83.57%). D'Elia F. et al. (9) reported that the low T staging accuracy, sensitivity and specificity of gastric cancer is caused mainly by over staging (stage T1 tumor as stage T2). They explained that the main causes of over staging are due to the difficulty in observing the multilayered pattern of the gastric wall in the areas where the gastric wall is thinner (prepylorus) and the partial volume averaging effects. With the use of DEsCT incorporating newer advanced technologies, the accuracy, sensitivity, and specificity for T staging of gastric carcinoma has improved by offering higher CNR and lower image noise and reducing beam hardening effects. Material decomposition images are capable of extracting quantitative information about the elemental and molecular composition of tissue and contrast materials basing on their attenuation properties. Water and iodine are often selected as the basis pair for material decomposition image presentation because their atomic numbers span the range of atomic numbers for materials generally found in medical imaging and approximate those of soft tissue and iodinated contrast material to result in material-attenuation images that are intuitive to interpret. It is a quantitative value and can be used as a useful parameter (24, 29). The iodine concentration derived from the iodine-based material decomposition images was normalized to that of iodine concentration of aorta. Serosal invasion by tumor brings about changes in the adjacent perigastric fat tissues, and it can be quantified accurately by measuring iodine concentration of the adjacent perigastric fat tissues. The normalized iodine concentration (nIC) of perigastric fat tissue adjacent to the lesion of T4 tumors was compared to that of T3 and lower stage and it was significantly lower both during AP and PVP (-0.048±0.01 vs -0.025±0.01 during AP; -0.043±0.02 vs -0.016±0.01 during PVP). The difference in between the nIC of two groups was higher during PVP than AP. We believe invasion of serosa by the tumor brings about changes in the vascularity of the adjacent perigastric fat tissue in comparison to non-serosal invasion tumors. During PVP, the contrast media is supposed to be diffused into the lesion like in the end stage of perfusion and leaked into the extravascular space also resulting in higher iodine value (30). This might be the better time to perform the analysis, as supported by the result of our study. Clinically N staging is as important as T staging in deciding the appropriate surgical treatment and in determining the prognosis of gastric cancer. Previous studies have reported that regional lymph nodes are considered involved when the short axis diameter is >6 mm for perigastric lymph nodes and >8 mm for extra-perigastric lymph nodes. Other criteria for malignant involvement include a nearly round shape (longitudinal: transverse diameter ratio <1.5); CT attenuation value of greater than 100 HU; loss of the normal fatty hilum; cluster nodes with or without associated reticular strands or solitary nodes with associated reticular strands, independent of their size; and marked or heterogeneous enhancement (7, 31-33). However, nodal staging on CT images is inherently difficult independent of the technique used. The wide ranges of accuracy (69-92%), sensitivity (78-92%), and specificity (62-85.7%) (32, 34-39) in the literature demonstrate this problem of CT in nodal staging. In this study, nIC of lymph nodes were measured and compared between the metastatic lymph node and non-metastatic group. Metastatic lymph nodes had significantly higher nIC values compared to non-metastatic lymph nodes during both AP and PVP (0.24±0.02 vs 0.12±0.04 during AP; and 0.45±0.03 vs 0.31±0.01 during PVP). The changes in the metastatic lymph nodes could be quantitatively

measured using the iodine based material decomposition images to differentiate from inflammatory lymph nodes that were not involved. Addition of predictive value of nIC along with other CT criteria will help improve the N staging of gastric carcinoma by CT imaging. This study had several notable limitations. First, this study was conducted with a relatively small number of patients, especially of the early staged gastric carcinoma. Further prospective studies with a larger number of patients are needed to set the proper parameters for TNM staging of gastric carcinoma. Second, during measurement of nIC, the placement of ROI in the very small area of peri gastric fat tissue was a daunting task and might have been cause of measurement error though every effort was poured in to minimize it. Third, comparison of lymph nodes one-to-one between CT images and surgery is nearly impossible; hence the metastatic lymph nodes with size less than 6 mm on CT were not included in the study. The exclusion of lymph nodes less than 6 mm is a cause of bias in measurement of nIC value of metastatic lymph node. Fourth, since DEsCT is a newer technology in TNM staging of gastric carcinoma and this being a preliminary study to evaluate its ability, further research is required along these lines to validate the results.

CONCLUSIONS

DEsCT imaging can provide monochromatic images ranging from 40-140 keV energy level and material decomposition images (iodine, water, calcium based). The monochromatic images at 70 keV energy level has lower image noise and increased CNR with better image quality and can be used to improve the T-staging of gastric carcinoma. Addition of MPR on 70 kev images further improves the result. The changes in perigastric fat tissue adjacent to the lesion by serosal invasion can be quantified accurately by measuring IC and can be used in diagnosing serosal invasion. Similarly changes in metastatic lymph nodes can also be quantified measuring IC to differentiate metastatic lymph node from non-metastatic lymph nodes. Distinction between serosal invasion and nodal involvement holds great importance clinically and helps surgeon decide the course of management and in evaluating prognosis. With the help of newer technology provided by introduction of DEsCT, detailed radiological preoperative evaluation of gastric carcinoma patients with improved accuracy is possible.

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