BRIEF ARTICLE

Quantitative measurement of contrast enhancement of esophageal squamous cell carcinoma on clinical MDCT

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Abstract

AIM: To investigate contrast-enhanced computed tomography (CECT) for discriminating esophageal squamous cell carcinoma (ESCC) from normal esophagus and evaluating outcomes within tumors after chemoradiotherapy (CRT).

METHODS: Sixty-four patients with surgical ESCC served as group A, and underwent thoracic contrast-enhanced scan with 16-section multidetector row CT 1 wk before surgery. Thirty-five patients with advanced ESCC receiving 4-wk CRT and showing response to CRT served as group B, and underwent CT scans similar with group A 4 wk after completion of CRT. In group A, differences in CT attenuation values (in HU) between the preoperative ESCC and background normal esophageal wall (delta CT_1), or between different background normal esophageal walls (delta CT_2) were compared. Furthermore, delta CT_1 between group A and B was also compared.

RESULTS: In group A, mean delta CT_1 was higher than delta CT_2 (23.86 ± 10.59 HU *vs* 6.24 ± 3.06 HU, $P < 0.05$). When a delta CT_1 of 10.025 HU was employed at a cut-off value to discriminate ESCC from normal esophagus, a sensitivity of 89.1% and specificity of 90.6% were achieved. Mean delta CT_1 was lower in group B than in group A (9.25 ± 10.86 *vs* 23.86 ± 10.59, $P < 0.05$), and a delta CT_1 of 15.45 HU was obtained at a cut-off value to assess the CRT changes with a sensitivity of 76.6% and specificity of 77.1%.

CONCLUSION: CECT might be a clinical technique for discriminating ESCC from normal esophagus, and evaluating outcome in the tumors treated with CRT.

INTRODUCTION

Esophageal carcinoma is one of the most frequent causes

of death from digestive systemic malignant tumors, and the squamous cell carcinoma is the frequent histological type[1]. Tumor resection is a well established curative treatment protocol for patients with nonmetastatic esophageal squamous cell carcinoma (ESCC)[2]. However, some patients with advanced ESCC have primary cancer associated with systemic spread at diagnosis, and the outcome of surgery alone for these patients was not satisfying[3,4]. In the process of the tumor cells spreading through the bloodstream to distant tissues, tumor angiogenesis plays a key role[5,6]. For patients with advanced esophageal carcinoma, chemoradiotherapy (CRT) has been established as an effective treatment which is widely performed in clinical settings[7].

Several imaging procedures, such as endoscopy and endoscopic ultrasound (EUS), have been used to assess response to neoadjuvant chemotherapy and radiation therapy by comparison of tumor volume between pre- and post-CRT imaging[8]. However, these methods are limited by their inability to traverse a malignant stricture occurring in 20-30% esophageal carcinoma patients and by their operator dependency[9,10]. EUS may also have a potential risk of perforation[11]. As a noninvasive imaging technique, computed tomography (CT) is the most common approach for evaluating cancers, and contrast-enhanced CT (CECT), which can overcome the limitations of endoscopy and EUS, has been clinically applied to detect esophageal primary tumors and lymph node or distant metastasis, and to assess the response to neoadjuvant chemotherapy and radiation therapy[12-14].

Furthermore, tumor angiogenesis is characterized by an increase in tumor blood vessel count, and this process will impact on CECT[15-19]. We presume that the level of CT enhancement might be interpreted as an indicator of tumor angiogenesis. To the best of our knowledge, few articles have focused on the CT attenuation value in esophageal tumor and background normal esophagus on CECT in patients treated with or without CRT. Thus, the objective of this study was to investigate the feasibility of CECT to quantitatively distinguish esophageal tumor from background normal esophagus, and for assessing therapeutic outcome in patients with cancer who received CRT in a clinical settings.

MATERIALS AND METHODS

Participants
The institutional ethics committee of our hospital approved this study, and written informed consent was obtained from each participant prior to the study.

According to the therapeutic strategy, there were two groups - group A and B - in our study. Patients were enrolled into group A according to the following inclusion criteria: (1) they had ESCC initially confirmed by endoscopic biopsy; (2) the mass was clearly visible on CECT images; (3) the patients did not receive any tumor-related treatment such as radiotherapy, or chemotherapy prior to the CT examination; and (4) there were no contraindica-

tions to tumor resection for therapy with thoracotomy. Patients were enrolled into group B if ESCC was pathologically confirmed, if there were contraindications to tumor resection for therapy with thoracotomy, if they received CRT and showed a response to CRT, if they underwent CECT at least 4 wk after the therapy, and if the mass was clearly visible on CECT images.

From January to November 2010, 64 consecutive patients (53 men and 11 women; mean age, 61.51 years; age range, 37-79 years) with endoscopic biopsy proven ESCC, who met the inclusion criteria, were enrolled into group A. In this group, the mean coverage of the tumor along the z-axis was 5.33 ± 2.85 cm (range 2.54-8.42 cm). The tumors were located in the lower thoracic portion of the esophagus in 10 patients, in both the midthoracic and lower thoracic portion in 17, in the midthoracic portion in 27, in both the upper thoracic and midthoracic portion in 8, and in upper thoracic portion in 2. One week after the CECT scan, all patients underwent tumor resection with thoracotomy. According to the postoperative pathology, all the surgical margins were not involved by this carcinoma.

During the same period, 35 patients (29 men, 6 women; mean age 56.75 years; age range from 47 to 76 years) with unresectable ESCC, who had already completed a CRT schedule for at least 4 wk, served as group B. The mean coverage of the tumor along the z-axis was 3.79 ± 2.13 cm (range 1.33-6.91 cm). The tumors were located in the lower thoracic portion of esophagus in 9 patients, in both the midthoracic and lower thoracic portion in 4, in the midthoracic portion in 7, in both the upper thoracic and midthoracic portion in 4, and in the upper thoracic portion in 11. CRT consisted of simultaneous radiotherapy and chemotherapy. For radiotherapy, the patients were irradiated using a 10-MV linear accelerator photon beam at a daily dose of 2 Gy, which was continued daily 5 times per week for 4 wk, to a total dose of 40 Gy. The target included the primary tumor and the enlarged regional lymph nodule. The chemotherapy schedule, which was initiated on day 1 of radiotherapy, consisted of cisplatin (7 mg/m^2 per day) by intravenous administration and 5-fluorouracil (350 mg/m^2 per day) by continuous intravenous infusion for 5 d[20,21]. All patients showed a therapeutic response to CRT, which was assessed 4 wk after the completion of CRT according to the therapeutic criteria defined by the World Health Organization[22].

Imaging acquisition
Patients in groups A and B underwent spiral thoracic enhanced scans with a 16-section multidetector row CT (MDCT) system (Aquilion 16 CFX Edition, Toshiba Medical System, Japan) 1 wk before tumor resection and 4 wk after completion of CRT, respectively. Each patient received 200-400 mL water as oral esophageal negative contrast material immediately before the examination. A 19-gauge cannula was placed into an antecubital fossa vein after the patient lay supine on the scanner table. Eighty milliliters of a nonionic contrast medium (Ultravist

Figure 1 Oblique sagittal reformatted computed tomography images (A) of a 75-year-old man with squamous cell carcinoma in the lower thoracic portion of the esophagus (black arrows). The surgical cut edge is determined by a radiologist and a pathologist working in consensus (white arrowhead); and the background normal esophagus (white arrows) has been chosen in the thoracic upper portion. To generate the enhanced attenuation, two regions of interest (B and C) for the esophageal cancer and for the background normal esophagus are drawn freehand around the tumor and around the esophageal wall, respectively; the enhanced attenuation values correspond to 84 HU and 57 HU, respectively.

300, Iopamidol, Schering, Germany) containing 300 mg of iodine per milliliter was administered intravenously as a bolus with a flow rate of 2.5-3.0 mL/s using an automatic injector (MEDRAD Vistron CT Injection System, Medrad company, USA). Enhanced CT was performed 35 s after the initiation of the bolus contrast injection using the following scanning parameters: 120 kV, 100 mAs, 0.5 s rotation time, a pitch of 0.938, 400 mm field of view, 7 mm section thickness, and 512 mm × 512 mm matrix. Each scan was performed during a breath-hold to minimize the movement of the esophagus. All data were reconstructed with a 1 mm section thickness at 1 mm intervals, and were then transferred to an image processing workstation (Vitrea 2.0 vital images, Minnesota, USA).

Image analysis

Image data in groups A and B were retrospectively reviewed on the image processing workstation by an experienced radiological professor (the corresponding author with 13 years of experience in thoracicoabdominal radiology), and an experienced radiologist (the first author with 4 years of experience in thoracicoabdominal radiology) by consensus to keep the accuracy of analysis focusing on the difference in attenuation values (ΔCT, in Hounsfield units) between the tumor and background normal esophageal wall (ΔCT_1, in Hounsfield units) in group A and B, or between background normal esophageal walls (ΔCT_2, in Hounsfield units) in group A.

In order to measure the attenuation of the tumor in groups, reconstructed axial images (Figure 1A) were used to reformat the oblique-sagittal images at 1.0 mm intervals with a slice thickness of 1.0 mm to display the extension of esophageal carcinoma. Standard mediastinal window images (window width, 400 HU; window level, 60 HU) were used for displaying the images. Based on the extension of the tumor on the oblique-sagittal view, ten contiguous transverse sections corresponding to the maximal segment of tumors were selected for the representative tumor sections. A reliable tumor region of interest (ROI) within the representative thickened esophageal wall was manually drawn in the transverse section, and the area of tumor ROI (area range: 36-408 mm^2) was more than 60% of that of the entire tumor in the section (Figure 1B). The tumor attenuation value was derived automatically by the software on this image processing workstation. To minimize partial volume averaging with surrounding tissues, care was taken to draw the ROI of the tumor to exclude periesophageal fat and intraluminal gas, and to avoid the necrotic area within the tumor. This previous process and analysis was repeated for each contiguous transverse level, until the ten representative tumor sections had been covered. All ten attenuation values were then averaged across all the sections to be regarded as the representative attenuation values for esophageal carcinomas.

For measuring the attenuation value of background normal esophagus in groups, the ROI of the normal esophagus was determined. In group A, the tumor did not involve the surgical cut edge in all patients confirmed by the postoperative pathology, and the residual portions of esophagus after surgery were determined as background normal esophagus. According to the postoperative pathology and the reformatted images in the oblique-sagittal plane (Figure 1A), five contiguous axial sections corresponding to the background normal esophagus were randomly selected for each patient in group A. In group B, the portions of background esophagus 5 cm away from the irradiating target were determined as background normal esophagus, and five contiguous axial sections corresponding to the background normal esophagus were also randomly selected. The measurement of CT values in the normal esophagus was similar to that in esophageal carcinoma.

Subsequently, ΔCT_1 was calculated by subtracting the referenced attenuation value for the background normal esophageal wall from the representative attenuation value for esophageal carcinomas. ΔCT_2 was defined as the standard deviation of the attenuation value for the portions of background normal esophagus, which was in accordance with the difference in attenuation values between background normal esophageal walls.

Table 1 Repeatability of measurements of ΔCT_1 in group A and group B (mean $\pm$ SD)

Group	Mean differences of replicated measurements			95% Interobserver correlation coefficient
	Differences between two sets of measurements	95% CI of the difference	95% limits of agreement	
A (HU)	-0.2 ± 9.03	-17.8 to 17.5	-18.26 to 17.86	0.9913 (0.9817 to 0.9933)
B (HU)	-1.2 ± 12.6	-26 to 23.5	-26.4 to 24	0.9956 (0.9911 to 0.9978)

ΔCT_1: Difference in attenuation value between esophageal tumor and background normal esophagus.

To clarify the inter-observer agreement on the measurement of ΔCT, we randomly assessed the reproducibility of ΔCT_1 measurement. Data from each group was reanalyzed by the other observers (the third author with 3 years of experience in thoracicoabdominal radiology, and the fourth author with 2 years of experience in radiology). We then compared two sets of the measurements, and if good agreement between the replicated measurements was achieved, values of the first set were regarded as the final ΔCT_1.

Statistical analysis
Repeatability between two sets of measurements for ΔCT_1 was assessed by Bland and Altman analysis[23]. The mean differences and their 95% CI between two sets of measurements, and 95% limits of agreement for ΔCT_1 were determined to evaluate the difference in replicated measurements. The interclass correlation coefficients and their 95% CI were applied to assess the level of agreement. If the interclass correlation coefficient was greater than 0.99, and the mean difference of the replicated measurements was close to zero, good agreement between the replicated measurements was considered to be obtained[23].

By using the statistical software (version 13.0 for Windows, SPSS Inc., Chicago, IL, USA), independent sample Student's *t* tests were subsequently performed to compare ΔCT_1 and ΔCT_2 in group A, and ΔCT_1 between group A and B. The probability value of less than 0.05 was considered to indicate a significant difference. If significant difference was proved, receiver operating characteristic (ROC) analysis was then carried out to determine the cutoff of ΔCT_1 for discriminating esophageal carcinoma from background normal esophagus, and for assessing the CRT change of esophageal carcinoma.

RESULTS

Repeatability of measurement of $\Delta CT1$ in groups
In group A, the mean CT attenuation value of background normal esophagus was 53.77 ± 7.04 HU (range, 30.98 to 68.62 HU). The mean CT attenuation value of esophageal carcinoma was 77.62 ± 9.13 HU (range, 63.18 to 106.23 HU) for the initial measurement. The first set of mean ΔCT_1 was 23.86 ± 10.59 HU (range, -1.85 to 44.86 HU). For the repeated measurement, mean CT attenuation value of esophageal carcinoma was

77.61 ± 9.11 HU (range, 63.06 to 105.86 HU), and the repeated set of mean ΔCT_1 was 23.83 ± 10.60 HU (range, -2.56 to 47.02 HU).

In group B, the mean CT value of background normal esophagus was 55.09 ± 7.30 HU (range, 37.68 to 71 HU). For the initial measurement, the mean CT value of esophageal cancer and mean ΔCT_1 were 64.35 ± 12.89 HU (range from 34.07 to 94.82 HU) and 9.25 ± 10.86 HU (range from -10.02 to 35.67 HU), respectively; and for the replicated measurement, the mean CT attenuation value of esophageal cancer and mean ΔCT_1 were 64.25 ± 12.99 HU (range from 33.98 to 64.26 HU) and 9.16 ± 10.84 HU (range from -10.39 to 34.24), respectively. A high level of repeatability of ΔCT_1 measurements was achieved in groups (Table 1).
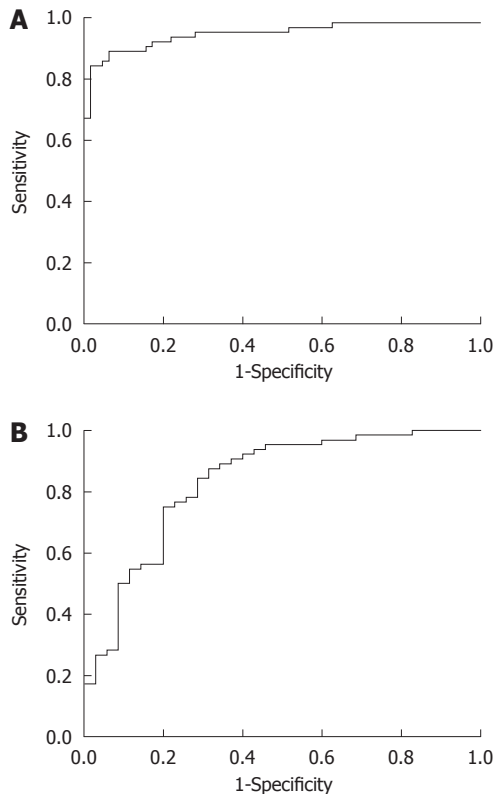
Difference in CT values: Between esophageal cancer and background normal esophagus vs between background normal esophageal walls
In patients with esophageal carcinoma in group A, the mean ΔCT_1 was 23.86 ± 10.59 HU, and mean ΔCT_2 was 6.24 ± 3.06 HU (range, 2.39 to 18.66 HU). ΔCT_1 was significantly higher than ΔCT_2 in group A ($P < 0.0001$). To discriminate the visual difference of esophageal carcinoma from that of background normal esophageal walls, the ROC curve analysis (Figure 2A) was performed between ΔCT_1 and ΔCT_2, and an area under the curve of 0.948 (95% CI: 0.906 to 0.99, $P < 0.0001$) was observed. By using 10.025 HU of ΔCT_1 as the cut-off value, the ROC curve showed a sensitivity of 89.1%, a specificity of 90.6%, a positive predictive value of 90.4%, a negative predictive value of 89.2%, and an accuracy of 89.8%.

Difference in CT values: Tumors with and without CRT
In patients treated with and without CRT, mean ΔCT_1 was 23.86 ± 10.59 HU and 9.25 ± 10.86 HU in group A and group B, respectively. Due to the treatment, mean ΔCT_1 was markedly decreased in group B compared with that in group A ($P < 0.0001$). To assess the therapeutic change, the ROC curve analysis (Figure 2B) was also performed between ΔCT_1 in groups, and an area under the curve of 0.833 (95% CI: 0.746 to 0.920, $P < 0.0001$) was observed. By using 15.45 HU of ΔCT_1 as the cut-off value, the ROC curve showed a sensitivity of 76.6%, a specificity of 77.1%, a positive predictive value of 64.29%, a negative predictive value of 85.96%, and an accuracy of 76.77%.

Figure 2 Receiver operating characteristic curve of difference in contrast enhancement between esophageal squamous cell carcinoma and background normal esophagus. A: Discriminating the tumor from background normal esophagus (area under ROC curve = 0.948, *P* < 0.0001); B: Discriminating between the therapeutic change of esophageal squamous carcinoma treated with and without chemoradiotherapy (area under ROC curve = 0.833, *P* < 0.0001).

DISCUSSION

In this study, an unenhanced CT scan was not performed prior to contrast-enhanced scan to control the patient radiation dose by lowering scan time. A 16-section MDCT was used to perform the enhancement data acquisitions, which has better collimation of X-ray beams and newer filter design compared with single section spiral CT[24,25]. As shown in our study, the measurement of difference in contrast enhancement between esophageal carcinoma and background normal esophageal wall might be a reproducible technique, because good agreement between replicated measurements of the difference was obtained. Thus, we used a contrast-enhanced scan with 16-section MDCT in the present study.

Clinically, the results of our study showed that the contrast-enhanced attenuation value within ESCC was significantly higher than that in the background normal esophageal wall. Our findings were consistent with those obtained by triple-phase dynamic CT (23.86 ± 10.59 HU *vs* 28.3 ± 17.1 HU)[12]. Our findings may be explained by the fact that ESCC is typically hypervascular[26,27], and the process of developing a new arterial vessel supply and the formation of tumor microvessels in the tumors could result in a marked increase of enhanced attenuation value.

Because of a significantly higher difference in CT enhancement between the tumor and background normal esophagus *vs* between background normal esophageal walls, the difference in CT enhancement between the tumor and background normal esophagus illustrated by ΔCT_1 could be used as a criterion to differentiate tumor from background normal esophagus. A threshold value of ΔCT_1 was obtained by performing ROC analysis. Our findings suggested that the cut-off ΔCT_1 of 10.025 HU had high sensitivity, specificity, positive predictive value, negative predictive value and accuracy at more than 85%. Therefore, a ΔCT_1 value of 10.025 HU may be used as a criterion to discriminate the microcirculation of ESCCs from that of the background normal esophagus.

Another finding in our study is that the difference in contrast enhancement between the tumor and background normal esophageal wall was significantly lower in patients treated with CRT than without CRT. These phenomena might be attributed to the cytotoxic effects of X-rays on the vascular endothelium cells within squamous cell carcinoma[28], and the tumor vascularity may shrink after CRT, resulting in lower CECT. We used ROC analysis to evaluate the therapeutic change within tumors and our findings suggested that the cut-off ΔCT_1 of 15.45 HU had sensitivity, specificity, negative predictive value and accuracy at more than 75%. Hence, a ΔCT_1 value of 15.45 HU could be used as a criterion to evaluate therapeutic changes in tumors treated by CRT.

Our research has limitations. Firstly, measurement of CT enhancement is a semi-quantitative method for assessing the tumor vascularity, and is significantly constrained by the impact of patient cardiac output and central blood volume. To try our best to overcome this limitation, we measured the extent of CT enhancement within the tumor by subtracting the attenuation value of background normal esophageal walls from that of esophageal tumors, which may help to avoid the confounding influence of cardiac output and central blood volume. Another limitation is that normal esophagus was more subject to partial volume averaging with adjacent tissue or air, which may influence the accuracy of the measurement of CT enhancements in the esophageal wall. To minimize partial volume averaging, the measurements of CT enhancement were analyzed on thin-section and magnifying images.

The cut-off value of difference in CT enhancement between ESCC and background normal esophagus (ΔCT_1 = 10.025 HU) could be used to quantitatively discriminate tumor from normal esophagus, and the cut-off value of difference in ΔCT_1 between the tumors treated with and without CRT (15.45 HU) could be used to assess the outcomes of CRT *in vivo* in clinical settings. Recently, fully automatic methods for 2D and 3D segmentation of liver structures from CT scans were developed to obtain high accuracy for demonstrating the liver volume, hepatic tumor and vessel morphology[29,30]. Automated methods for 3D segmentation of esophagus from CT scans had also developed to obtain high accuracy for showing the

anatomy of esophagus[31]. Based on the difference in CT enhancement between ESCC and background normal esophagus, we hope to develop the techniques of automatic segmentation for depicting the profile of ESCC for surgical planning and to determine the therapeutic outcomes of CRT, which will be performed in our future study.

COMMENTS

Background
Esophageal squamous cell carcinoma (ESCC) is one of the most frequent causes of death from digestive systemic malignant tumors. In the process of the tumor cells spreading through the bloodstream to distant tissues, tumor angiogenesis plays a key role and is characterized by an increase in tumor blood vessel count, which will impact on contrast-enhanced computed tomography (CECT). However, few articles have focused on the CT attenuation value in esophageal tumor and background normal esophagus on CECT in patients treated with or without chemoradiotherapy (CRT).

Research frontiers
CT attenuation values (in HU) of ESCC and background normal esophageal walls were measured on thoracic contrast-enhanced CT data. The differences in CT attenuation values between surgical ESCC and background normal esophageal wall (ΔCT_1), and between different background normal esophageal walls (ΔCT_2) were compared for discriminating ESCC from normal esophagus. In addition, the differences in ΔCT_1 between patients with ESCC treated with and without CRT was compared for evaluating the CRT outcomes.

Innovations and breakthroughs
The cut-off value of difference in CT enhancement between ESCC and background normal esophagus (ΔCT_1 = 10.025 HU) could be used to quantitatively discriminate the tumor from normal esophagus, and the cut-off value of difference in ΔCT_1 between the tumors treated with and without CRT (15.45 HU) could be used to assess the outcomes of CRT *in vivo* in a clinical setting.

Applications
Based on the difference in CT enhancement between ESCC and background normal esophagus, we hope to develop the techniques of automatic segmentation for depicting the profile of ESCC for surgical planning and for determining the therapeutic outcomes of CRT.

Terminology
Thoracic contrast-enhanced CT is a valuable procedure to quantitatively measure the difference in CT enhancement between ESCC and background normal esophageal wall. It is hoped that this can be used to develop automatic segmentation techniques for depicting the profile of ESCC for surgical planning and determination of the therapeutic outcomes of CRT.

Peer review
In this paper, the authors demonstrated that difference in CT enhancement between ESCC and background normal esophagus could quantitatively discriminate the tumor from normal esophagus. The addressed research topic is of great importance in the field and the presented work effectively illustrates the final finding of the study.

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