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Absolute CT perfusion parameter values after the neoadjuvant chemoradiotherapy of the squamous cell esophageal carcinoma correlate with the histopathologic tumor regression grade

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ABSTRACT

Purpose: To analyze value of the computed tomography (CT) perfusion imaging in response evaluation of the esophageal carcinoma to neoadjuvant chemoradiotherapy (nCRT) using the histopathology as reference standard.
Methods: Forty patients with the squamous cell esophageal carcinoma were re-evaluated after the nCRT by CT examination, which included low-dose CT perfusion study that was analyzed using the deconvolution-based CT perfusion software (Perfusion 3.0, GE). Histopathologic assessment of tumor regression grade (TRG) according to Mandard's criteria served as reference standard of response evaluation. Statistical analysis was performed using Spearman's rank correlation coefficient (r_S) and Kruskal–Wallis's test.
Results: The perfusion CT parameter values, measured after the nCRT in the segment of the esophagus that had been affected by neoplasm prior to therapy, significantly correlated with the TRG: blood flow (BF) ($r_S = 0.851$; $p < 0.001$), blood volume (BV) ($r_S = 0.732$; $p < 0.001$) and mean transit time (MTT) ($r_S = -0.386$; $p = 0.014$). Median values of BF and BV significantly differed among TRG 1–4 groups ($p < 0.001$), while maximal esophageal wall thickness did not ($p = 0.102$). Median BF and BV were gradually rose and MTT decreased as TRG increased, from 21.4 ml/min/100 g (BF), 1.6 ml/100 g (BV) and 8.6 s (MTT) in TRG 1 group, to 37.3 ml/min/100 g, 3.5 ml/100 g and 7.5 s in TRG 2 group, 81.4 ml/min/100 g, 4.1 ml/100 g and 3.8 s in TRG 3 group, and 121.1 ml/min/100 g, 4.9 ml/100 g and 3.7 s in TRG 4 group. In all 15 patients who achieved complete histopathologic regression (TRG 1), BF was <30.0 ml/min/100 g.
Conclusions: CT perfusion could improve the accuracy in response evaluation of the esophageal carcinoma to nCRT.

1. Introduction

Since the results of many studies have shown that neoadjuvant chemoradiotherapy (nCRT) followed by surgery improve the outcome of the esophageal carcinoma, this therapeutic regimen has become the standard of care for patients with the locally advanced esophageal carcinoma [1]. The study of Mandard A-M and colleagues proved, and further studies supported, that the histopathologic tumor regression grade (TRG) of the esophageal carcinoma after the nCRT was the most significant independent predictive factor of survival after surgery [2]. Complete response to nCRT was the strongest predictor of longer survival in patients with esophageal cancer who were treated by trimodality therapy [2].

Therefore, the main challenge of diagnostic imaging of the esophageal carcinoma has been actually displaced from the primary staging to restaging, i.e. monitoring the response to nCRT. Computed tomography (CT) and endoscopic ultrasonography (EUS)

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; TRG, tumor regression grade; BF, blood flow; BV, blood volume; MTT, mean transit time; PS, permeability surface; CR, complete regression; EC, esophageal carcinoma; SCC, squamous cell carcinoma; DCE-CT, dynamic contrast-enhanced computed tomography.

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showed suboptimal accuracy in restaging the esophageal carcinoma after the nCRT [3–6]. The studies using the magnetic resonance imaging (MRI) in the response monitoring of the esophageal cancer to the nCRT are lacking, except few studies of functional MRI techniques such as diffusion-weighted imaging (DWI) [7]. It has been reported that the ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) improved the diagnostic accuracy in the response evaluation of the esophageal carcinoma to nCRT [3,8].

Dynamic contrast-enhanced computed tomography (DCE-CT), which is also known as CT perfusion, is an imaging modality that enables noninvasive estimation of tumor vascularization in vivo [9,10]. Considering the promising results of few studies in which CT perfusion was analyzed in colorectal and head and neck cancer [11–13], we presupposed that this imaging modality could be also useful in the response assessment of the esophageal cancer to nCRT. Accordingly, the aim of our study was to evaluate the value of DCE-CT in assessing the response of the esophageal cancer to nCRT using the histopathologic analysis of the esophageal specimens after the esophagectomy, which was performed according to the Mandard's criteria [2], as a reference standard of assessment of the tumor regression grade.

2. Patients and methods

2.1. Patients

Forty consecutive patients with the locally advanced esophageal cancer who received nCRT, from June 2008 to December 2014, were enrolled in this retrospective study. Inclusion criteria were: (1) administration of nCRT, (2) carrying out of CT perfusion study after the nCRT, and (3) performance of surgical esophagectomy and pathologic analysis of the resected esophagus, which included estimation of the TRG according to Mandard's criteria.

Institutional Ethics Board approved the study, and informed written consent for the CT perfusion series was obtained from each patient.

2.2. Diagnostics before the nCRT

Before the nCRT, the patients underwent endoscopy with the tumor biopsy and CT examination for staging purposes.

Squamous cell carcinoma (SCC) of the esophagus was proved in the endoscopic biopsy specimens in all patients in the study group prior to nCRT.

The conventional portal venous phase CT of the neck, thorax and the abdomen, was performed for the staging purposes. This initial CT examination localized the tumor, and recorded its length, maximal esophageal wall thickness, tumor (T), node (N) and clinical stage (Table 1) [6,14].

2.3. nCRT regimen

The patients were treated with concomitant preoperative chemotherapy and radiation. External beam radiotherapy was administered using 3D conformal technique with a total dose of 45–50.4 Gy applied in 24–28 fractions, 1.8 Gy per fraction, five times a week. Radiotherapy was delivered with high-energy photons (10, 15 MeV) on linear accelerators, through 3–4 fields, over a period of 5–6 weeks. Concomitantly with radiotherapy, the patients received chemotherapy, which consisted of 50 mg/m^2 cisplatinum, 400 mg/m^2 5-fluorouracil and 20 mg/m^2 leucovorin (CIS/5-FU/LV). Chemotherapy was divided in 4-5 cycles that were delivered every 14 days, concurrently with radiotherapy and started two days before radiotherapy.

Table 1
Clinicopathologic characteristics of esophageal cancer assessed by CT before the nCRT.

Localization[a]	Cervical esophagus	1 patent
	Upper esophagus	22 pts
	Middle esophagus	14 pts
	Lower esophagus	3 pts
Length of tumor[b]	67 ± 24 mm (30–130 mm)	
Maximal esophageal wall thickness[b]	18 mm (1–35 mm)	
T	T3	30 patients
stage[c]	T4	10 pts
N	N0	13 patients
stage[c]	N1	7 pts
	N2	16 pts
	N3	4 pts
Clinical	IIA	15 patients
stage[c]	IIIA	9 pts
	IIIB	6 pts
	IIIC	10 pts

[a] Portion of the esophagus in which center of tumor was localized.
[b] Variables were presented as mean ± SD or median values (depending on normality of distribution), and range from minimum to maximum value.
[c] According to the CT criteria of staging, which were adjusted to the 7th edition of TNM classification [6,14].

2.4. Diagnostics after the nCRT

Upon completion of neoadjuvant treatment, after 4–8 weeks, the response to nCRT was evaluated using the endoscopy and CT examination, which included low-dose CT perfusion study. CT was performed with the 64-detector row CT (LightSpeed VCT, GE Health-care Technologies).

2.5. CT perfusion study

First series was an unenhanced low-dose thoracic CT scan, which was performed to plan the CT perfusion study (axial-mode, 5 mm-reconstructed section thickness, 1-s rotation time, detector coverage 40 mm: 8 images per rotation, 80 kV, 40 mAs, 25-cm scan field of view, 16-24 slices, 2-3 s total exposure time). Eight contagious sections at the level of the greatest wall thickness area were chosen for the following CT perfusion study and spatial coordinates were recorded. Second series was a low-dose CT perfusion study. For the perfusion CT study, 50 ml of the nonionic iodinated contrast (370 mg/ml of iodine), followed by 30 ml of saline, was administered intravenously using the pump injector (Urlich-Missuri, Urlich, Germany), at a flow rate of 4 ml/s, through a 16-gauge cannula that was placed in the ante-cubital vein. Using the cine-mode acquisition, eight contagious sections, with 5-mm reconstructed axial thickness (totally 40 mm *z*-axis coverage), which were previously chosen from the unenhanced series, were scanned repeatedly at 1-s intervals (80 kV, 40 mAs, 25-cm scan field of view, 512 × 512 matrix) (Figs. 1–3a). Scanning started 5 s after the beginning of the intravenous contrast injection, and total scan duration was 50 s (400 images per a study). Patients were advised to breathe quietly during the dynamic CT scanning.

Third series was a portal venous phase CT of the neck, thorax and the abdomen, which was performed after the intravenous injection of 60–100 ml iodinated contrast (helical-mode, 0.625 mm section thickness, 120 kV, 120–750 mAs in tube current modulation mode, 39.5 mm/s table speed, 0.7 s rotation time, 50-cm scan field of view, scan delay 55 s, 5-mm reconstructed sections). Maximal esophageal wall thickness in the segment that was involved by neoplasm before the nCRT was measured on this CT examination.

All CT series were transferred to the workstation (Advantage 4.3, GE Health-care Technologies), and analyzed by single radiologist (corresponding author, with fifteen years of experi-