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Quantitative assessment of first-pass perfusion using a low-dose method at multidetector CT in oesophageal squamous cell carcinoma: Correlation with VEGF expression

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AIM: To investigate the correlation between vascular endothelial cell growth factor (VEGF) expression and first-pass perfusion parameters at multidetector computed tomography (MDCT) using a low-dose technique, and to determine how to discriminate VEGF positivity from VEGF negativity by perfusion CT in oesophageal squamous cell carcinomas.

MATERIALS AND METHODS: Thirty-two patients with oesophageal squamous cell carcinomas underwent first-pass perfusion with 64-section MDCT at 50 mAs. Perfusion parameters, including perfusion, peak enhanced density (PED), time to peak (TTP), and blood volume (BV), were measured. Postoperative specimens were assessed for VEGF expression. Correlation tests were performed to determine the associations between each CT perfusion parameter and VEGF expression. The cut-off values of perfusion parameters were obtained statistically to discriminate VEGF positivity from VEGF negativity.

RESULTS: Mean perfusion, PED, TTP, and BV were 38.47 ± 30.26 ml/min/ml, 24.68 ± 9.65 HU, 28.35 ± 9.03 s, and 11.82 ± 6.06 ml/100 g, respectively. PED or BV were significantly higher in the VEGF-positive group than in the VEGF-negative group (all $p < 0.05$), but no significant difference in perfusion or TTP was found between the VEGF-positive and VEGF-negative groups (all $p > 0.05$). In VEGF positivity, PED and BV were correlated with VEGF expression ($r = 0.576$ and 0.765, respectively; all $p < 0.05$), whereas perfusion and TTP were not ($r = 0.361$ and 0.239, respectively; all $p > 0.05$). A threshold of BV (10.23 ml/100 g) achieved a sensitivity of 94.4%, and a specificity of 92.9% for discriminating VEGF positivity from VEGF negativity.

CONCLUSION: BV could reflect tumour VEGF expression, and could be an indicator for evaluating angiogenesis in oesophageal tumours.

Introduction

Oesophageal squamous cell carcinoma is one of the common malignant tumours worldwide, and angiogenesis

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in the tumours has become a leading research theme because angiogenesis scores might predict lymph node involvement, metastases, and outcome.[1–3] To prevent angiogenesis effectively requires better understanding of the angiogenic behaviour of the tumour. Traditionally, histological staining of tumour tissues, including microvessel staining and vascular endothelial cell growth factor (VEGF) staining, has been used to evaluate angiogenesis.[2,3] However, these procedures are invasive and indirect methods of assessing vascularity, and cannot provide *in vivo* information regarding tumour angiogenesis.

With the advances in functional imaging techniques, computed tomography (CT) perfusion has become a valuable technique to assess tumour vascularity in oesophageal squamous cell carcinoma *in vivo*.[4–7] However, the use of previous perfusion CT techniques, which were classically achieved at 100 mAs, are limited by the radiation dose. According to the principle of ALARA (as low as reasonably achievable) suggested by the International Commission of Radiological Protection,[8] it is necessary to reduce the radiation dose in perfusion CT. As previously used by Chen et al.,[9] decreasing the tube current–time product by half for a conventional CT perfusion study may maintain the accuracy of the perfusion parameters without compromising scan quality. Therefore, this low-dose method was introduced into the present study. Regarding the correlation between CT perfusion parameters and tumour angiogenesis in oesophageal cancer, the correlation between perfusion parameters and microvessel density (MVD) have been previously investigated.[5] However, the correlation between CT perfusion parameters and VEGF expression in oesophageal cancer, and how to discriminate VEGF positivity from VEGF negativity in tumours using perfusion CT were not determined in the previous study. Thus, the aim of the present study was to investigate the correlations between each CT first-pass perfusion parameter obtained by this low-dose method, and VEGF expression within oesophageal squamous cell carcinomas; and to identify the optimal threshold of perfusion CT parameters to discriminate VEGF positivity from VEGF negativity to elucidate tumour angiogenesis.

Materials and methods

Patients

This prospective study was approved by the institutional review board of West China Hospital of Sichuan University, and written informed consent was obtained from each patient prior to the study. Patients were enrolled into this study according to the following inclusion criteria: (1) oesophageal squamous cell carcinomas were initially confirmed by endoscopic biopsy; (2) the thickened oesophageal wall could be clearly seen on the CT images; (3) the coverage of the tumour along the *z*-axis was not more than 10 cm; and (4) there were no contraindications to tumour resection with thoracotomy for therapy. Patients were excluded from the present study if they had renal impairment or contrast medium allergy, or if they had already received cancer-related therapy.

Between February 2007 and January 2008, 32 consecutive patients (28 men, four women; mean age 59.12 years; age range 41–81 years) with biopsy-proven oesophageal squamous cell carcinoma, who met the inclusion criteria, agreed to participate in the study and formed this cohort. According to the anatomical distributions, the tumours were in the lower thoracic portion of oesophagus in 14 patients, in both the mid-thoracic and lower thoracic portion in seven, in the mid-thoracic portion in nine, in both the upper thoracic and mid-thoracic portion in one, and in the upper thoracic portion in one. The mean coverage of the tumour along the *z*–axis was 38.95 ± 14.05 mm. To decrease the radiation dose to the patient, all patients underwent the low-dose CT perfusion technique at 50 mAs, which is half the conventional tube current–time product for thoracic CT perfusion studies.[9] One week after the CT perfusion examinations, all patients underwent tumour resection and regional lymph node dissection with thoracotomy. During this interval between imaging and surgery, none of the examined patients received chemotherapy or radiotherapy. All cases were reconfirmed by postoperative histopathology. Based on the histopathological assessment of the regional lymph node resection, 18 and 14 patients had tumours that were stage N0 and N1, respectively. No distant haematogenous metastases were found in this cohort.

CT perfusion technique

All patients were examined using a 64-section multidetector CT (MDCT) (Philips Medical System, Best, The Netherlands). Prior to the image acquisition, 200–400 ml water was immediately used as an oral oesophageal negative contrast material. A thoracic or thoraco-abdominal examination was initially performed without intravenous contrast material to locate the oesophageal tumour. The following imaging parameters were used: 120 kV, 100 mAs, 110 mm/s table feed, 0.4 s rotation time, collimation of 32 × 1.25 mm, 350 mm scanning field of view (SFOV), and 512–512 mm^2 matrix. The tumour was identified by a supervising radiological associate professor (T.w.C.) with 12 years of experience in thoraco-abdominal radiology, and the scanning coordinates, which was focused on the 10 cm area around the tumour to encompass the entire visible tumour, were noted and used to plan the subsequent CT perfusion examination.

For CT perfusion imaging, a pump injector (MEORAO–Stellant, MEORAO Company, Germany) was used to inject 50 ml iodinated contrast medium (iopromide, Ultravist 300, Schering, Germany) containing 300 mg iodine/ml as a bolus into the antecubital fossa vein at a rate of 6–7 ml/s. The dynamic CT acquisition encompassing the entire visible tumour commenced 5 s (fixed time on the scanning system) after the start of the intravenous injection to enable the acquisition of baseline unenhanced images, and it continued for a total of 55 s, during which the patient was instructed to breathe gently to minimize the respiratory excursion. In detail, the dynamic study consisted of a total of