Esophageal cancer is the fourth most common cancer in China with five-year survival rates ranging from 15% to 40% (1–3). Patients with early-stage esophageal cancer are usually treated with endoscopic submucosal dissection (ESD) or esophagectomy. However, for patients with unresectable advanced esophageal cancer or who cannot tolerate esophagectomy, chemoradiation therapy (CRT) is a priority. CRT prolonged lifetime of many patients with esophageal cancer, but some patients cannot benefit from it, which depends on the patients’ response (4). Meanwhile, side effects caused by CRT including bone marrow suppression, esophagitis, pericarditis, and pneumonia should not be overlooked (3). Thus, useful methods are required to assess and predict the response to CRT.

Conventional imaging modalities, including X-ray, computed tomography (CT) and magnetic resonance imaging (MRI), have been used to assess CRT response for esophageal cancer. These imaging modalities focus on the morphologic changes of esophageal mucosa, tumor size, and enhancement. Positron emission tomography-computed tomography is valuable to assess the volumetric change and metabolic status of tumor. Published studies have demonstrated that functional MRI can be employed as a potential method for monitoring and predicting treatment response in esophageal cancer (5–14). Functional imaging by dynamic contrast-enhanced MRI (DCE-MRI) has been investigated in recent years to assess vascular permeability. Previous studies have investigated the...
potential role of DCE-MRI in evaluating treatment response in head, neck, breast, oral, cervical, rectal cancers, and soft tissue sarcoma (7–14). Some studies have reported the value of DCE-MRI using pharmacokinetic parameters in patients with esophageal cancer (4, 14–16). In the literature, DCE-MRI has been used in esophageal cancer to differentiate between adenocarcinoma and squamous cell carcinoma (15), assess chemotherapy response (14), and distinguish adenocarcinoma from normal esophageal wall (16).

In this study, we aimed to investigate the performance of DCE-MRI parameters in assessing and predicting treatment response after CRT in patients with advanced esophageal cancer. We focused on evaluating treatment response between pre-CRT and post-CRT and compared complete responders and non-complete responders in a larger sample size than previously reported (14); in addition, we analyzed the changes in absolute values and ratios of DCE-MRI parameters.

Methods
Patients
This retrospective study was approved by the institutional review board of our hospital and the requirement for written informed consent was waived due to the retrospective nature of the study. From September 2014 to December 2016, patients who had undergone esophageal DCE-MRI scanning were screened. Inclusion criteria were: pathologically confirmed advanced esophageal squamous cancer by esophagoscopy; 3.0 T DCE-MRI scanning prior to concurrent CRT (pre-CRT); 3.0 T DCE-MRI 4 weeks after CRT (post-CRT); and adequate MRI quality for analysis.

From September 2014 to December 2016, 112 patients with suspicious esophageal lesions underwent DCE-MRI. The following patients were excluded: 18 patients with T1-stage esophageal cancer or high-grade intraepithelial neoplasia, 8 patients with leiomyoma, 23 patients without pre-CRT or post-CRT MRI examinations, and 4 patients with poor image artifacts. Finally, 59 patients were included in this retrospective study (Table 1). According to Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 (17), there were 38 patients with complete response, 9 patients with partial response, 8 patients with stable disease, and 4 patients with progressive disease. For the purpose of analysis, patients were grouped as complete response (CR) group (n=38) and non-complete response (non-CR) group (n=21).

Chemoradiotherapy
Radiation therapy at a dose of 60 Gy (2Gy/fraction, 5 fractions/week) was delivered to primary tumor site and involved lymph nodes. Chemotherapy was performed concurrently with radiation therapy by using liposomal paclitaxel 35 mg/m² plus cisplatin 25 mg/m² administered on day 1 weekly for 6 weeks.

MRI protocols
MRI examinations were performed on a 3.0 Tesla MRI scanner (MAGNETOM Trio Tim; Siemens) with a 16-channel torso coil. The MRI sequences included: transverse T1-weighted imaging, transverse and sagittal T2-weighted imaging, and transverse DCE-MRI. DCE-MRI scanning included two parts: before contrast injection, transverse volume interpolated breath-hold examination (VIBE) sequences were scanned with three flip angles (α=5°,10°,15°) to calculate T1 mapping; then, DCE images were acquired with VIBE sequence (repetition time, 5.22 ms; echo time, 1.81 ms; field of view, 21×28 cm²; matrix, 256×138; slice thickness, 3 mm; number of phases, 32; temporal resolution, 7s). A bolus of MRI contrast (Gadodiamide, Omniscan, GE Healthcare) was injected at a rate of 2.5 mL/s through a 20-gauge antecubital intravenous line at the third phase of DCE scanning. Bolus injection was performed with a MRI-compatible power injector (Spectris; Stellant MR Injection System) followed by 15 mL saline flush.

DCE-MRI analysis
Two digestive radiologists with 5 and 9 years of experience, respectively, studied the parameters on successive magnetic resonance images in consensus. All DCE-MRI data were transferred in Digital Imaging and Communications in Medicine (DICOM) format and processed with OmniKinetics software (GE Healthcare) by extended Tofts Liner model. Individual based arterial input function (AIF) was picked for each case because it varies between individuals in reflection of cardiac output, vascular tone and renal function. Referring to T2-weighted imaging and contrast-enhanced T1-weighted imaging, all regions of interest (ROIs) of esophageal cancer were manually set, encompassing the entire tumor area but excluding necrosis, peripheral fat, and blood vessels. The heart motion might lead to unclear tumor border. Thus, when we drew the ROI of the tumor, we made the ROI slightly smaller in size than observed tumor size to reduce the influence of partial volume effect. Three quantitative parameters obtained from DCE-MRI: \( K^{\text{trans}} \) (min⁻¹), transfer constant; \( K_e \) (min⁻¹), efflux rate constant; and \( V_r \) ratio of extracellular-extravascular space volume to tissue volume.

Statistical analysis
All statistical analyses were performed using SPSS 21.0 statistical software (IBM Corp.). The Kolmogorov-Smirnov’s test was used to determine whether the quantitative parameters are subjected to normal distribution. Numerically distributed data were presented as means ± standard deviation; not normally distributed data were presented by median and range. Categorical data (including gender, location, clinical T-stage and N-stage) were presented by median and range. Categor
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(K_{ep} and V_e). Independent sample t test was used to identify significant differences of the parameters between the CR and non-CR groups. Receiver operating characteristic (ROC) analyses were performed to find a reasonable threshold to differentiate CRT good responders from poor responders. The optimal thresholds were obtained by calculating the maximal Youden index (Youden index = sensitivity + specificity-1). Meanwhile, the areas under the curve (AUCs) were compared using nonparametric methods for comparison of ROC curves. Comparisons were considered statistically significant for P < 0.05.

### Results

The demographic data of all patients are summarized in Table 1. There were 26 males (mean age, 61.8±10.1 years) and 12 females (mean age, 65.9±6.7 years) in the CR group, 16 males (mean age, 67.2±8.6 years) and 5 females (mean age, 65.4±6.0 years) in the non-CR group. No statistically significant difference was identified in gender, age, and location of esophageal cancer between the CR and non-CR groups. There was significant difference in clinical T-stage (P = 0.032) between the CR and non-CR groups, while no difference was observed in clinical N-stage (P = 0.212).

Comparisons of DCE-MRI parameters between pre-CRT and post-CRT are shown in Table 2. Both K_{trans} and K_{ep} significantly decreased from pre-CRT to post-CRT in the CR group (P < 0.001). The K_{ep} value also showed a marked reduction in the non-CR group (P = 0.028). K_{trans} also decreased in the non-CR group, but it did not approach statistical significance (P = 0.199). Although V_e values increased after CRT in both groups, the differences were not significant. Representative cases of the CR and non-CR groups are presented in Figs. 1 and 2, respectively. On pseudocolor images, warm colors imply a higher value of the parameter, while cool colors imply lower values.

Table 3 shows comparisons of DCE-MRI parameters between the CR and non-CR groups in unpaired analysis. In pre-CRT measurements, the K_{trans} values of the CR group were significantly higher than that of the non-CR group (P = 0.047). In assessment of treatment response to CRT, post-K_{trans} and post-K_{ep} values were significantly lower in the CR group than in the non-CR group (P = 0.002, P < 0.001). The changes in value and ratios of K_{trans} (ΔK_{trans}, rΔK_{trans}) and K_{ep} (ΔK_{ep}, rΔK_{ep}) showed significant difference between the CR and non-CR groups. From pre-CRT to post-CRT, the K_{trans} values showed tendency to decrease in both CR and non-CR groups (35% and 2.7% reduction, respectively). The K_{ep} values showed 41.6% decrease in the CR group and 6.4% in the non-CR group. The post-ΔV_e values were lower when compared with pre-ΔV_e in both groups, without reaching statistical significance. The performance of K_{trans}, K_{ep}, and V_e parameters in predicting treatment response were assessed by ROC curve analysis (Table 4). In comparison with the other pre-CRT parameters, pre-K_{trans} values indicated good diagnostic performance (AUC=0.678). For post-CRT measurements, post-K_{trans} showed the highest AUC of 0.817, with a cutoff value of 1.031, sensitivity of 94.7%, and specificity of 57.1%. In terms of change, the AUC of ΔK_{trans} was highest.
at 0.816, with an optimal cutoff value of -0.206, sensitivity of 52.6%, and specificity of 95.2%. In terms of ratio of change, ΔK_trans resulted in the highest AUC of 0.840, with the optimal cutoff value of -0.144, sensitivity of 89.5%, and specificity of 61.9%. ROC curves of diagnostic performance of the parameters for detecting CRT response were shown in Fig. 3.

Discussion

DCE-MRI is a widely used imaging method reflecting vascular perfusion and endothelial permeability of tumor microcirculation, which are regarded as the most important factors in assessment of CRT response. This study investigated the role of quantitative DCE-MRI parameters of pre- and post-CRT to assess and predict treatment response for patients with advanced esophageal cancer.

Our data showed that there was significant difference in clinical T-stage between the CR and non-CR groups, while no changes were observed in clinical N-stage, gender, age, and location of tumor. The percentage of clinical T2 stage patients in the non-CR group was lower than that in the CR group, suggesting that patients with higher T-stage esophageal cancer might have a poorer CRT response. Consistent with studies on oral cancer and esophageal cancer, our results also demonstrated that an advanced T-stage indicated a poor clinical response (10, 16).

The K_trans and K_ep values are closely associated with the degree of tumor microcirculation and angiogenesis. Compared with normal blood vessels, tumor neovascularization leads to increased permeability and perfusion, which means higher K_trans and K_ep values. Before CRT, the K_trans value was significantly higher in the CR group than in the non-CR group. Therefore, we assume that high pre-K_trans value is associated with good response. Our finding is in agreement with a recent study in patients with esophageal cancer that has also shown better treatment response with higher pre-CRT K_trans values (14). Other studies have also suggested that tumors with high K_trans values may have better treatment response compared with those with low K_trans values, because of better delivery of the chemotherapeutic agents and greater radiosensitivity (18–21). However, previous DCE-MRI studies were unable to show any correlation between pretreatment K_trans values and treatment response for oral cancer and rectal cancer (10, 18). We postulate that lower K_trans value in the non-CR group may indicate relatively lower blood perfusion which reduces the effectiveness of chemoradiation. Our observation is in accordance with previous investigations (18, 22–24). Among pre-CRT parameters, pre-K_trans values showed the highest AUC in predicting treatment response, suggesting that it can be a promising MRI biomarker.

We also found that the K_trans value in the CR group showed a significant decrease after CRT, a finding that corresponded well...
Figure 2. a–h. MRI of a 70-year-old woman with progressive disease. Pre-CRT axial T1-weighted enhanced image (a) shows a mass in the middle thoracic segment of the esophagus. The tumor shows inhomogeneous enhancement. The color-coded $K^{\text{trans}}$ map (b) shows the mix color in the corresponding tumor ($K^{\text{trans}}$, 0.430 min$^{-1}$). The color-coded $K_{\text{ep}}$ map (c) shows the dominantly red color in the corresponding tumor ($K_{\text{ep}}$, 1.742 min$^{-1}$). The color-coded $V_e$ map (d) shows the dominantly green color in the corresponding tumor ($V_e$, 0.227). Post-CRT axial T1-weighted enhanced image (e) shows residual wall thickening with high signal intensity in the corresponding tumor bed. The color-coded $K^{\text{trans}}$ map (f) shows increased red color in the corresponding tumor bed ($K^{\text{trans}}$, 0.598 min$^{-1}$). The color-coded $K_{\text{ep}}$ map (g) shows mix color in the corresponding tumor bed ($K_{\text{ep}}$, 1.129 min$^{-1}$). The color-coded $V_e$ map (h) shows increased red color in the corresponding tumor bed ($V_e$, 0.654).

Figure 3. a–c. ROC curves of post-$K^{\text{trans}}$ and post-$K_{\text{ep}}$ (a), $\Delta K^{\text{trans}}$ and $\Delta K_{\text{ep}}$ (b), $r\Delta K^{\text{trans}}$ and $r\Delta K_{\text{ep}}$ (c) in assessing good treatment responders (post-$K^{\text{trans}}$, AUC=0.719; post-$K_{\text{ep}}$, AUC=0.817; $\Delta K^{\text{trans}}$, AUC=0.816; $\Delta K_{\text{ep}}$, AUC=0.757; $r\Delta K^{\text{trans}}$, AUC=0.840; $r\Delta K_{\text{ep}}$, AUC=0.813).
with those of previous studies (10, 22, 25). Kim et al. (22) attributed the contrasting changes and ratios of $K^{\text{trans}}$ after CRT to a larger fibrotic area in good responders, but a substantial, residual, viable tumor area in poor responders. Other studies explained the decrease of $K^{\text{trans}}$ value by lower microvessel density after CRT (23–26). This opinion also explains the increase in $V_e$ value after CRT, although change and ratio of $V_e$ value showed no statistical difference between pre- and post-CRT in this study. Our findings bear some similarities to the findings in a recent study, which revealed that higher $K^{\text{trans}}$ values before therapy, lower $K^{\text{trans}}$ values after therapy, and a large reduction in relative $K^{\text{trans}}$ indicate good response (10, 18, 20, 22). The absolute $r\Delta K^{\text{ep}}$ of good responders in previous studies are divergent, ranging from 8.6% to 38.4% (10, 18, 20, 22). The present study revealed that the $K^{\text{ep}}$ values representing vessel permeability decreased after CRT in both groups. Among post-CRT measurements, the post-$K^{\text{ep}}$ value resulted in better diagnostic performance in assessing treatment response (AUC = 0.817). Meanwhile, the absolute $\Delta K^{\text{ep}}$ and $r\Delta K^{\text{ep}}$ values in the CR group were significantly higher than those in the non-CR group. These findings are supported by previous studies in which the range of absolute $r\Delta K^{\text{ep}}$ was 20.3%–37.3% (10, 20, 27, 28). However, our study is inconsistent with a previous evaluation of treatment response in 25 patients with esophageal cancer (14). We speculate that these diverse results may be associated with the sample size and tumor heterogeneity. Thus, a larger sample size is needed to verify the results, and further investigation is warranted to determine whether tumor heterogeneity affects the quantitative parameters of DCE-MRI.

Previous studies reported that CRT could cause a significant increase in the $V_e$ value.
which was associated with a better response (12, 14). A study assessing chemotherapy response in patients with osteosarcoma revealed that $V_e$ might serve as a prognostic biomarker (29). Whereas, our data revealed no significant change in $V_e$ values from pre- to post-CRT in the CR and non-CR groups. Other investigators also failed to find significant differences in the $V_e$ value between the good and poor responders (18, 22). The findings might be attributed to the effectiveness of CRT in inhibiting the generation of tumor cells, leading to increase in the extravascular extracellular space (EES) and the volumetric proportion of the EES (14). The $V_e$ value represents the motion space of water molecules, and is affected by blood flow. Increased blood flow can increase the contrast agent getting into the EES, so $V_e$ cannot be used alone to evaluate the blood perfusion and EES. $V_e$ is a comprehensive factor, which means that it is not definite in the evaluation of tumor angiogenesis.

Our study suffers from some limitations. First, the sample size in this present study might affect the accuracy of the results. Therefore, we need a larger sample size in further studies. Second, we did not compare DCE-MRI parameters with data from diffusion-weighted imaging (DWI). Past findings suggested that DWI could potentially provide complementary information about treatment response assessment and prediction (30, 31). Further study of the correlation analysis of DWI and DCE-MRI would be necessary for esophageal carcinoma. Finally, we did not investigate tumor heterogeneity. The diverse results in previous studies may be associated with tumor heterogeneity. Histogram analysis of DCE-MRI parameters might provide quantitative information about tumor heterogeneity.

Reportedly, some immunohistochemical, blood-based, mRNA-based, and gene expression profiling biomarkers are associated with esophageal cancer detection, diagnosis, treatment, and prognosis (32). Thus, further investigations of the correlation between the above-mentioned cancer biomarkers and MRI biomarkers are warranted.

In conclusion, our observations demonstrate that DCE-MRI parameters have the potential to assess and predict treatment response to CRT. Particularly, pre-CRT $K^{\text{trans}}$ was valuable in predicting treatment response. Moreover, marked reductions in $K^{\text{trans}}$ and $K_{ep}$ values were associated with good CRT response. Finally, in ROC analysis of diagnostic performance, $r\Delta K^{\text{trans}}$, the ratio of change in $K^{\text{trans}}$ value, showed substantial advantage for assessing treatment response to CRT.

**Conflict of interest disclosure**

The authors declared no conflicts of interest.

**References**


