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Chemoradiotherapy of esophageal cancer

The diffusion-weighted magnetic resonance imaging (DWI) predicts the early response of esophageal squamous cell carcinoma to concurrent chemoradiotherapy

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ABSTRACT

Purpose: To investigate the predictive value of serial diffusion-weighted MRI (DWI) on tumor response of the concurrent chemoradiotherapy (CCRT) for esophageal squamous cell carcinoma (ESCC) and to determine the optimal time point of DWI measurements.

Methods and materials: From June 2010 to October 2011, 38 ESCC patients were consecutively enrolled into this prospective cohort study. During their treatment, the longitudinal DWIs were acquired at beginning and every week during the course of CCRT. ADC maps were generated from there DWIs. The tumor responses were evaluated according to the RECIST.

Results: (1) At completion of CCRT, 20 (52.6%) and 18 (47.4%) patients were evaluated as CR and PR, respectively. Over the time points of measures, the series of ADC values (10^{-3} mm^2/s) in whole GTV were consistently characterized with higher (all $p < 0.05$) for these CR patients as their means (std) were 2.24 (0.49), 2.23 (0.51), 2.44 (0.57), 2.54 (0.52), 2.70 (0.46), 2.80 (0.55), 2.92 (0.62), compared with these PR patients as 1.83 (0.31), 1.79 (0.21), 1.87 (0.30), 1.97 (0.37), 2.15 (0.44), 2.26 (0.46), 2.32 (0.51), respectively. However, the ADC change rates (ΔADC) of two groups were found to be similar. These results were also supported by the multivariate ANOVA analyses. The same analysis results of DWI based GTV volumes were also found. (2) The comparisons of logistic regression analysis indicated that only the ADC values at Week 3 (15 fractions) were an independent prognostic factor of tumor response (OR = 0.303, $p = 0.003$). ROC curve analysis showed that Area Under Curve for ADC values of the end of 2nd and 3rd weeks were biggest (0.822) and the prediction efficacy was comparatively optimized. The corresponding cut-off values were 2.11 and 2.14 (10^{-3} mm^2/s), respectively. (3) Additional analyses on those eight patients with tumor local recurrence within 1 year demonstrated the level-off after the continuously increased ADC values till Week 4.

Conclusions: DWI can be used as a biomarker to predict TE of esophageal cancers in early time during CCRT. The treatment-induced change in ADC of whole GTV during the first 2–3 weeks can be highly predictive to TE. The unchanged ADC value in late period may indicate the high tendency of tumor recurrence after 1 year.

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Concurrent chemoradiotherapy (CCRT) with or without surgery is currently regarded as the standard treatment for locally advanced esophageal carcinoma (EC). A good evaluation, especially at early time, on the therapeutic effect (TE, i.e. tumor response) of CCRT for EC is essential for the choice and adjustment of subsequent therapeutic managements. However, traditionally image techniques such as CT and esophagogram had limitations in early predicting or evaluating TE. Recently, a functional imaging technique, diffusion-weighted magnetic resonance imaging (DWI) (particularly the apparent diffusion coefficient (ADC) obtained from DWI) has been actively studied for its potential in evaluating TE of CCRT for multiple cancers due to its capacity of detecting tumor changes at the molecular or cellular level [1–6]. Among these studies, one prospective study was initiated in our institution in 2010, with the study objective of investigating DWI/ADC as an image biomarker for CCRT of esophageal squamous cell carcinoma (ESCC) and, particularly, searching for optimal DWI acquisition time and ADC threshold.

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Materials and methods

From 06/01/2010 to 10/31/2011, 38 patients who met the eligible criteria of the study (below) were identified. All patients underwent the institutional standard tests and procedures.

Inclusion criteria

The diagnosis of ESCC was confirmed by tumor tissue pathology. The Karnofsky performance status (KPS) score was $\geqslant$70. No distant metastasis was found under routine medical care. The patient had agreed to have DWI exams before and during the course of CCRT.

Clinical data collection

At baseline, the patient clinical characteristics including sex, age, tumor site, lesion length and TNM stages were collected for the analysis.

Radiotherapy

All patients had the following procedures for radiotherapy. First, one CT simulation was performed with scanning range covering the lung, neck and upper abdomen. The CT images were electronically transferred to a treatment planning system (TPS) through local network. Second, based on the CT images and esophagogram, the treating physician outlined the gross tumor volume (GTV), the clinical target volume (CTV), the planning target volume (PTV), and the organs at risk (OAR) (including both lungs, heart, and spinal cord) on the TPS. The target volumes were delineated based on the following guidelines. The GTV were determined by the wall of the esophagus expending $\geqslant$0.5 cm and the mediastinal LNs with a short-axis diameter of $\geqslant$1.0 cm [7,8]. The CTV was defined and contoured by extending 0.5 cm around the GTV in the axial direction and 2.0 cm in the superior and inferior directions. Following that, the PTV was outlined around the CTV with a positive margin of 0.5 cm in the axial direction and 1.0 cm in the superior and inferior directions. Third, the prescription dose for each patient was 60 Gy in 30 daily fractions and the dose received by 95% of the PTV (PTV D_{95}) should be more than 100% of the prescription dose. Last, the OARs had the following dose restrictions: lungs $V_5 \leqslant$ 55–58%, $V_{20} \leqslant$ 25–30%, $V_{30} \leqslant$ 18–20%, the mean dose of heart $\leqslant$30 Gy, and the maximum dose (Dmax) of spinal cord <45 Gy. After the careful examination and verification on the treatment plan by the supervised radiotherapy physicist and physician, the treating physician approved the treatment plans, which was then delivered with either 3-DCRT or IMRT.

Chemotherapy

Chemotherapy was given concurrently at the first and fifth weeks of radiotherapy. The regimen of either FP (cisplatin 25 mg/$m^2 \times$ 3 days, 5-fluorouracil (5-FU) 450–500 mg/$m^2 \times$ 5 days) or TP (paclitaxel 135 mg/m^2, d1, cisplatin 25 mg/m^2, d2, 3, 4) was universally given.

DWI acquisition

All the enrolled patients had seven MRIs taken before the first fraction of radiotherapy and every week during of the course of treatment. The sequences of each MRI acquisition included the conventional T1-weighted (T1W1) and T2-weighted (T2W1), and DWI. The *b* values (diffusion-sensitive factor) of 0 and 600 s/mm^2 were selected according to a previous pathological study in our institution [9], showing that the tumor lengths measured by DWI scan of b = 600 s/mm^2 were close to the real tumor lengths based on surgical specimen with a high concordance with pathology.

For each patient, the DWI-defined GTVs at various time points were manually delineated based on the DWIs acquired before, during and after CRT using a software tool (MIM, MIM Software Inc.). These DWIs were used to generate ADC maps. The ADC values reported in this paper are the mean ADC values calculated based the 3D ADC maps of the DWI-defined GTVs. The change rate of ADC (ΔADC) was calculated by $\Delta ADC = (ADC_x - ADC_0)/ADC_0 * 100\%$, where ADC_0 was the ADC value from the baseline DWI (i.e. acquired before radiotherapy), x was a time point during or after CRT. For some patients whose DWI hyperintense disappeared at a time point during treatment, the DWI based GTV volume at the time point was recorded as 0.

Follow-up and evaluation of TE

Until 3/15/2015, all patients were followed-up for over 1 year (the longest for 53 months). The TE was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [10] and the TE of the primary tumor immediately after CCRT was the analysis endpoint.

Statistical tool and method

One-Sample Kolmogorov–Smirnov method was used to test normal distribution. The independent two-samples T test and multivariate ANOVA statistical analysis for the repeated measurements were used to associate the change of DWI parameters during the course of CCRT between the complete response (CR) and partial response (PR) patients. Logistic Regression Model was performed to find the factors that may affect TE. Furthermore, ROC (receive operating characteristic) curve analysis was used to judge prognosis efficacy and to identify threshold. The survival rates were estimated by the Kaplan–Meier method with log-rank test for the differences between the groups of interest. The SPSS 16.0 statistical software was used.

Results

Clinical characteristics of the patients

The study population included 38 patients (25 male and 13 female), with their ages ranging from 47 to 77 (median 61) years old. The tumor primary distributions by site were cervical (3 patients), upper-thoracic (9 patients), middle-thoracic (23 patients, 60.5%), and lower-thoracic (3 patients). The esophagogram-based tumor lengths before the CCRT ranged from 2.4 to 10.2 (median 5.7) cm. Among all the patients, 6, 10 and 22 patients were determined to be at the T2, T3 and T4 stages, respectively. A total of 35 patients were found to have local LN metastasis based on CT or MRI and were assigned to be at the N1–2 stages, with 1, 14 and 23 patients at TNM I, II and III stage, respectively.

Description of therapeutic response

All the enrolled patients had completed CCRT. Per the RECIST [10], there were 20 (52.6%) and 18 (47.4%) were determined as CR and PR, respectively. The overall response rate to CCRT was 100%, while the 1, 2, 3-year survival rates of CR and PR groups were 80.0%, 65.0%, 50.0% and 50.0%, 27.8%, 22.2%, respectively (χ^2 = 5.126, p = 0.024) (Fig. 2b). The mean ± standard deviation of ADC values (10^{-3} mm^2/s) and GTV volumes (cm^3) based on the 3D map at the 7 time points were 2.04 ± 0.46, 2.02 ± 0.45, 2.17 ± 0.54, 2.27 ± 0.53, 2.44 ± 0.53, 2.55 ± 0.57, 2.64 ± 0.64 and