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Original contribution

Dynamic contrast-enhanced MRI of gastric cancer: Correlations of the pharmacokinetic parameters with histological type, Lauren classification, and angiogenesis

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ABSTRACT

Purpose: To compare the pharmacokinetic parameters derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in gastric cancers of different histological type and Lauren classification, and to investigate whether DCE-MRI parameters correlate with vascular endothelial growth factor (VEGF) expression levels in gastric cancer.

Methods: Included were 32 patients with gastric cancer who underwent DCE-MRI of the upper abdomen before tumor resection. DCE-MRI parameters including the volume transfer coefficient (K^{trans}), reverse reflux rate constant (K_{ep}), and extracellular extravascular volume fraction (V_e) were calculated from the tumor region. Postoperative specimens were used for determination of histological differentiation (i.e., non-mucinous, mucinous, or signet-ring-cell adenocarcinoma) as well as Lauren classification (intestinal type or diffuse type). VEGF expression was examined for assessing angiogenesis. DCE-MRI parameters with different histological type and Lauren classification were compared using independent samples *t*-test and analysis of variance, respectively. Correlations between DCE-MRI parameters and VEGF expression grades were tested using Spearman correlation analysis.

Results: Among gastric adenocarcinomas of three different histological types, mucinous adenocarcinomas showed a higher V_e and lower K^{trans} than the others ($P < 0.01$). Between the two Lauren classifications, the diffuse type showed a higher V_e than the intestinal type ($P < 0.001$). The mean K^{trans} showed a significantly positive correlation with VEGF ($r = 0.762$, $P < 0.001$).

Conclusion: DCE-MRI permits noninvasive prediction of tumor histological type and Lauren classification and estimation of tumor angiogenesis in gastric cancer. DCE-MRI parameters can be used as imaging biomarkers to predict the biologic aggressiveness of a tumor as well as patient prognosis.

1. Introduction

Gastric cancer (GC) is the second most common malignancy with a high prevalence and mortality worldwide [1]. The 5-year survival and recurrence rates of GC are directly related to its histological type and Lauren classification, which involves specific molecular mechanisms, treatment strategies, and prognoses [2–4]. Identification of pretherapeutic, predictive markers for both the treatment response and prognosis is essential for individual-oriented cancer treatment [5]. Although pathologic examination of tumor specimens or mucosal biopsy by gastroscopy is still the gold standard for characterization of GC, there is a pressing need for an improved noninvasive method for differentiating different types of GC.

Angiogenesis is now considered one of the major events that play important roles in the growth, progression, and metastasis of solid tumors [6]. Vascular endothelial growth factor (VEGF) is one of the key angiogenic factors as well as a selective mitogen for endothelial cells in angiogenesis [7]. The expression of molecular markers including VEGF has been demonstrated to correlate with prognosis of patients with GC [8,9]. Generally, angiogenesis is measured by immunostaining, which is somewhat invasive, depending on the availability of postoperative tissue or biopsy material.

As a rapid and less invasive technique, gadolinium chelates-based dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) carries significant advantages over histological methods for measuring angiogenesis. It provides a pharmacokinetic model that enables the quantification of contrast agent exchange between the intravascular

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and the interstitial space and thus the assessment of the functional features of a target tissue, including tissue blood flow, capillary permeability, and interstitial volume. It has been widely used to reveal microvasculature and perfusion in various clinical applications, e.g., for the development of antiangiogenic strategies and tumor therapy monitoring [10]. DCE-MRI was reported to be useful for characterizing the perfusion dynamics in GCs and providing prognostic information [11]. DCE-MRI parameters might be potential imaging biomarkers for predicting prognosis or may assist in the selection of appropriate patients for extended surgical procedures and for trials of adjuvant chemotherapy.

To our knowledge, the correlation between pharmacokinetic parameters and classification of GC has not been reported previously. The purpose of this prospective study was to compare the DCE-MRI parameters of GCs of different histological type and Lauren classification and to analyze the correlations between DCE-MRI parameters and VEGF expression levels.

2. Materials and methods

2.1. Ethics statement

This prospective study was approved by the Institutional Review Board of the Affiliated Tongji Hospital of Tongji University (ShangHai, China) and was carried out in accordance with the Declaration of Helsinki. All patients were informed of the experimental objectives, procedures, and possible damage, and all provided signed informed consent prior to the study.

2.2. Patients

Between June 2014 and March 2015, 32 patients (24 men and 8 women) in our hospital underwent DCE-MRI for evaluation of GC before surgery and were included in this study. The mean age of all patients was 59 years (range: 36–74 years), and the mean ages of men and women were 58 and 62 years (range: 36–74 and 45–70 years), respectively. The time between MRI examination and surgery ranged from 1 to 11 days (mean, 3.2 days).

Patients included in this study met all of the following inclusion criteria: GC histologically confirmed by gastroscopic biopsy or intraoperative or postoperative pathology; absence of any absolute contradictions to MRI such as cardiac pacemaker or defibrillator, nerve stimulator, insulin pump, aneurysm clip, or cochlear implant; glomerular filtration rate ≥ 30 mL/min to accommodate the challenge of contrast agent administration; ability to tolerate a long period of breath-holding (15–20 s); and tumors >10 mm in diameter to contain a large-enough the region of interest (ROI) for data analysis.

Patients were excluded from this study if they presented one of the following exclusion criteria: history of radiotherapy or chemotherapy; histological diagnosis of a benign gastric ulcer; contradictions to surgery; history of allergic reactions to intravenous contrast material; or severe motion artifact contaminations in DCE-MRI results.

After MRI, 30 patients were treated with regional lymphadenectomy in combination with total gastrectomy (n = 7) or subtotal gastrectomy Billoth type II (n = 23). The remaining patients underwent palliative surgery (n = 2). Tumors were found located in the upper stomach (fundus and cardia) (n = 6), the lower stomach (antrum and pylorus) (n = 16), or the body of the stomach (n = 10).

2.3. MRI data acquisition

All imaging was conducted with a 3T whole-body MRI system (MAGNETOM Verio; Siemens Medical Systems, Erlangen, Germany) using a standard 6-channel phase array body-matrix coil with the patient in the feet-first, supine position. A 22-gauge intravenous catheter was placed in an arm vein and attached to an MRI-compatible power injector (Optistar® LE, Mallinckrodt, Hazelwood, MO).

The patients were subjected to fasting for >6 h on the day of the experiment to reduce alimentary residue in the gastrointestinal tract. To reduce the artifacts arising from peristaltic gastric movement, roceanisodamine hydrochloride (10 mg; Minsheng Pharmaceuticals, Hangzhou, China) was administered intramuscularly 5–10 min before the MR examination unless contraindicated (glaucoma, prostate hypertrophy, asthma, or severe heart disease). In addition, all patients were asked to ingest 800–1000 mL water to adequately distend the stomach approximately 5 min before the MRI experiments. The following MRI sequences were used for all patients.

Axial T1-weighted gradient echo imaging (T1WI) was performed with a generalized auto-calibrating partially parallel acquisition (GRAPPA) acceleration factor of 2, repetition time (TR) = 130 ms, echo time (TE) = 2.46 ms, field of view (FOV) = 400 × 300 mm^2, matrix size = 320 × 240, slice thickness = 5 mm, slice gap = 1 mm, flip angle = 70°, bandwidth = 270 Hz/pixel, and acquisition time = 36 s.

Axial breath hold T2-weighted half acquisition single-shot turbo spin-echo (HASTE) imaging (T2WI) was performed using a GRAPPA acceleration factor of 2, TR/TE = 1200/99 ms, FOV = 380 × 285 mm^2, matrix size = 320 × 240, slice thickness = 5 mm, slice gap = 1 mm, flip angle = 160° and bandwidth = 504 Hz/pixel, and acquisition time = 38 s. Three-dimensional T1-weighted spoiled gradient-echo volumetric interpolated breath-hold examination (VIBE) was performed with TR/TE = 5.78/1.79 ms, FOV = 300 × 300 mm^2, matrix size = 256 × 189, slice thickness = 5 mm, slice gap = 1 mm, flip angle = 15°, bandwidth = 260 Hz/pixel. Gadopentetate dimeglumine (Beilu Pharmaceuticals, Beijing, China) was intravenously injected at a bolus (0.1 mmol/kg), followed by flushing with 16 mL saline (2.5 mL/s). For precontrast T1 mapping, the T1-weighted VIBE images were obtained using two different flip angles (2° or 14°). For DCE-MRI, the T1-weighted VIBE sequence was obtained immediately after gadopententate dimeglumine injection over the same volume as the pre-contrast T1 maps. The acquisition time was 15 s, and the sequence was repeated 20 times at 10-s intervals.

2.4. MRI data analysis

All MRI data were transferred to a commercially available workstation (Syngo; Siemens Healthcare, Erlangen, Germany) and analyzed by the same one abdominal radiologist with 5 years' experience in clinical MRI who was aware that the patients had GC but was blinded to the pathological features. From the DCE-MRI data, parametric maps of the volume transfer coefficient (K^{trans}), reverse reflux rate constant (K_{ep}), extracellular extravascular volume fraction (V_e), and the initial area under the curve (iAUC) of gadolinium concentrations during the first 60 s were generated using Tissue4D software (Siemens Healthcare) with the Tofts model [12]. Physiologically, K^{trans} represents the exchange rate constant of the transmission of contrast media from the vascular to the interstitial space, whereas K_{ep} represents the transmission back from the interstitial to the vascular space. Therefore, K^{trans} and K_{ep} reflect tissue permeability. V_e represents the volume of extracellular extravascular space per unit volume of tissue. The extracellular extravascular space and vascular space are balanced in size and shape in normal tissues to ensure adequate supply of nutrients and oxygen to the tissue, but the balance is disrupted in tumors. In most tumors, the V_e is enlarged and differs substantially among tumor types and aggressiveness [13]. In addition, iAUC is a model-free parameter of DCE-MRI reflecting tissue perfusion characteristics.

To generate the K^{trans} map, T1 maps were first generated using the T1-weighted VIBE images acquired with two different flip angles and further registered to the motion-corrected images. The signal intensity was then converted to gadolinium concentration. First, the arterial input function (AIF) was calculated in Tissue 4D [14]. Then the T1 maps, the gadolinium concentration time-courses, and AIF were used