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Research article

Volume fractions of DCE-MRI parameter as early predictor of histologic response in soft tissue sarcoma: A feasibility study

Wei Xia[a], Zhuangzhi Yan[b,*], Xin Gao[a,*]

[a] Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences, No.88 Keling Road, Suzhou New District, Jiangsu, 215163, China
[b] School of Communication and Information Engineering, Shanghai University, 99 Shangda Road, Shanghai, 200444, China

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ABSTRACT

Objective: To find early predictors of histologic response in soft tissue sarcoma through volume transfer constant (K^{trans}) analysis based on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Materials and methods: 11 Patients with soft tissue sarcoma of the lower extremity that underwent preoperative chemoradiotherapy followed by limb salvage surgery were included in this retrospective study. For each patient, DCE-MRI data sets were collected before and two weeks after therapy initiation, and histologic tumor cell necrosis rate (TCNR) was reported at surgery. The DCE-MRI volumes were aligned by registration. Then, the aligned volumes were used to obtain the K^{trans} variation map. Accordingly, three sub-volumes (with increased, decreased or unchanged K^{trans}) were defined and identified, and fractions of the sub-volumes, denoted as F_+, F_- and F_0, respectively, were calculated. The predictive ability of volume fractions was determined by using area under a receiver operating characteristic curve (AUC). Linear regression analysis was performed to investigate the relationship between TCNR and volume fractions. In addition, the K^{trans} values of the sub-volumes were compared.

Results: The AUC for F_- (0.896) and F_0 (0.833) were larger than that for change of tumor longest diameter ΔD (0.625) and the change of mean K^{trans} $\overline{\Delta K^{trans}}$ (0.792). Moreover, the regression results indicated that TCNR was directly proportional to F_0 ($R^2 = 0.75$, $P = 0.0003$), while it was inversely proportional to F_- ($R^2 = 0.77$, $P = 0.0002$). However, TCNR had relatively weak linear relationship with $\overline{\Delta K^{trans}}$ ($R^2 = 0.64$, $P = 0.0018$). Additionally, TCNR did not have linear relationship with DD ($R^2 = 0.16$, $P = 0.1246$).

Conclusion: The volume fraction F_- and F_0 have potential as early predictors of soft tissue sarcoma histologic response.

1. Introduction

Sarcoma is a kind of cancer that grows in different types of tissues, such as fat, nerves, blood vessels, deep skin layers, muscles, bones, tendons, and cartilage. Soft tissue and bone sarcomas are the main types of sarcoma. Soft tissue sarcomas arise from soft tissues and their incidence is higher than that of bone sarcomas. In America, approximately 11,930 new cases of soft tissue sarcomas are diagnosed each year, and soft tissue sarcoma is the cause of nearly 4870 deaths annually [1]. Preoperative chemoradiotherapy has been reported as an effective strategy for the treatment of soft tissue sarcoma, and early prediction of treatment response might be helpful to determine optimal timing of chemotherapy to achieve good outcomes [2].

Anatomic imaging is beneficial in diagnosing the conditions of patients after therapy, but it is not helpful for the early prediction of treatment response. The change in the longest diameter of a tumor is utilized as an indicator in the Response Evaluation Criteria in Solid Tumors (RECIST) [3] and is often used for treatment response evaluation in routine care. However, the changes in tumor size lag behind the physiological changes in tumor cells, and the profile of tumors may experience little change in anatomic images over a long time after therapy has been applied [4,5]. Therefore, traditional morphological evaluation methods may not be appropriate for the early prediction of treatment response.

For soft tissue sarcoma, as the growth of tumor is highly dependent on the development of vessels and blood flow, the parameter K^{trans} obtained from DCE-MRI that indicates the blood perfusion and microvascular permeability has great potential as an important reference marker of vasculature in clinical evaluation of treatment response [5]. However, current evaluation methods [2] mainly utilize the average K^{trans} value of the whole tumor to predict treatment response, and they may neglect the K^{trans} variation in tumor sub-region.

* Corresponding authors.
E-mail addresses: zzyan@shu.edu.cn (Z. Yan), xingaosam@yahoo.com (X. Gao).

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Recently, voxel-wise analysis method such as the parametric response map (PRM) has been introduced [6]. The PRM identifies tumor sub-regions on the basis of changes in parameters derived from images, and the proportions of tumor sub-regions are considered as biomarkers of treatment outcome. The major advantage of PRM is its results are interpretable and quantitative metric of heterogeneity. PRM was initially applied to high-grade gliomas to generate relative cerebral blood volume (rCBV) and flow (rCBF) maps to predict survival [6], and it can also be applied to other studies such as the head and neck cancer study to obtain apparent diffusion coefficient (ADC) maps for detecting tumor control situation [7]. However, the early prediction of histologic response in soft tissue sarcoma using voxel-wise analysis method has not been well investigated.

Therefore, the purpose of this study was to develop a voxel-wise analysis method that could provide early predictors of histologic response in soft tissue sarcoma based on DCE-MRI.

2. Materials and methods

2.1. Data collection

Institutional Review Board approval was obtained and patient informed consent was waived because of the retrospective nature of this study. A total of 15 patients that underwent preoperative chemoradiotherapy followed by limb salvage surgery were included, and the data of all patients were downloaded from the TCIA website, which were generated by a quantitative imaging network (QIN) study [2,8,9]. A total of four patients were excluded from the analysis for the following reasons: one patient did not have DCE-MRI image data after therapy initiation, and the other three patients had tumors that were not located on the lower extremity owing to the different blood supply situation may influence the pharmacokinetic modelling. Therefore, a total of 11 patients with soft tissue sarcoma of the lower extremity were included in this study (age range 25–62 years; mean age 52 years). Among these patients, eight were men (age range 25–59 years; mean age 51 years) and three were women (age range 40–62 years; mean age 54 years). There were seven histological types of sarcoma in this patient cohort: two myxoid liposarcoma, two myxoid/round cell liposarcoma, one myxofibrosarcoma, one spindle cell sarcoma, one undifferentiated pleomorphic sarcoma, three synovial sarcoma, and one pleomorphic liposarcoma. The patients were treated with antiangiogenic drug (sorafenib), followed by three cycles of epirubicin/ifosfamide two weeks after initiation of sorafenib treatment. Epirubicin was omitted at cycle 2 and then the radiation (28 Gy) was administered. Limb salvage surgery was conducted after chemoradiation therapy [2]. All specimens of the primary tumors were examined for histologic response at the time of surgery by the pathologist who estimated the amount of viable tumor and reported the tumor cell necrosis rate (TCNR). Treatment response was defined as follows [2]: TCNR of surgical specimens no less than 95% indicated optimal response to preoperative treatment; TCNR of surgical specimens less than 95% meant sub-optimal response. Three patients were reported having optimal response and eight patients were reported having sub-optimal response.

DCE-MRI volume data at two time points were used in this study [2]: within seven days before the start of treatment (t_0) and approximately two weeks after therapy initiation (t_1), the intervals between t_1 and the time of surgery ranged from 35 to 69 days, with an average of 52 days. The DCE-MRI data was acquired by a Siemens Trio TIM 3T system, with body coil as transmitter and a body matrix phased array coil combined with a spine matrix phased array as the receiver. Then, a 3D RF-spoiled gradient echo sequence was used to acquire DCE-MRI volume covering the entire tumor. The volume size was $448 \times 448 \times 20$, the voxel size was $0.8 \times 0.8 \times 5\ mm^3$, the flip angle was 10°, and TE/TR = 1.5/6.0 ms. A sequence of volumes was acquired along the time line during the DCE-MRI acquisition process, and the imaging time interval was 7–16 s depending on tumor size. After the acquisition of five baseline image volumes, the gadolinium contrast agent (Prohance) IV injection was carried out with 0.1 mmol/kg at 2 mL/s, followed by a saline solution flush of 20 mL. The entire tumor volume of interest (VOI) within the DCE-MRI volume was delineated by a radiologist.

2.2. Registration of DCE-MRI volumes

Image registration is a prerequisite process for voxel-wise analysis to correct motion artifacts and tumor size changes [10,11]. For the soft tissue sarcoma of the limbs, the lesions can deform with the patients' motion and muscle contraction during the process of DCE-MRI acquisition, and also the tumor may have heterogeneous changes in dimensions between t_0 and t_1. To ensure DCE-MRI volumes were spatially aligned, a sequence image registration was employed. In sequence image registration, the most enhanced volume of the volume sequence at t_0 was taken as the reference volume, and the remaining volumes at t_0 and the volumes at t_1 were taken as moving volumes. A two-tier registration was adopted. First, a rigid registration was adopted to correct rotation and translation, using sum of squared difference as similarity metric and the gradient descent as optimization method. Subsequently, a deformable registration with the free-form B-spline deformation model was implemented to correct heterogeneous deformation of tumor [11,12], and the optimization method L-BFGS-B [13] was employed to minimize the negative of mutual information, which was the objective function. The registration procedure was implemented using Insight Segmentation and Registration Toolkit (ITK, https://itk.org/).

2.3. Generation of Voxel-wise K^{trans} maps

The extended Tofts pharmacokinetic model [14,15] was used to estimate the voxel-wise K^{trans} from the registered DCE-MRI volumes. The pharmacokinetic analysis required the measurement of contrast agent concentration $C(t)$ during the DCE-MRI acquisition process. However, the $C(t)$ cannot be measured on the DCE-MRI volumes directly. Since we did not have the intrinsic T_1-measurements, and the purpose of DCE-MRI analysis is to determine the relative vascular change, it was indicated that an approximate calculation [16] would be sufficient to draw correct conclusions, thus $C(t)$ was derived from the change of tissue signal intensity $S(t)$ after the injection of contrast agent:

$$C(t) = S(t) - S(0) \tag{1}$$

where $S(0)$ was the signal intensity before the injection of contrast agent.

In the pharmacokinetic model, an arterial input function $C_p(t)$ that determined the blood contrast agent concentration should be defined within a region of interest (ROI) from major artery adjacent to the tumor in the image [2]. In this study, a ROI on the femoral artery was used for $C_p(t)$ measurement. The $C_p(t)$ was fitted to the most popular biexponential Weinmann plasma curve [14,15]:

$$C_p(t) = a_1 e^{-m_1 t} + a_2 e^{-m_2 t} \tag{2}$$

where a_1, a_2, m_1, and m_2 were parameters that can be calculated from the signal intensity of the ROI on the femoral artery by nonlinear least-squares curve fitting based on Eqs. (1) and (2).

According to the extended Tofts pharmacokinetic model [14,15], the tumor contrast agent concentration $C_t(t)$ was

$$C_t(t) = K^{\text{trans}} \int_0^t C_p(\tau) e^{-(K^{\text{ep}})(t-\tau)} d\tau + V_p C_p(t) \tag{3}$$

where K^{ep} was the efflux rate constant, and V_p was the blood plasma volume fraction.

By substituting the estimated $C_p(t)$ into Eq. (3), $C_t(t)$ was written as