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COLORECTAL CANCER WITH LIVER METASTASIS AND TREATMENT WITH ANTI-ANGIOGENIC DRUGS: RESPONSE EVALUATION WITH DIFFUSION-WEIGHTED MRI

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SUMMARY

Colorectal cancer is the third most common malignancy and the third leading cause of cancer-related death worldwide. Recently, the introduction of novel drugs (anti-angiogenic drugs) has led to a significant improvement in the survival rates of patients with metastatic colorectal cancer. The RECIST (Response Evaluation Criteria for Solid Tumors) parameters cannot adequately detect important effects of treatment and response to the application of these new drugs. New radiologic methods, such as diffusion-weighted MRI, could help to assess the quality and quantity of the response more accurately. Diffusion-weighted MRI imaging is based on a technique sensitive to the Brownian motion of water molecules over short distances.

This article describes our experience with this method in patients with liver metastasis from colorectal cancer after treatment with bevacizumab.

Introduction

Colorectal cancer is the third most common malignancy and the third leading cause of cancer-related death worldwide. The recent introduction of a new type of drugs (anti-angiogenic drugs) has led to a significant improvement in the survival rates of patients with metastatic colorectal cancer, with an increase in the median overall survival (about 26 months).

Bevacizumab is a humanized monoclonal antibody, developed against vascular endothelial growth factor (VEGF) for the treatment of metastatic cancer. The RECIST (Response Evaluation Criteria for Solid Tumors) parameters cannot adequately detect important effects of treatment and response to these new drugs. New radiologic methods, such as diffusion-weighted MRI, could be used to assess the quality and quantity of the response more accurately. Diffusion-weighted MRI imaging is based on a technique sensitive to the Brownian motion of water molecules over short distances. This method, taking advantage of the elevated cellularity and the consequent reduction of the intracellular spaces in liver metastases, compared to normal tissue, produces scan images in which the intensity of signal is related to the random motion of water molecules. This is possible due to the presence of intense magnetic field impulses, applied before and after a 180° radiofrequency impulse. The level of scan diffusion weighing is defined by 'factor b' (expressed in s/mm^2). Thus, the scan will result more intense the smaller the water diffusion coefficient is in the intercellular spaces of liver metastases increasing the likeli-

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hood of the lesion being malignant.
In oncology, this new approach to liver metastasis imaging could detect lesions that are not visible with standard MRI scans. In addition, this technique could be employed to evaluate the efficacy of chemotherapy treatment associated with new molecular target agents, such as bevacizumab.

Materials and methods
During the period between April 2009 and May 2011, 22 patients (8 female, 14 male) were included in our study. We performed diffusion-weighted MRI to study liver metastases from colorectal cancer, after verifying that the patients had no contraindications to MRI and obtaining informed consent. All patients had undergone colon resection three to five years before our study and were brought to our attention after the detection of liver metastases during a follow-up CT scan with contrast medium. All patients had no evidence of cirrhosis or fatty liver disease.
MRI scans were performed with a 1,5 Tesla unit with surface coils or phased array. Diffusion study was carried out using a single breath hold single-shot echo-planar spin sequence and according to the following acquisition parameters: TR 1440, TE minimum, slices 5/mm, Nex 5. We obtained a set of eight images with the application of four different b-values (50, 300, 800, 1000 mm^2/sec). Acquisition time for each sequence was about 30 seconds, achieving good quality images in apnea. Apparent diffusion coefficient (ADC) values were evaluated on the basis of corresponding ADC maps on a workstation using the GE FuncTool software. A ROI (region of interest) was applied to each hepatic lesion, where the software calculated the individual ADC values for every single patient. The mean ADC values were considered for statistical analysis.
All patients were evaluated before, and three months after, first-line chemotherapy based on the combination of FOLFIRI regimen and bevacizumab. For each patient, ADC values were compared before and after treatment, as well as after a six-month follow-up period, in order to evaluate the efficacy of the treatment.

Results
The ADC values found in lesion-free liver were between 2,31 x 10^{-3} and 2,67 x 10^{-3} mm^2/sec. The ADC values in hepatic metastases before treatment were between 2,02 x 10^{-3} and 2,70 x 10^{-3} mm^2/sec (mean value 2,37 x 10^{-3}). The ADC values found in hepatic metastases after chemotherapy were between 1,70 x 10^{-3} and 2,00 x 10^{-3} mm^2/sec (mean value 1,88 x 10^{-3}). Finally, the ADC values in hepatic metastases during a six-month follow-up were between 2,68 x 10^{-3} and 3,35 x 10^{-3} mm^2/sec (mean value 2,95 x 10^{-3}).
In one patient, we discovered a lesion with ADC values of 8,66 both before and after chemotherapy. This lesion was consecutively diagnosed as a cystic one. In all the other patients, the ADC value found before treatment (t0) was always higher than the post-treatment (t1) value in all lesions. Nevertheless, the basal value (t0) was still lower than the six-month follow up ADC (t2) (Figure 1).

Discussions and Conclusions
We excluded patients with cirrhosis and/or fatty liver, considering that pathological aberrations of liver parenchyma would affect diffusion of water molecules, thus conditioning ADC values. All lesions had a post-chemotherapy ADC value at three months that was lower than the basal one. In fact, several earlier studies have demonstrated that cell hypertrophy, induced by anti-angiogenic agents or inflammatory factors, may result in a restriction of interstitial water motility with a consequent

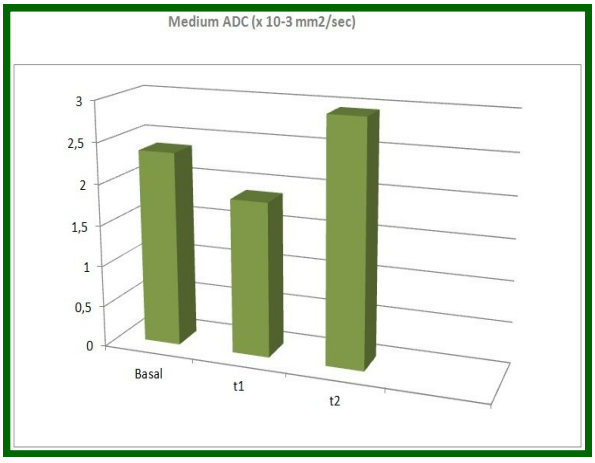

Figure 1: The ADC value found before treatment (basal) was always higher than the post-treatment (t1) value in all lesions. Nevertheless, the basal value (basal) was still lower than the six-month follow up ADC (t2), due to the reduction of cellularity for cell necrosis.

reduction of ADC. Therefore, prolonging the administration of chemotherapy, an increased ADC value, higher than t0, could probably be achieved due to induced necrosis with a consequent reduction in cellularity.

In the recent years, the appearance of a new category of drugs (anti-angiogenic drugs) has led to a significant improvement in the survival rates of metastatic colorectal cancer patients, increasing the median overall survival (about 26 months). Using these novel biologic drugs has also resulted in the need to develop new treatment response evaluation methods. The classic RECIST criteria cannot be applied to these new drugs with satisfactory results.

The application of new radiologic methods, such as diffusion-weighted MRI, could be helpful to assess the quality and quantity of the response rate more accurately. This modern imaging technique has three main advantages: the possibility of rationalizing the use of the new drugs, with an improved cost-benefit ratio in both clinical and economic terms; the correlation between changes in the bio-molecular structure and response to systemic treatment; and, finally, a more specific selection of patients for surgical resection with higher chances of long-term survival.

However, large scale randomized controlled trials are necessary to confirm the diagnostic accuracy of diffusion-weighted MRI compared with standard radiologic techniques.

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