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***Observational Study***

**Predict the liver metastasis of gastrointestinal tract cancer by diffusion-weighted imaging of apparent diffusion coefficient values**

Zheng DX *et al.*ADC DWI predict gastrointestinal tract cancer

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**Abstract**

**AIM:** To determine efficacy of chemotherapy on liver metastasis of gastrointestinal tract cancer can be predicted by apparent diffusion coefficient values (ADCs) of diffusion-weighted imaging (DWI).

**METHODS:** A total of 86 patients selected carefully with liver metastasis of gastrointestinal tract cancer (156 metastatic lesions) who were diagnosed in our hospital were included in the following research. The maximum diameters of these tumors were compared with each other before treatment, 2 wk after treatment, and 12 wk after treatment. These selected patients were classified as the effective group and the ineffective group, respectively, according to the maximum diameter of the tumor after 12 wk of treatment; and the ADCs values at different treatment times between the two groups were also compared. And then, Spearman rank correlation was also used to analyze the relationship between ADCs and these tumor diameters. Receiver operating characteristic curve (ROC curve) was then used to analyze the ADC values before treatment to predict the patient’s sensitivity and specificity degree of efficacy to the chemotherapy.

**RESULTS**: There was no difference in age between the two groups and in maximum tumor diameter before treatment and 2 wk after treatment. However, after 12 wk of treatment, maximum tumor diameter in the effective group was significantly lower compared with the ineffective group (*P* < 0.05). Before treatment, ADC values in the ineffective group was significantly higher than the effective group (*P* < 0.05). There was no difference in ADC values between the effective and ineffective groups after 2 and 12 wk of treatment. However, ADC values were significantly higher after 2 and 12 wk of treatment compared to before treatment in the effective group (*P* < 0.05). Spearman rank correlation analysis showed that ADC value before treatment and the reduced percentage of the maximum tumor diameter after 12 wk of treatment was negatively correlated, while the increase in percentage of ADC value 12 wk after treatment and the decrease in percentage of the maximum tumor diameter had a significant positive correlation. The results of the ROC curve show that ADC with a chemotherapy ineffective threshold value of 1.14 × 10-3 mm2/s before treatment had a sensitivity and specificity of 94.3% and 76.7%, respectively.

**CONCLUSION:** DWI ADCs can be used to predict the response of patients with liver metastasis of gastrointestinal tract cancer to chemotherapy with high sensitivity and specificity.

**Key words:** Gastrointestinal tract cancer; Chemotherapy; Liver metastatic tumor; Magnetic resonance imaging

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**Core tip:** A total of 86 patients with liver metastasis of gastrointestinal tract cancer were classified as effective group and ineffective group according to the maximum diameter of the tumor after treatment; and apparent diffusion coefficient values (ADCs) values at different treatment times between the two groups were compared. The results improved that ADC values before treatment can be used to predict chemotherapy response to liver metastasis of gastrointestinal tract cancer, which has high sensitivity and a relatively high specificity.

Zheng DX, Meng SC, Liu QJ, Li CT, Shang XD, Zhu YS, Bai TJ, Xu SM. Predict the liver metastasis of gastrointestinal tract cancer by diffusion-weighted imaging of apparent diffusion coefficient values. *World J Gastroenterol* 2015; In press**INTRODUCTION**

Gastrointestinal cancer is the most common malignant tumor, which has a high incidence and shows a rising trend[1-3]. Surgical resection is currently the primary treatment for gastrointestinal cancer. However, surgical resection alone has a low survival rate[1,4-6] due to its high incidence of invasion and metastasis. According to the statistics, liver metastasis occurs in approximately 45% of patients[7,8]. Patients with liver metastasis are not suitable for surgery. Thus, chemotherapy is the main treatment method that can improve patient survival and make patients more suitable for surgery[9,10]. Thus, the prediction and evaluation of the effectiveness of chemotherapy in patients with liver metastatic tumor is important for the survival status of patients and development of treatment programs. Clinically, chemotherapy efficacy monitoring has been primarily made through CT/MRI and other imaging modalities for measuring tumor size. However, Tumor size changes measured by radiological imaging methods are often late than functional changes; and it is difficult to predict the efficacy of chemotherapy at an early stage. In recent years, Diffusion-weighted imaging (DWI) has been discovered as a functional magnetic resonance examination method, and the apparent diffusion coefficient (ADC) of DWI signal intensity can be accurately quantified to enable the evaluation of chemotherapeutic efficacy before tumor size changes[11,12]. DWI is a new method for assessing the efficacy of cancer treatment. Although it has already being applied in the clinical applications[13,14], there are few studies on its applications and its prediction results of therapy remains unclear. Therefore, this study investigates the prediction results of the efficacy of chemotherapy in patients with liver metastasis of gastrointestinal tract cancer by DWI apparent diffusion coefficient, aiming to provide a new method for clinical evaluation.

**MATERIALS AND METHODS**

***Clinical data***

From June 2012 to April 2015, a total of 86 patients treated for liver metastasis of gastrointestinal tract cancer in Taishan medical college affiliated Liaocheng second people's hospital and Liaocheng third people's hospital were included in this study. Among these patients, there were 50 male patients and 36 female patients. Age ranged from 44-75 years old, with an average of 58.2 ± 6.1 years. Among these 86 patients, 28 patients with gastric cancer had 52 metastases and 58 patients with colorectal cancer had 104 metastases. Thus, a total of 156 metastatic lesions were included in this study.

***Examination method***

GE 1.5T HDX superconducting MRI (United States) and GE SIGNA HDe 1.5T MR scanner were used for testing. The patient was placed in supine position so that the coil cans wraparound the upper abdomen. The patient was instructed to breathe uniformly and located at the xiphoid. Then, DWI scanning was carried out (Figure 1A and B). DWI scan results are analyzed to generate the ADC values, and the images were reviewed in a blinded fashion by two radiologists.

***Treatment regimen***

All patients underwent chemotherapy based on the following specific regimen (LV5FU2 plan): CF 200 mg /m2/d iv bolus, 1-2 d; 5-FU 400 mg / m2/ iv bolus, first 1-2 d; 5-FU 600 mg/m2/d iv bolus, first 1-2 d, repeated every two weeks.

***Efficacy assessment of chemotherapy on tumors***

Tumor size (maximum diameter) was measured after 12 wk of each treatment, during the last week of chemotherapy treatment. Valid chemotherapy was either lesions disappeared or sum of maximum diameter reduce to > 30%, otherwise was invalid.

***Observation indexes***

Maximum diameters of metastatic tumors were measured before treatment, after 2 wk of treatment, and after 12 wk of treatment. Patients were classified into effective group and ineffective group based on tumor size after 12 wk of treatment. ADC values measured before treatment, after 2 wk of treatment and after 12 wk of treatment were compared between the effective group and ineffective group. Spearman’s rank correlation analysis was used to determine the correlation between the ADC values with the tumor diameters. ROC curve analysis of ADC values before treatment was used to predict patients with or without sensitivity and specificity for chemotherapy.

***Statistical analysis***

SPSS16.0 software was used for statistical analysis. Data were presented as mean ± SD. Differences between groups were analyzed using *t*-test. *P* < 0.05 was considered statistically significant. Spearman’s rank correlation analysis was used to analyze the correlation of ADC value changes with the diameter changes of metastasis tumor. ROC curve analysis of ADC values before treatment was used to predict the sensitivity and specificity of metastatic tumors to chemotherapy.

**RESULTS**

***Comparison of clinical data between the effective and ineffective group***

Among the 156 metastatic lesions found in 86 patients with gastrointestinal cancer, 27 (17.3%) lesions were located in the left lobe of the liver and 129 (82.7%) lesions were located in the right lobe of the liver. After chemotherapy, 73 lesions (46.8%) were classified into the effective group, and 83 lesions (53.2%) were classified into the ineffective. There was no significant difference in average age between the effective group and ineffective group (*P* > 0.05), as shown in Table 1. There was no significant difference in the maximum diameter of tumors before chemotherapy between the effective group and ineffective group (*P* > 0.05), as shown in Table 1. Two weeks after chemotherapy, tumor diameter in the effective group was smaller than that in the ineffective group; but the difference was not statistically significant (*P* > 0.05), as shown in Table 1. Moreover, after 12 wk of chemotherapy, tumor size in the effective group was significantly smaller than that in the ineffective group (*P* < 0.05), as shown in Table 2.

***Changes in ADC values between the effective group and ineffective group***

ADC values before treatment in the ineffective group was significantly higher than that in the effective group (*P* < 0.05). There was no significant difference in ADC values after 2 wk and 12 wk of treatment between the effective group and the ineffective group (*P* > 0.05). Moreover, ADC values were significantly increased in the effective group after 2 wk and 12 wk of treatment compared with before treatment (T = 17.047, 14.860; *P* = 0.000, 0.000). ADC value after 2 wk and 12 wk of treatment increased by 24.8% and 32.7%, respectively, in the effective group; while ADC value after 2 wk and 12 wk of treatment increased by3.2% and 4.0%, respectively, in ineffective group.

***Relationship between ADC value and tumor diameter changes***

Spearman rank correlation analysis revealed that before treatment, there was no significant correlation between ADC values and the mean value of the maximum diameter of tumor (*P* > 0.05). After 2 wk and 12 wk of treatment, there was also no significant correlation between ADC values and the mean maximum diameter of tumors (*P* > 0.05). ADC values before treatment and the reduced percentage of the maximum diameter of tumor after 12 wk of treatment was significantly negatively correlated (*P* < 0.05). The increase percentage of ADC values after 12 wk of treatment and the reduced percentage of the maximum tumor diameter was significantly positively correlated (*P* < 0.05). Moreover, the reduced percentage of tumor size and the maximum diameter of metastatic tumors before treatment did not reveal any significant correlation (*P* > 0.05), as shown in Table 3.

***Analysis of the sensitivity and specificity of ADC value for the evaluation of the effectiveness of chemotherapy***

By ROC curve analysis, the area under the curve was 0.934 (95%CI: 0.878-0.990). With an ADC ineffectiveness chemotherapy threshold value before treatment of 1.14 × 10-3 mm2/s, the sensitivity and specificity for predicting the ineffectiveness chemotherapy to metastatic tumors are 94.3% and 76.7%, respectively (Figure 2).

**DISCUSSION**

Liver metastatic tumors are derived from gastrointestinal cancer and other digestive tract cancers, and are also a common cause of death in gastrointestinal tumors[15]. Even though surgical resection is an effective treatment of gastrointestinal cancers, the proportion of patients who are suitable for surgery are very few, which is only about 15% of gastrointestinal cancers[16-18]. Therefore, chemotherapy is an important treatment for patients not suitable for surgical resection. Studies have shown that effective chemotherapy can significantly reduce the size of metastatic tumors so that patients will be suitable for surgery, thereby prolonging the survival of patients[19-22]. However, chemotherapy may be ineffective in some patients due to individual differences. If we can predict the ineffectiveness of chemotherapy in patients at an early stage, the treatment plan could be changed in a timely manner. In recent years, DWI has been found to be able to assess the efficacy of cancer treatment. ADC is an index used to measure the intensity of DWI. Animal studies have shown that ADC values for predicting metastatic tumors in the effective group were significantly higher than the ineffective group[23,24]. However, there are few studies on the use of ADC values for predicting the effectiveness of chemotherapy on metastatic tumors in vivo. Therefore, patients with liver metastases in gastrointestinal cancer at our hospital were selected for this study to investigate whether ADC values could predict liver metastatic tumor response to chemotherapy.

***Correlation analysis of the efficacy of chemotherapy***

It is very important to evaluate the efficacy of chemotherapy at an early stage. Early analysis of the effect of chemotherapy can provide guidance in selecting clinical therapeutic regimens, thereby improving the prognosis of patients. The results of this study revealed that there was no significant difference in metastatic tumor size before treatment and after 2 wk of treatment between patients in the effective group and ineffective group. Moreover, maximum diameter of metastatic tumors after 12 wk of treatment in the effective group was significantly smaller than the ineffective group (*P* < 0.05). As previously explained, chemotherapy can cause liver metastatic tumor size to change. However, there is no correlation between the maximum metastatic tumor diameter before treatment and the reduced percentage of tumor diameter after treatment. The results have shown that the size of the lesion and chemotherapy response is not related.

ADC value before chemotherapy in the ineffective group was significantly higher than the effective group, and ADC values before treatment and the reduced percentage of metastatic tumor diameter were negatively correlated. These results show that ADC values before chemotherapy and chemotherapy response are correlated. A high ADC value indicates that patients with Liver metastatic tumors may be ineffective to chemotherapy. Some studies have reported that ADC values can reflect the tissue density. The higher the ADC values, the lower the tissue density[15,25-26]. In addition, our research result showed ADC value increased in the effectiveness chemotherapy, which is consistent with that study, in which tissue density was reduced after chemotherapy and tend to be normal. This may be due to the strong ability of tumor cells to proliferate before chemotherapy, an abundant cytoplasm, and a reduced extracellular space. Therefore, as density becomes greater, and ADC value becomes lower. In addition, after effective chemotherapy on tissues, tumor cells are injured, raptures and dies. Therefore, tissues become less dense, diffusion motion of water molecules in the tissue increases and ADC value increases[27,28]. We found that early treatment in the effective group can significantly increase ADC values, and the ineffective group has not obtained this phenomenon. This may be due to the occurrence of tumor cells necrosis after chemotherapy in the effective group. First, early tumor cell necrosis swelling occurs. Then, cell walls burst and crack. Water molecular activity increases in the cell[29,30]; thus, ADC value increases. The treatment in ineffective group does not injure or kill tumor cells; thus, tumor tissues continue to increase, cell density increases or remain unchanged, diffusion motion of water molecules in the tumor tissues are reduced or remain unchanged, ADC value decreases or remain unchanged.

***ADC values before treatment predicts sensitivity and specificity of chemotherapy response to liver metastasis of gastrointestinal tract cancer***

Further ROC curve results showed that sensitivity and specificity for predicting the efficacy of chemotherapy on patients with liver metastatic tumors before treatment with 1.14 × 10-3 mm2/s as a threshold are 94.3% and 76.7%, respectively. The results have shown that sensitivity was high and specificity was relatively low. As described, this method has high clinical application value in predicting the efficacy of chemotherapy in patients with liver metastatic tumors due to high sensitivity. The relatively low specificity of this method, as described in other tumors, may also have a similar predictive effect. Studies have reported significant changes in ADC values in breast cancer, which are consistent with these results[31-33].

***Limitations and outlook***

The method of using ADC values before treatment to predict the efficacy of chemotherapy has advantages of providing fast and accurate results, as well as its noninvasiveness. In clinical practice, this method can be extensively applied to the patient to predict the efficacy of chemotherapy in patients with liver metastasis of gastrointestinal tract cancer, in order to determine the corresponding changes in treatment for patients who are ineffectiveness of chemotherapy at an early stage. However, this study is mainly for patients with liver metastasis of gastrointestinal tract cancer. It remains unclear whether this method can have a similar effect in other cancer patients. Thus, further research can focus on whether the evaluation of ADC values before treatment can also be applied to other cancers for chemotherapy reactions. This study did not take into account individual differences between each patient. Hence there is a need to further improve the experimental design of this study confirm these results.

In conclusion, ADC values before treatment can be used to predict chemotherapy response to liver metastasis of gastrointestinal tract cancer, which has high sensitivity and a relatively high specificity. In clinical application, this has an important value in predicting the efficacy of chemotherapy on liver metastasis of gastrointestinal tract cancer.

**COMMENTS**

***Background***

Gastrointestinal cancer is the most common malignant tumor, which has a high incidence and shows a rising trend. Surgical resection is currently the primary treatment for gastrointestinal cancer. However, surgical resection alone has a low survival rate due to its high incidence of invasion and metastasis. According to the statistics, liver metastasis occurs in approximately 45% of patients.

***Research frontiers***

In recent years, diffusion-weighted imaging (DWI) has been found to be able to assess the efficacy of cancer treatment. Apparent diffusion coefficient values (ADCs) is an index used to measure the intensity of DWI. Animal studies have shown that ADC values for predicting metastatic tumors in the effective group were significantly higher than the ineffective group.

***Innovations and breakthroughs***

ADC values before treatment can be used to predict chemotherapy response to liver metastasis of gastrointestinal tract cancer, which has high sensitivity and a relatively high specificity.

***Applications***

In clinical application, this has an important value in predicting the efficacy of chemotherapy on liver metastasis of gastrointestinal tract cancer.

***Peer- review***

Patients with liver metastases in gastrointestinal cancer at our hospital were selected for this study to investigate whether ADC values could predict liver metastatic tumor response to chemotherapy. The results demonstrated that ADC values before treatment can be used to predict chemotherapy response to liver metastasis of gastrointestinal tract cancer, which has high sensitivity and a relatively high specificity.

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**Table 1 Comparison of clinical data between the effective and ineffective groups**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Groups** | **Average age (yr)** | **Maximum tumor diameter (cm)** | | | | |
|  |  | **Before treatment** |  | **After 2 wk of treatment** |  | **After 12 wk of treatment** |
| Effective group (*n* = 73) | 57.7 ± 5.9 | 3.45 ± 0.81 |  | 3.29 ± 0.75 |  | 1.87 ± 0.38 |
| Ineffective group (*n* = 83) | 59.6 ± 6.2 | 3.62 ± 0.85 |  | 3.47 ± 0.88 |  | 3.45 ± 0.62 |
| *t* value | 1.953 | 1.274 |  | 1.365 |  | 18.874 |
| *P* value | 0.053 | 0.205 |  | 0.174 |  | 0.000 |

**Table 2 Changes in apparent diffusion coefficient values before and after chemotherapy treatment between the effective and ineffective groups**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Groups** | **Before treatment** | **After 2 wk of treatment** | **After 12 wk of treatment** | **After 2 wk of treatment** | |  | **After 12 wk of treatment** | |
|  |  |  |  | ***t* value** | ***P* value** |  | ***t* value** | ***P* value** |
| Effective group | 1.01 ± 0.06 | 1.26 ± 0.11 | 1.34 ± 0.18 | 17.047 | 0 |  | 14.86 | 0 |
| Ineffective group | 1.24 ± 0.08 | 1.26 ± 0.05 | 1.22 ± 0.17 | 1.931 | 0.055 |  | 0.97 | 0.334 |
| t value | 2.747 | 1.491 | 1.783 | / | / |  | / | / |
| P value | 0.007 | 0.138 | 0.077 | / | / |  | / | / |

**Table 3 Relationship between apparent diffusion coefficient values and tumor diameter changes**

|  |  |  |
| --- | --- | --- |
| **Correlation** | ***r* value** | ***P* value** |
| ADC values before treatment *vs* mean maximum tumor diameter | 0.124 | 0.108 |
| ADC values 2 wk after treatment *vs* mean maximum tumor diameter after 2 wk of treatment | 0.093 | 0.183 |
| ADC values after 12 wk of treatment *vs* mean maximum tumor diameter after 12 wk of treatment | 0.052 | 0.118 |
| ADC values before treatment *vs* reduce percentage of the mean maximum tumor diameter after 12 wk of treatment | -0.718 | 0.001 |
| Increased percentage of ADC values after 12 wk of treatment *vs* reduced percentage of maximum tumor diameter | 0.742 | 0.002 |
| Percent decrease in tumor size *vs* mean maximum diameter of metastatic tumors before treatment | -0.015 | 0.279 |

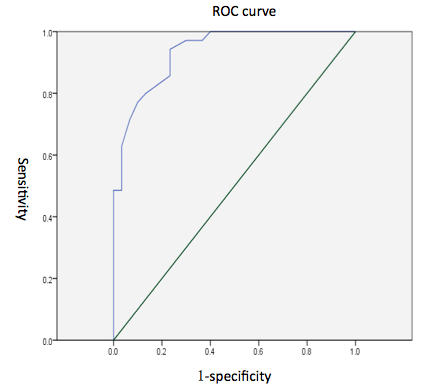
ADC: Apparent diffusion coefficient.



(A)

(B)

**Figure 1 Diffusion-weighted imaging results for patients with liver metastasis of gastrointestinal tract cancer.** A: Diffusion-weighted imaging (DWI) figure shows right anterior lobe of liver with surrounding high signal, clear boundary, and significant contrast; B: DWI figure shows the right posterior lobes of livers withhuge and irregular high signal intensity, surrounding small satellite focis were visible with a blending tendency, clear boundary, and significant contrast.



**Figure 2 Receiver operating characteristic curve Area under the curve is 0.934, the optimal diagnostic point is 1.14 × 10-3 mm2/s, and sensitivity and specificity is 94.3% and 76.7%, respectively.**