Multi-modal magnetic resonance imaging in efficacy assessment of combined therapy for glioma

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Abstract: Objective: To study the application of multi-modal magnetic resonance imaging (MRI) in efficacy assessment of therapy for glioma. Methods: We enrolled 108 patients with glioma confirmed by biopsy in this retrospective study. They were randomized into the observation group (n = 54) and the control group (n = 54). Multi-modal MRI was used in the observation group and CT scan was used in the control group to detect the normal and cancer tissues in brain for apparent diffusion coefficient (ADC), early-phase enhancement rate, and the type of dynamic contrast enhanced time intensity curve (TIC) shape. The detections were performed again after surgical resection of glioma and chemoradiotherapy. The rate of complete resection after the first surgery and the differences in the ADC before and after chemoradiotherapy were compared between the two groups. The early-phase enhancement rate and the type of TIC shape of the cancer tissue before and after chemoradiotherapy were compared with those of the normal tissue. The association between patients’ survival rates and the results of multi-modal MRI were also analyzed. Results: The difference in the ADC before and after chemoradiotherapy was statistically significant in both groups (both P < 0.05). The rate of complete resection after the first surgery was significantly lower in the observation group than in the control group (P < 0.05). There were statistical differences between the early-phase enhancement rates of the normal tissues and those of the cancer tissues before and after chemoradiotherapy (all P < 0.001). The type of TIC shape of the normal tissue was persistent enhancement, while that of the tumor tissue was mostly high enhancement with plateau before chemoradiotherapy and was persistent enhancement in 79.63% of cases after chemoradiotherapy. The difference in the type of TIC shape was statistically significant (P < 0.001). In the observation group, the one-year survival rate was 90.74%, the three-year survival rate was 79.63%, and the five-year survival rate was 66.67%, all significantly higher than those of the control group (all P < 0.001). Conclusion: Multi-modal MRI provides accurate information about the ADC and early-phase enhancement rate of the tissues, the rate of complete resection of cancer tissues, and semi-quantitative analysis by TIC. Moreover, it compares the tissues before and after chemoradiotherapy to determine the effectiveness of the treatment, and then provides reference for planning of subsequent treatment.

Keywords: Multi-modal MRI, glioma, CT scan, chemoradiotherapy, efficacy assessment

Introduction

Glioma is the most common type of primary brain tumor with a high incidence, accounting for about 60% of intracranial tumors, and considered as one of the refractory brain tumors in neurosurgical treatment [1]. Due to the aggressive tumor growth, the overall efficacy of treatment is poor. High-grade glioma is characterized by anaplasia, thereby resulting in a high recurrence rate and poor prognosis, thus rendering it a serious threat to human health [2]. At present, surgical resection combined with chemoradiotherapy is a major therapy for glioma. However, the effects of the treatment vary due to the complex structure of the brain featuring small and numerous functional units, and different sensitivity of each patient to chemoradiotherapy. Therefore, efficacy assessment is the key to the subsequent planning for glioma treatment [3].

Studies have shown that multi-modal magnetic resonance imaging (MRI) has high accuracy in distinguishing between tumors and normal tissues, thanks to its sensitivity for delineating soft tissues [4]. Multi-modal MRI is a system for imageological examination with various func-
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tions, including dynamic susceptibility contrast material-enhanced (DSC) MRI, diffusion-weighted imaging (DWI), and susceptibility-weighted imaging (SWI) [5]. Different from other conventional imaging devices, multi-modal MRI can monitor tumor location in real time and has higher sensitivity for soft tissues, as it can effectively identify tumor and normal tissues, and explicitly reveal the differentiation of cancer tissues and tumor grades [6]. The integration of multiple functions enables multi-modal MRI to be more accurate for diagnosis and evaluation of tumor diseases, which is conducive to the efficacy evaluation of treatment. This advantage, in turn, will help plan and carry out subsequent treatment [7]. Therefore, this study focused on the role of multi-modal MRI in the efficacy assessment of the surgery and chemoradiotherapy for glioma. It was designed to provide evidence for the clinical efficacy assessment of chemoradiotherapy and the improvement in the efficacy of glioma treatment.

Materials and methods

General information

A total of 108 patients diagnosed with glioma by biopsy were recruited in this study after approval from the Ethics Committee of The Third People's Hospital of Linyi. Inclusion criteria: Patients who met the diagnostic criteria for glioma defined by The 2016 World Health Organization Classification of Tumors of the Central Nervous System and by conventional molecular diagnosis; patients with glioma confirmed by biopsy; patients who received surgery from the same group of doctors; patients who never received chemoradiotherapy; patients who volunteered to participate in the study and signed informed consent [8]. Exclusion criteria: Patients with behavioral or mental disorders; patients who were pregnant or lactating women; patients who underwent cardiac surgery or implanted with pacemaker or prosthetic valve; patients who underwent aneurysm surgery or had aneurysm clips; patients who had metallic implants in the body or in the eyes; patients who were accompanied by other diseases that would affect the results of this study.

Methods

We enrolled 108 patients with glioma confirmed by biopsy to this retrospective study. They were randomized into the observation group (n = 54) and the control group (n = 54). Multi-modal MRI was used in the observation group, and CT scan was applied in the control group to detect the normal and cancer tissues in brain for apparent diffusion coefficient (ADC), early-phase enhancement rate, and the type of dynamic contrast enhanced time intensity curve (TIC) shape. The control group received examination using Siemens Scope 16-Slice CT scanner (Siemens, Germany). With Signa HDxt 3.0 T magnetic resonance scanner (GE Healthcare, China), the observation group received routine MRI including transverse T1-weighted imaging (T1WI), T2-weighted imaging, fluid-attenuated inversion recovery, and DWI, sagittal T1WI, and contrast-enhanced transverse, coronal and sagittal T1WI [9]. Functional MRI was performed using a Philips Ingenia 3.0T Magnetic Resonance System (Royal Philips Electronics, the Netherlands) [10]. The values of the parameters of pulsed-continuous arterial spin labeling were set as: repetition time (TR), 400 ms; echo time (TE), 16 ms; matrix size, 128 * 128; field of view (FOV), 240 mm * 240 mm. Diffusion tensor imaging (DTI) was performed using spin-echo echo-planar imaging sequence with 36 directions of diffusion. The values of the parameters of DTI were set as: b, 0 s/mm² and 800 s/mm²; TR, 1,677 ms; TE, 83 ms; matrix size, 144 * 144; FOV, 220 mm * 220 mm. The values of the parameters of SWI were set as: TR, 31 ms; TE, minimum; matrix size, 768 * 768; FOV, 230 mm * 230 mm. Point-resolved spectroscopy sequence was applied for 1H-Magnetic Resonance Spectroscopy, with the values of the parameters set as: TR, 1,000 ms; TE, 144 ms. Tumors were located using axial and sagittal T2-weighted images. After the first surgical resection, the rate of complete resection was measured in both groups, and chemoradiotherapy was tailored to the specific conditions of each patient. In 1997, the World Health Organization classified gliomas into four grades according to their degree of malignancy, of which grade I-II were referred to as low-grade and grade III-IV as high-grade. Patients with low-grade gliomas have good prognosis, but those with high-grade gliomas have poor prognosis with markedly shortened survival period and substantially elevated recurrence rates after surgery [11].
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Measurements

The rate of complete resection after the first surgery and ADC before and after chemoradiotherapy were compared between the two groups. ADC was calculated as $\ln(S_2-S_1)/(b_1-b_2)$. Early-phase enhancement rate and the type of TIC shape were compared among normal tissues and cancer tissues before and after chemoradiotherapy. Early-phase enhancement rate was calculated as $(SI_c-SI)/SI \times 100\%$ ($SI_c$: signal intensity on contrast-enhanced image; $SI$: signal intensity on image before contrast enhancement). One-, three-, and five-year survival rates were compared between the two groups.

Statistical analysis

All statistical data were processed using SPSS 21.0 software package. Measurement data are expressed as mean ± standard deviation ($\bar{x} \pm sd$). Comparisons between two groups were based on independent t-tests. The Wilcoxon rank-sum test was used for ranked variables, denoted by $H$. All the enumeration data are expressed as cases/percentage ($n/%$), and were compared based on chi-squared tests and F-tests. $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

There were no statistical differences between the two groups in baseline characteristics including gender, age, body mass index, etc. (all $P > 0.05$). See Table 1.

Comparison of rates of complete resection after the first surgery and the ADC values before and after chemoradiotherapy

The rate of complete resection after the first surgery in the observation group was significantly lower than that of the control group (53.70% vs. 75.93%, $P < 0.05$, $\chi^2 = 5.850$). There were significant differences in the ADC value between the two groups before and after chemoradiotherapy ($P = 0.002$, $P < 0.001$). See Table 2, Figures 1 and 2.

Comparison of early-phase enhancement rates and types of TIC shape

The early-phase enhancement rate of normal tissues was 3.70%, which was significantly different from that of cancer tissue before and after chemoradiotherapy (55.56% and 10.19%, respectively). The differences in the early-phase enhancement rates of cancer tissue before and after chemoradiotherapy were also statistically significant ($P < 0.001$, $\chi^2 = 96.910$). The type of TIC shape of normal tissue was persistent enhancement, while that of tumor tissue was mostly high enhancement with plateau before chemoradiotherapy (86.11%), and was persistent enhancement after chemotherapy in most cases (79.63%). The differences in the types of TIC shape before and after chemoradiotherapy were statistically significant ($P < 0.001$, $\chi^2 = 191.01$). See Table 3, Figures 3 and 4.

Comparison of survival rates

The one-, three-, five-year survival rates of the observation group were all significantly higher.

Table 1. Comparison of baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>The control group (n = 54)</th>
<th>The observation group (n = 54)</th>
<th>$t$/$\chi^2$/$H$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>34</td>
<td>0.162</td>
<td>0.693</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>32.28 ± 3.23</td>
<td>32.32 ± 3.26</td>
<td>0.064</td>
<td>0.949</td>
</tr>
<tr>
<td>Mean tumor volume/mm³</td>
<td>27.96 ± 2.14</td>
<td>28.01 ± 2.17</td>
<td>0.122</td>
<td>0.901</td>
</tr>
<tr>
<td>Tumor grade/cases (n/%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0.232</td>
<td>0.891</td>
</tr>
<tr>
<td>II</td>
<td>25 (46.30)</td>
<td>26 (48.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17 (31.48)</td>
<td>18 (33.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>12 (22.22)</td>
<td>10 (18.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor site/cases (n/%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>21 (38.89)</td>
<td>22 (40.74)</td>
<td>0.214</td>
<td>0.972</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>13 (24.07)</td>
<td>14 (25.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>15 (27.78)</td>
<td>14 (25.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>5 (9.26)</td>
<td>4 (7.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.84 ± 4.70</td>
<td>25.41 ± 4.27</td>
<td>0.498</td>
<td>0.620</td>
</tr>
</tbody>
</table>

Note: BMI: body mass index.
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Table 2. Comparison of ADC values (\(\bar{X} \pm sd \times 10^3\) mm\(^2\)/s) and rates of complete resection (n (%))

<table>
<thead>
<tr>
<th>Rate of complete resection after the first surgery</th>
<th>ADC of cancer tissue before chemoradiotherapy</th>
<th>ADC of cancer tissue after chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation group (n = 54)</td>
<td>29 (53.70)</td>
<td>1.07 (\pm) 0.24</td>
</tr>
<tr>
<td>The control group (n = 54)</td>
<td>41 (75.93)</td>
<td>1.21 (\pm) 0.22</td>
</tr>
<tr>
<td>(P)</td>
<td>0.015</td>
<td>0.002</td>
</tr>
<tr>
<td>(t/\chi^2)</td>
<td>5.850</td>
<td>3.160</td>
</tr>
</tbody>
</table>

Note: ADC: apparent diffusion coefficient.

Discussion

Glioma is the most common type of primary malignant brain tumor and is regarded as a neurosurgical disease with high incidence, recurrence and mortality rates [12]. It has been reported that the development of glioma is the result of both exogenous pathogenic factors and genetic susceptibility that cause carcinogenic mutations in glial cells at the cellular genetic and epigenetic levels [13]. But the integrity of the theory has not been proved, and it is difficult to carry out the clinical treatment to cure glioma. Therefore, as an indirect approach to improve the prognosis, the early evaluation of treatment efficacy provides reference for the subsequent planning of chemoradiotherapy. The expansion of the size of glioma can cause mass effect, causing such clinical symptoms as headache, nausea, vomiting and blurred vision, and reducing patients’ quality of life due to obstruction of blood circulation, an increase in venous blood pressure and accumulation of fluid in the interstitial space [14]. Studies have shown that surgical resection combined with chemoradiotherapy is currently a preferred treatment for patients with glioma, but the same dosage and course of treatment of chemoradiotherapy may result in different therapeutic effects due to individual differences in the sensitivity to chemoradiotherapy [15]. Therefore, the treatment efficacy needs to be evaluated to screen patients with poor sensitivity, so that chemoradiotherapy can be tailored to the patient’s condition to improve treatment efficiency and survival [16].

Rohde et al. found that multi-modal MRI had a unique advantage of producing images with different modalities, allowing it to distinguish the differences between tissues and identify the location and volume of cancer tissues, all in a way clearer and accurate than CT-scan and X-ray [17]. In multi-modal MRI, DSC can track foreign markers, locate tumors in real time, and observe the effectiveness of chemotherapy drugs in tumors [18]; magnetic resonance spectroscopy can perform quantitative analy-
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sis of human tissues based on magnetic resonance imaging, and effectively distinguish tumors from normal tissues [19]; DWI can reflect the degree of malignancy of the tumor with ADC, a quantitative parameter; lower ADC values indicate more malignant tumors [20]; SWI can effectively identify tumor grade by the degree of intratumoral susceptibility signals; the greater the degree, the higher the tumor grade is [21]. Therefore, multi-modal MRI can be effective in distinguishing normal soft tissues and cancer tissues, and in identifying the degree of malignancy of the tumor. It can be applied to evaluation of the efficacy of chemoradiotherapy after surgery of glioma resection and the analysis of changes in parameters before and after chemoradiotherapy, so as to assess the effect of chemoradiotherapy on tumor cells [22].

A previous study showed that multi-modal MRI is more accurate than CT scans and other detection equipment in detecting the volume and location of tumors. Higher accuracy in detection is conducive to improvement in the detection rates of residual tumor after resection, thereby allowing the individualized treatment plan to be consistent with the patient’s condition and improving patient’s treatment effect and prognosis [23]. The results of this study showed that the difference in the ADC before and after chemoradiotherapy was statistically significant in both groups. The rate of complete resection after the first surgery in the control group was significantly higher than that in the observation group, indicating that CT scan has higher detection rates of complete resection than MRI. Therefore, the control group had smaller dosage and shorter course of treatment than the observation group during chemoradiotherapy following surgery due to a lower rate of complete resection measured by MRI. The early-phase enhancement rate of normal tissues was significantly different from that of cancer tissues before and after chemoradiotherapy, and there was also significant difference in the early-phase enhancement rate of cancer tissues before and after chemoradiotherapy. The type of TIC shape of normal tissue was persistent enhancement, while that of tumor tissue was high enhancement with plateau in most cases before chemoradiotherapy and persistent enhancement after chemoradiotherapy. There were significant differences in the types of TIC shape before and after chemoradiotherapy, indicating that there were differences in the early-phase enhancement rates and the types of TIC shape not only between normal tissues and cancer tissues before and after chemoradiotherapy, but also between cancer tissues before and after chemoradiotherapy. After chemoradiotherapy, cancer tissues were higher in ADC value, but significantly lower in the early-phase enhancement rate, and the type of TIC shape changed from high enhancement with plateau to persistent enhancement in most cases. The findings showed that the type of TIC shape of cancer tissues after chemoradiotherapy was the same as that of normal tissues in the observation group, suggesting that patients’ conditions were improved. The findings of MRI were multi-dimensional, revealing changes of the glioma

**Table 3. Comparison of early-phase enhancement rates and types of TIC shape (n (%))**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Normal tissue (n = 108)</th>
<th>Cancer tissue before chemoradiotherapy (n = 108)</th>
<th>Cancer tissue after chemoradiotherapy (n = 108)</th>
<th>P</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-phase enhancement rate</td>
<td>4 (3.70)</td>
<td>60 (55.56)</td>
<td>11 (10.19)</td>
<td>0.000</td>
<td>96.910</td>
</tr>
<tr>
<td>TIC (persistent enhancement)</td>
<td>108 (100.00)</td>
<td>15 (13.89)</td>
<td>86 (79.63)</td>
<td>0.000</td>
<td>191.071</td>
</tr>
</tbody>
</table>

Note: TIC: dynamic contrast-enhanced time-intensity curve.

**Figure 3.** Comparison of early-phase enhancement rates and types of TIC shape between normal tissues and tumor tissues before and after chemoradiotherapy.
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Figure 4. Multi-modal MRI images. Graph group 1: Images of left brain occupying patients in the observation group before chemoradiotherapy. Graph group 2: Images of patients after four cycles of chemoradiotherapy. A. Diffusion-weighted imaging; B. Magnetic resonance spectroscopy; C. Contrast-enhanced T1-weighted imaging; D. T2-weighted imaging; E. T1-weighted imaging; F. Contrast-enhanced T2 fluid-attenuated inversion recovery imaging.

Figure 5. Survival curves of two groups of patients.

through multiple images and different exposures, indicating that multi-modal MRI can show changes in soft tissue from multiple parameters, and can objectively reflect the treatment effects of chemoradiotherapy on tumors [24]. In this study, chemoradiotherapy reduced the malignancy of glioma and effectively improved patient’s condition. The one-, three-, and five-year survival rates of the observation group were significantly higher than those of the control group, which were not consistent with the difference in the rate of complete resection measured before chemoradiotherapy. After surgical resection, each patient underwent chemoradiotherapy according to the results of the corresponding detection technique, indicating that the differences in survival rates were caused by different accuracy between CT scan and multi-modal MRI, which led to the difference in calculating the rate of complete resection after the first surgery and affected subsequent planning of chemoradiotherapy. The survival period of patients in the observation group was significantly longer than that in the control group, indicating that the multi-modal MRI evaluated the rate of complete resection more accurately than CT scans; higher accuracy enabled the dosage and course of treatment of chemoradiotherapy to be more consistent with the patient’s own condition. The results showed that the sensitivity of multi-modal MRI to cancer tissue is higher than that of CT scan. Greater sensitivity increases the efficiency of chemoradiotherapy and improves patient’s condition. The results of this study were consistent with previous studies, demonstrating the credibility of the study. However, the limited sample size of this study cannot fully demonstrate the miss rate of multi-modal MRI. This technique still requires further research.

In conclusion, multi-modal MRI provides accurate information about the ADC and early-phase enhancement rates of the tissue, and semi-quantitative analysis by TIC. Moreover, it com-
compares the tissues before and after chemoradiotherapy to determine effectiveness of the treatment, and then provide reference for subsequent treatment. If the results of multi-modal MRI show insufficient efficacy, the treatment plan can be changed promptly to prevent unsatisfactory treatment effect due to mistakes or defects in the plan.

Disclosure of conflict of interest

None.

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