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Original Article

Predictive value of DCE-MRIs for tumor regression and sensitivity after concurrent chemoradiotherapy for nasopharyngeal carcinomas

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Abstract: Objective: The aim of this study was to examine the predictive value of DCE-MRI for tumor regression and sensitivity after concurrent chemoradiotherapy for nasopharyngeal carcinoma. Method: A total of 45 patients diagnosed with nasopharyngeal carcinoma, from June 2017 to December 2017, were enrolled in the study. All patients received MRI examinations before chemotherapy and were given intensity-modulated radiotherapy after 2 cycles of induction chemotherapy. Quantitative parameters before chemotherapy, at 50 Gy of radiotherapy, and at the end of radiotherapy were compared. The correlation of quantitative parameters and Regression rate during chemoradiotherapy was studied. Patients were divided into the sensitive group, efficacy intermediate group, and treatment resistant group, according to RS0 and symptoms. Parameters at 50 Gy in patients with different sensitivities were compared. Results: Parameters of Ktrans, Kep, and Ve in the nasopharyngeal carcinoma area were significantly higher than those in the lateral pterygoid muscle ($P<0.05$). Ktrans had the highest sensitivity and Kep had the highest specificity. Ktrans and Kep values, after treatment, were significantly lower than those before treatment. Ve, after treatment, was significantly increased ($P<0.05$). At 50 Gy, Ktrans was negatively correlated with RS0 ($r=-0.613$ $P<0.05$), Kep was negatively correlated with RS0 ($r=-0.626$ $P<0.05$), and Ve was not correlated with RS0 ($r=0.022$ $P=0.887$). Ktrans and Kep in the sensitive group were significantly higher than those in the efficacy intermediate group and treatment resistance group ($P<0.05$). Ve of the sensitive group was slightly lower than that in the efficacy intermediate group and treatment resistance group ($P>0.05$). Conclusion: Quantitative DEC-MRI is applicable to effectively evaluate the efficacy of chemoradiotherapy in patients with nasopharyngeal carcinoma. It can predict tumor regression and treatment sensitivity of nasopharyngeal carcinoma after treatment, providing more reliable data for efficacy assessment and prediction of nasopharyngeal carcinomas.

Keywords: DCE-MRI, nasopharyngeal carcinoma, concurrent chemoradiotherapy, tumor regression, sensitivity, prediction

Introduction

Nasopharyngeal carcinoma is a common head and neck malignant tumor, with poorly differentiated squamous cell carcinoma as the main pathological type [1]. Studies have shown that the pathogenesis of nasopharyngeal carcinoma is closely associated with genetics and EB virus infections [2, 3]. Early symptoms of nasopharyngeal carcinoma mainly present as lymphadenectasis in the neck. This is always ignored and the disease typically develops to the late stage, once definitely diagnosed [4]. With the development of medical technology, although the overall survival of nasopharyngeal carcinoma patients has increased, high recurrence rates and metastasis rates are still problems that should be resolved [5, 6]. For patients with unsatisfactory treatment efficacy, timely adjustment of treatment protocol is necessary, making evaluation of nasopharyngeal carcinoma particularly important.

The efficacy of nasopharyngeal carcinoma is evaluated with conventional CT and MRI scans. Compared with CTs, MRIs have the characteristics of multidirectional and multi-sequence imaging, displaying the location and size of lesions more clearly [7]. The principle feature of conventional MRIs is to demonstrate the changes

Table 1. General information table [n, (%)]

Clinical data	Number of cases n=45
Sex	
Male	31 (68.89)
Female	14 (31.11)
Age	
≥50	26 (57.78)
<50	19 (42.22)
BMI	
≥21	24 (53.33)
<21	21 (46.67)
Whether or not smoking	
Yes	28 (62.22)
No	17 (37.78)
Pathological staging	
Stage II	27 (60.00)
Stage III	13 (28.89)
Stage IV	5 (11.11)
Coagulation function	
APTT s	28.24±2.03
PT s	11.56±1.18
FIB g/l	3.21±0.25
TT s	14.71±1.53

of tumor morphology and signal [7]. Presently, the efficacy of nasopharyngeal carcinoma treatment is mainly evaluated by size changes of tumors and the lymph nodes before and after treatment. Actually, the size of the tumor will not change at the early stage, which makes it impossible to provide accurate information according to the change of tumor morphology [8]. In recent years, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been applied in the efficacy evaluation of nasopharyngeal carcinomas [9, 10]. However, these studies were mostly carried out using semi-quantitative analysis. The operation method is relatively simple but will be easily affected by scanning parameters. This makes multi-center studies and the accurate reflection of concentration changes in the contrast agent difficult [11]. Quantitative analysis improves all of the above deficiencies and reflects the changes of pathological tissues from the level of cellular molecular function [12]. However, quantitative analysis is, currently, more applied in diagnosis and efficacy evaluation of malignant tumors, such as glioma [13] and esophageal cancer [14]. Its application in nasopharyngeal carcinoma has been rarely reported.

Therefore, the current study examined the predictive value of DCE-MRI for tumor regression and sensitivity after concurrent chemo-radiotherapy for nasopharyngeal carcinomas, aiming to provide a more reliable imaging reference for efficacy evaluations of nasopharyngeal carcinomas.

Materials and methods

General information

A total of 45 patients diagnosed with nasopharyngeal carcinoma were enrolled in the study. The patients were (51.16±10.65) years old and included 31 males and 14 females. Stage II, stage III, and stage IV of nasopharyngeal carcinoma were respectively diagnosed in 27, 13, and 5 patients (**Table 1**). All patients received MRI examinations before chemotherapy and were given intensity-modulated radiotherapy after 2 cycles of induction chemotherapy.

Inclusion and exclusion criteria

Inclusion criteria: Patients pathologically diagnosed with nasopharyngeal carcinomas [15] were included. Exclusion criteria: Patients with severe hepatic-renal dysfunction or other tumors were excluded; Patients receiving other relevant treatments prior to the initial MRI scan were excluded; Patients with cognitive impairment and communication disorders were excluded; Patients that did not cooperate with the trial were excluded. All patients and family members agreed to participate in the study and provided informed consent. This study was approved by the Ethics Committee.

Treatment protocol

All patients were given TP-induced chemotherapy plus intensity-modulated radiotherapy. Two weeks after chemotherapy, intensity-modulated radiotherapy was performed by adopting 6MV-X conventional fractionation radiation. The radiation dose was 2 Gy/time at a frequency of 5 times/week. Radiotherapy lasted 7 weeks and the total radiation doses were 70 Gy.

MRI scans

A total of three scans were performed in this study. Scans, each time, included both the MRI routine scan and DCE-MRI scan. They were performed, respectively, at 24 hours before che-

motherapy, at the 50 Gy of radiation dose, and at the end of radiotherapy. The Sonata 1.5T superconducting magnetic resonance instrument and standard head coils from Siemens, Germany, were adopted. Enhanced scanning contrast agent was the gadodiamide injection purchased from GE Company, USA. Before receiving the scans, all patients removed metallic foreign bodies in the body and were place in the supine position, with the head entering the scanner first.

Routine MRI scans

T2WI fast spin echo sequences were adopted. The time of repeat (TR) was 3600 ms and the time of echo (TE) was 85 ms. T2WI spin echo sequences were used with the TR 660 ms and TE 8 ms. Slice thickness was 3 mm and the slice gap was 1 mm. The number of the excitation was 2, while the matrix was 308 × 256.

DCE-MRI scans

Location of lesions was determined with reference to MRI plain scan images. The slice with larger lesions was selected as the center of scanning. The Turbo FLASH sequence was used for T1WI scans, with the five flip angles scanned first. Parameters of scanning were TR198 ms and TE1.03 ms. FOV was 240 mm × 210 mm, the slice thickness was 5 mm, the slice gap was 1.2 mm, the matrix was 126 × 98, the scanning time per cycle was 4 seconds, and there was a total of 10 slices. After scanning, the contrast agent was injected through elbow veins with the high-pressure injector (total volume was 0.2 mmol/kg, while the rate was 2 mL/s). After injection, 20 mL of normal saline was used to flush the catheters at the same rate. Finally, routine enhancement scans were performed, including the axial, sagittal, and coronal T1WI examinations. The fat suppressed T1WI sequence was adopted for enhanced scanning.

Image data processing

Imaging data of DCE-MRIs was processed by nordicICE (version 2.3.6) software and was input as the sequence. The Tofts two-compartment model was selected as the pharmacokinetic model, with the Population AIF curve as the arterial input curve. The larger slice of the lesions was selected when setting the value and the pseudo-color image, consistent with the above quantitative parameters, was obtained by calculation. The entire lesion area was outlined on the original image. Cluster analysis was used to determine the region of interest (ROI) and other quantitative parameter values were finally obtained. The volumetric transport constant (Ktrans) of the contrast agent from the inside of the vascular to the outside of the vascular, the rate constant (Kep) of the contrast agent from the outside of the vascular to the plasma, and volume (Ve) of the contrast agent outside of the vascular were repeatedly measured 3 times. The average of the 3 measurement results was used for statistical analysis.

Outcome measurements

Tumor areas, before treatment, at 50 Gy, and after chemotherapy, were measured and tumor regression rates were calculated. Regression rate (RS0) = (pre-treatment tumor area - post-treatment tumor area)/pre-treatment tumor area × 100%. As the tumor was in remission, the patients were divided into the treatment-sensitive group (all target lesions were removed, RS0=100%), efficacy intermediate group (partial tumor remission, RS0≥30%), and treatment resistant group (tumors unrelieved or disease progression, RS0<30%).

Statistical analysis

SPSS20.0 software (Beijing NDTimes Technology Co., Ltd.) was adopted for statistical analysis. Count data was analyzed with the Chi-squared test, while measurement data was compared with Student's t-test. Data, before and after treatment, were analyzed with paired t-test. Correlation was analyzed with Pearson's correlation and the figures of the study were plotted with GraphPad Prism 6 software. $P< 0.05$ implies statistical significance.

Results

Higher quantitative parameters observed in nasopharyngeal carcinoma areas

Values of Ktrans, Kep, and Ve in nasopharyngeal carcinoma areas were significantly higher than those in the lateral pterygoid muscle ($P<0.05$) (**Table 2**).

Table 2. Quantitative parameters of DCE-MRI in tumor areas and lateral flank of nasopharyngeal carcinomas before treatment

Parameter index	Tumor area of nasopharyngeal carcinoma	Lateral nasal alar muscle	t	P
Ktrans (min^{-1})	0.263±0.106	0.109±0.097	7.190	<0.001
Kep (min^{-1})	0.815±0.312	0.487±0.321	4.915	<0.001
Ve	0.346±0.095	0.239±0.125	4.572	<0.001

Table 3. Diagnostic effectiveness of quantitative parameters for nasopharyngeal carcinomas

Diagnostic efficiency	Ktrans	Kep	Ve
Optimal diagnostic threshold	0.192	0.489	0.274
Sensitivity (%)	82.22%	53.33%	46.67%
Specificity (%)	84.44%	91.11%	73.33%
AUC	0.930	0.827	0.698

Table 4. Quantitative parameters before and after treatment

Quantitative parameters	Pre-radiotherapy	Radiotherapy 50 Gy	End of radiotherapy	F	P
Ktrans (min^{-1})	0.261±0.114	0.193±0.073	0.177±0.064	11.98	<0.001
Kep (min^{-1})	0.809±0.311	0.478±0.184	0.313±0.156	55.60	<0.001
Ve	0.335±0.076	0.484±0.132	0.491±0.136	25.14	<0.001

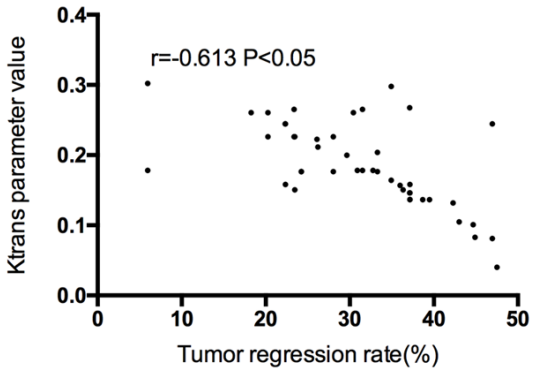

Figure 1. Correlation between Ktrans values and RS0 in 50 Gy radiotherapy. Ktrans was negatively correlated with RS0 at 50 Gy of radiotherapy (r=-0.613 P<0.05).

Ktrans has the most diagnostic efficacy

The parameter with the highest sensitivity was Ktrans, while the parameter with the highest specificity was Kep (**Table 3**).

Radiotherapy significantly affects quantitative parameters

Values of Ktrans and Kep decreased significantly, while the value of Ve increased significantly, compared those before treatment (P<0.05) (**Table 4**).

Ktrans and Kep negatively correlated with RS0

Ktrans was negatively correlated with RS0 at 50 Gy (r=-0.613 P<0.05). The value of Kep was negatively correlated with RS0 (r=-0.626 P<0.05). The value of Ve was not significantly correlated with RS0 (r=0.022 P=0.887) (**Figures 1-3**).

Quantitative DCE-MRI shows prediction value

After radiotherapy, Ktrans and Kep values in the sensitive group were significantly higher than those in the efficacy intermediate group and treatment resistant group (P<0.05). However, Ve values in the sensitive group were slightly lower than those in the efficacy intermediate group and treatment resistant group. Differences were not significantly significant (P>0.05) (**Table 5**).

Discussion

A vascular-dependent malignant tumor, nasopharyngeal carcinoma cells grow rapidly and are of higher permeability in tumor areas due to the immature development of micro vessels. This results in higher Ktrans and Kep values in tumors before treatment [16]. Quantitative DCE-MRI is to convert the time-signal intensity curve that reflects the dynamic contrast agent absorption in the body measured by the hemodynamic model to the time-concentration curve. This helps to obtain hemodynamic parameters Ktrans, Kep, and Ve, reflecting blood perfusion and distribution of contrast agents in tumors [17]. Therefore, quantitative DCE-MRI enables researchers to introduce the exchange process of intravascular and extravascular contrast agents by fusing the pharmacokinetic model, describing the formation and penetration of tumor microvascular [18]. For example, studies applying DCE-MRI to esophageal cancer found that patients with complete remis-

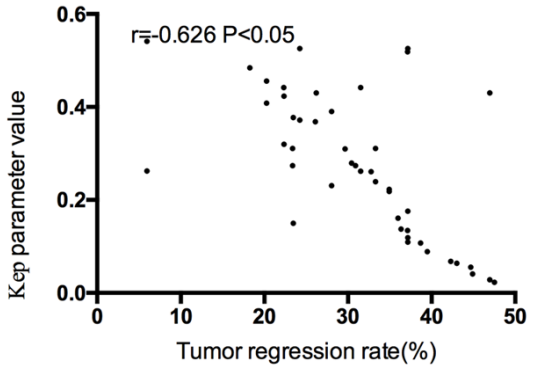

Figure 2. Correlation between Kep values and RS0 in 50 Gy radiotherapy. Kep was negatively correlated with RS0 (r=-0.626 P<0.05).

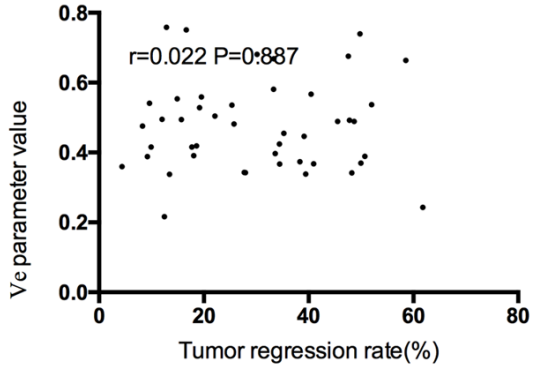

Figure 3. Correlation between Ve values and RS0 in 50 Gy radiotherapy. Ve was not correlated with RS0 (r=0.022, P=0.887).

sion during treatment had a higher Ktrans value than those with partial remission [19]. Ktrans is a complicated function, involving tumor blood flow, endothelial permeability, and endothelial surface area. Interpretation of Ktrans primarily depends on the potential physiological remission and tissues type under assessment. The major factor deciding the kinetics of contrast reagent is blood perfusion. Therefore, Ktrans is equivalent to the unit volume of blood perfusion [20]. Chemoradiotherapy prevents the generation of cardiac tumors because of its inhibition effects on expression of vascular endothelial growth factor [21].

Results of this study suggest that parameters Ktrans, Kep, and Ve in the nasopharyngeal carcinoma tumor areas were significantly higher than those in the lateral pterygoid muscle, before treatment. Results imply that MRIs could distinguish the differences between tumor tissue and normal tissue by measuring values of Ktrans, Kep, and Ve. This study compared the diagnostic efficacy of the three parameters. Results suggest that Ktrans had the highest sensitivity and Kep had the highest specificity, implying that Ktrans has the most diagnostic efficacy in distinguishing tumor tissues from normal tissues. Studies [22] on application of DCE-MRI in breast cancer have also reached the same conclusion. The current study recorded and compared quantitative parameters before treatment, at 50 Gy, and after radiotherapy. Results showed that the values of Ktrans and Kep significantly decreased, while Ve significantly increased after treatment, compared with those before treatment. Differences were statistically significant (P<0.05). Some studies [23] have shown that radio-chemotherapy will induce the deformation and necrosis of capillary walls, consequently reducing blood perfusion of tumor tissues, reducing osmotic pressure of the blood vessel walls, and decreasing values of Ktrans and Kep after radio-chemotherapy. Ve value increases maybe because the radiotherapy leads to osmotic pressure decreases of the tumor vessel walls, slows the flow rate of contrast agents, prolongs the residence time of contrast agents in the tissue vessels and outside the vascular, and eventually leads to an increase of Ve values [24]. Other studies have shown [19] that, after chemotherapy for esophageal cancer, values of Ktrans and Kep in the complete remission group were decreased, compared those before treatment, while the value of Ve was increased, consistent with present results. Results also showed that Ktrans and Kep values in the tissues which are more sensitive to radiotherapy decreased more pronouncedly. This may be because that, in tumor areas with rich blood perfusion, the oxygen content in microcirculation is high, vascular permeability is high, and sensitivity to the chemotherapy is high. Thus, the correlation with Ktrans values is the greatest [25]. Lastly, this study divided patients into the sensitive group, efficacy intermediate group, and treatment resistant group, according to the tumor regression rate and treatment efficacy. Parameters of patients with different sensitivities, before treatment, were compared. Results showed that Ktrans and Kep values of patients in the sensitive group, before treatment, were significantly higher than those in the efficacy intermediate group and treatment resistance group. Differences were statistically significant (P< 0.05). However, Ve values in the sensitive group were slightly lower than those in the efficacy

Table 5. Comparison of parameters of patients with different sensitivities

Parameter	Sensitive group n=20	Efficacy intermediate group n=11	Treatment resistant group n=9	F	P
Ktrans (min^{-1})	0.261±0.109	0.186±0.069	0.163±0.063	4.576	<0.05
Kep (min^{-1})	0.715±0.308	0.412±0.173	0.276±0.145	11.56	<0.05
Ve	0.392±0.119	0.405±0.115	0.412±0.063	0.122	0.886

intermediate group and treatment resistance group. Differences were not significant (P> 0.05). Some studies [26, 27] have found that, by applying quantitative DCE-MRI to chemoradiotherapy of head and neck cancer patients, blood volumes and Ktrans in the sensitive group, before treatment, were higher than those in the efficacy intermediate group. This is consistent with present conclusions and present correlation analysis results. Therefore, it is believed that quantitative DCE-MRI is valuable in predicting tumor regression and treatment sensitivity of nasopharyngeal carcinomas.

In summary, quantitative DEC-MRI will effectively evaluate the efficacy of radio-chemotherapy in nasopharyngeal carcinoma patients. It can effectively predict tumor regression and treatment sensitivity of nasopharyngeal carcinomas, after treatment, providing more reliable data for the evaluation and prediction of efficacy for nasopharyngeal carcinoma treatment. However, in this study, the optimization of sequence scanning was not ample. More accurate results should obtained if the time resolution can be further improved in the future. In this study, the grouping experiments were not precisely performed. Only the short-term effects of nasopharyngeal carcinoma were evaluated. In follow-up studies, present researchers will carry out the grouping experiments in a more precise manner, comparatively evaluating short term and long-term effects of nasopharyngeal carcinomas.

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Disclosure of conflict of interest

None.

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