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Original Article

Prediction of short-term treatment outcome of nasopharyngeal carcinoma based on voxel incoherent motion imaging and arterial spin labeling quantitative parameters

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ABSTRACT

Purpose: To evaluate the early response of chemoradiotherapy (CRT) in nasopharyngeal carcinoma (NPC) based on intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) and three-dimensional pseudo-continuous arterial spin labeling (3D pCASL).

Materials and methods: Forty patients diagnosed with NPC were recruited and divided into complete remission (CR) and partial remission (PR) group after CRT. All patients underwent IVIM and ASL and the related parameters was obtained. These parameters include pure diffusion coefficient (D), pseudo-diffusion coefficient (D*), perfusion fraction (f), average blood flow (BF_{avg}), minimum blood flow (BF_{min}), and maximum blood flow (BF_{max}). Student's *t* test was used to compare the difference in ASL and IVIM derived parameters between CR and PR. The Areas under curve (AUC) of the receiver operating characteristic (ROC) was used to analyze the diagnostic performance of each parameter of ASL and IVIM to the treatment outcome.

Results: the D value of IVIM in CR group was lower than that of the PR group ($P = 0.014$),. Among the parameters of ASL, the BF_{avg} and BF_{max} of the CR group were higher than those of the PR group($p = 0.004,0.013$), but the BF_{min} had no statistical significance in the two groups ($P = 0.54$) . AUC of D, BF_{avg}, and BF_{max} is about 0.731, 0.753, and 0.724, respectively, all of their combined AUC diagnosis was 0.812.

Conclusion: The early response of NPC after CRT can predict by IVIM's diffusion parameters and ASL-related blood flow parameters.

Nasopharyngeal carcinoma (NPC) is a common malignant tumor of the head and neck which popular in Southeast Asia, including China. Although NPC is sensitive to radiotherapy and chemotherapy, the causes of treatment failure are often related to local recurrence and distant metastasis, accounting for 5–15%, and 15–30% of patients, respectively [1,2]. Studies have shown that the level of blood oxygen in the tumor is closely related to the prognosis of NPC [3,4], but there is a lack of an effective and non-invasive method for prediction and evaluation of treatment response at present. Therefore, a non-invasive imaging tool is needed to reflect the information of internal blood oxygen of NPC to guide clinical treatment.

Conventional diffusion-weighted magnetic resonance imaging (DWI-MRI) is a functional imaging technique that can measure the motion of water molecules and quantitatively analyze the microstructure of tissues based on a single exponential model. The apparent diffusion coefficient (ADC) obtained from conventional DWI-MRI can quantify the movement of water molecules, but it ignores the effect of microcirculation perfusion on the diffusion signal intensity, thus it can not accurately reflect

Abbreviations: NPC, nasopharyngeal carcinoma; IVIM-DWI, intravoxel incoherent motion diffusion-weighted imaging; 3DpCASL, three-dimensional quasi-continuous arterial spin labeling; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; CRT, chemoradiotherapy; D, pure diffusion coefficient; D*, pseudo-diffusion coefficient; f, perfusion fraction; ADC, apparent diffusion coefficient; BFavg, average of blood flow; BF_{min}, minimum blood flow; BF_{max}, maximum blood flow; AUC, area under the curve; CR, complete remission; PR, partial remission.

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the real diffusion characteristics in the tissue. Intravoxel incoherent movement diffusion-weighted imaging (IVIM-DWI) has the ability to distinguish the diffusion of water molecules in tissues from the perfusion of capillary microcirculation so that it can be used as a means to measure blood perfusion in vivo [5], cervical lymph node metastasis [6], differentiation of nasopharyngeal carcinoma [7], and evaluation of treatment outcome [8–14] . Therefore, IVIM-DWI has a good application prospect in clinical applications.

The three-dimensional quasi-continuous arterial spin labeling (3DpCASL) technique does not need a contrast agent, which has a high signal-to-noise ratio and can reflect tumor blood oxygen indirectly by noninvasive quantitative analysis for information of tissue blood perfusion. it has been found that there was a good correlation between ASL and the parameter of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). ASL may be an alternative method for DCE-MRI to evaluate the perfusion level of NPC in the future [15]. At present, ASL has been reported in the differentiation of nasopharyngeal diseases, grading of head and neck squamous cell carcinoma, evaluation of tumor hypoxia, and prediction of glioma efficacy [16–19], but it has not been used to predict the efficacy of radiotherapy and chemotherapy in NPC.

Some researchers reported that the perfusion parameters of IVIM-DWI are meaningless so it is inconsistent in the evaluation of tumor efficacy [8,9,14,20]. Therefore, we assume that IVIM-DWI and 3DpCASL be combined to better predict the efficacy of NPC before treatment by exploring the perfusion and diffusion characteristics. It is possible to become a model of treatment prediction for NPC and provide a basis for individualized treatment and improve the prognosis of patients in the future.

1. Material and methods

1.1. Patients

This prospective study was approved by the local institutional review board. From October 2019 to October 2020 newly diagnosed patients with NPC proven by histology were prospectively collected and Informed consent was obtained before the examination. The primary tumor (T staging), lymph node metastasis (N staging), and distant metastasis (M staging) were classified according to the 8th edition of the AJCC staging system. The inclusion criteria for all patients were: (1) pathologically diagnosed as NPC, (2) had not received any treatment before MRI examination, (3) were treated with intensity-modulated radiotherapy and chemotherapy. The exclusion criteria for all patiens were: (1) any treatment that has been given, (2) contraindications for magnetic resonance imaging, (3) complications of head and neck diseases or other tumors, (4) with distant metastasis.

1.2. MRI examination

GE Discovery MR750W 3.0 T magnetic resonance scanner and head and neck joint coil were used. All patients underwent conventional MR scan of the nasopharynx, followed by IVIM and 3D pCASL scans and enhanced scan. Conventional MR scans included axial T1WI (TR=568 ms, TE=14.3 ms), T2WI-FS (TR=3897 ms, TE=95 ms), coronal T2WII-Deal (TR=3000 ms, TE=68 ms, slice thickness=5 mm), and axial, sagittal, and coronal T1WI-FS (TR = 400–850 ms, TE=18 ms) enhanced scans. FOV= 22 cm × 22 cm, slice thickness= 5 mm, slice gap= 1 mm.

IVIM-DWI sequence scanning parameters: the axial DWI, TR= 4000 ms, TE= 62.8 ms, slice thickness= 5 mm, slice gap= 1 mm, bandwidth= 250 Hz/pixe, matri= 128 × 128, FOV= 22 cm × 22 cm, 11 b values (NEX): 0(1), 30 (4), 50 (4), 80(2), 100 (2), 150 (2), 150 (1), 200 (2),400 (2), 600 (2), 800(4),and1000(4) s/mm^2. The imaging time for this sequence was 4 min and 8 s

3D-pCASL sequence with a fast spin-echo (FSE) spiral acquisition was performed, with the following parameters: PLD (post label delay)= 1525 ms, FOV= 22 cm × 22 cm, TR= 4640 ms, TE= 10.7 ms, slice thickness= 5 mm, slice gap= 1 mm, bandwidth= 62.50 Hz/pixel, matrix= 512 × 8; NEX= 3. The imaging time for this sequence was 4 min and 21 s

1.3. Patient treatment

All the patients received chemoradiotherapy in the radiotherapy department after routine MRI scant. Intensity-modulated radiation therapy was used in radiotherapy with a total dose of 70.4–72.6 Gy (PGTV). In the course of radiotherapy, patients received 2–3 cycles of platinum synchronous chemotherapy, intravenous infusion, 7 days as a cycle, 21 days interval, intravenous drip. The patients underwent MRI examination again at the end of radiotherapy, including routine plain scan and enhanced scan.

1.4. IVIM-DWI and 3D pCASL post-processing image analysis

On contrast-enhanced T1w images, the maximum diameters of the tumor were measured by two independent head-and-neck radiologists who were blinded to the data of curative effect. we calculate the tumor regression rate (RS)after 3 months CRT, The formula is RS= (maximum diameter of a tumor before treatment-maximum diameter of tumor 3 months after CRT) / maximum diameter of a tumor before treatment × 100%. According to the evaluation standard of treatment outcome of solid tumor (response evaluation criteria in solid tumors, RECIST) 1.1 [21], the tumor remission was divided into three groups: (1) complete remission group (CR), RS= 100%; (2) partial remission group (PR), RS ≥ 30%; (3) disease stable group (SD), non-PR/PD group; (4) disease progression group (PD): lesions increased by 20%, non-CR/PR/SD before lesions increased. If the reports were inconsistent, the two observers were asked to redraw the ROI.

1.5. IVIM-DWI and 3D pCASL data processing and Analysis

The IVIM and ASL raw data obtained are transferred into the GE-AW4.6 workstation Functool software for post-processing. On the image of IVIM-DWI, the two experienced radiologists manually delineate the region of interest(ROI) along the edge of the tumor at the maximum slice, ROI should include at least 2/3 of the lesion area. At the same time, reference should be made to plain scan and conventional enhanced scan images to avoid bleeding, necrosis, adjacent bone, air, etc. The IVIM parameters D(pure diffusion), D* , (pseudo-diffusion coefficient), and *f*(perfusion fraction) were measured.

The 3DpCASL images were fused with the axial T2WI-FS images, then, the region of interest(ROI), including all the entire tumor lesion, was drawn. To avoid obvious necrosis and artifacts, the enhanced images were used as a reference. The average blood flow (BF_{avg}), minimum blood flow (BF_{min}), and maximum blood flow (BF_{max}) were obtained by post-processing.

1.6. Statistical analysis

Continue variables were presented mean ± standard deviation. Kolmogorov-Smirnov test was used for normal distribution test, with all IVIM-DWI and 3DpCASL parameters revealing approximately normal distribution. Student's *t* test was used to analyze the difference in IVIM-DWI and 3D pCASL parameters between CR and PR groups. Receiver operating characteristic (ROC) curves were performed to predict the diagnostic efficacy of NPC. Statistical analyses were performed using the statistical analysis software SPSS (version 22.0; IBM) and Graphpad Prism 8.0(Graphpad Software). $p < 0.05$ indicated statistical significance.

Table 1
Characteristics of 40 patients with NPC.

	40
Gender	
Male	29
Female	11
Age (years)	45.4 ± 11.9
Overall stage	
I	2 (5%)
II	16 (40%)
III	17 (43%)
IV	5 (12%)
Primary tumor staging	
T1/2	22 (55%)
T3/4	18 (45%)
Nodal staging	
N0/1	30 (75%)
N2/3	10 (25%)
M	0

2. Results

2.1. General data

A total of 44 patients were initially enrolled, 2 cases were excluded because of the severe magnetic sensitivity artifacts caused by skull base bone and air cavity, and 2 cases lost follow-up were not included in the statistics. Lastly, other 40 patients were included in the study. There were 21 cases in the CR group and 19 cases in the PR group (19 cases in the PR group, 0 cases in the SD group, and 0 cases in the PD group) after 3 months of CRT. The basic clinical features are shown in Table 1. The average maximum diameters of nasopharyngeal lesions have no statistical significance in the CR group and the PR group before treatment (2.27 ± 0.77 cm vs. 2.20 ± 0.77 cm, $P = 0.773$).

2.2. Differences of parameters and diagnostic performance among different groups

Among the related parameters of IVIM-DWI and 3DpCASL before treatment, the D value in the CR group was lower than that of the PR group and the BF_{avg} and BF_{max} of the CR group were higher than those of the PR group Fig.1 and 2. The mean±SD values were as follows: the D= 0.71 ± 0.12 (× 10^{-3} mm^2/s) for CR group vs. 0.85 ± 0.22 (× 10^{-3} mm^2/s) for PR group ($P = 0.014$). There was no statistical significance in D* and f ($p = 0.899$, 0.568) . BF_{avg}= 85.05 ± 23.11 (mL/min/100 g) for CR group vs. 62.25 ± 23.57 for PR group. BF_{max}= 136.86 ± 52.407 (mL/min/100 g) for CR group vs. 99.42 ± 35.47 (mL/min/100 g) for PR group, and the difference was statistically significant ($p < 0.05$), but the parameter BF_{min} had no statistical significance($p = 0.54$) (Table 2).

Further ROC comparison of the parameters showed that AUC of BF was significantly higher before treatment, the AUC of ROC for predicting the treatment outcome of NPC was 0.731, and the AUC for BF_{max} was 0.753 and 0.724, respectively Fig. 3. Among all the parameters, BF_{avg} is the best parameter for predicting the short-term efficacy of CRT in patients with NPC. The sensitivity and specificity of IVIM-DWI and 3DpCASL parameters are summarized in Table 3. The AUC of D, BF_{avg}, and BF_{max} combined to predict the treatment outcome of NPC was 0.812 Fig. 3, Table 4.

3. Discussion

Early prediction of the efficacy of CRT for NPC is helpful for the clinical formulation of personalized treatment strategies. This study showed that the D value in CR group is lower than those of the PR group, and the BF_{avg} and BF_{max} of the CR group are higher than those of the PR group. The diffusion-related IVIM parameters (D) may be more helpful to predict the short-term effect of NPC than the perfusion-related parameters (f and D*), and the 3DpcASL-related parameters BF_{avg} and

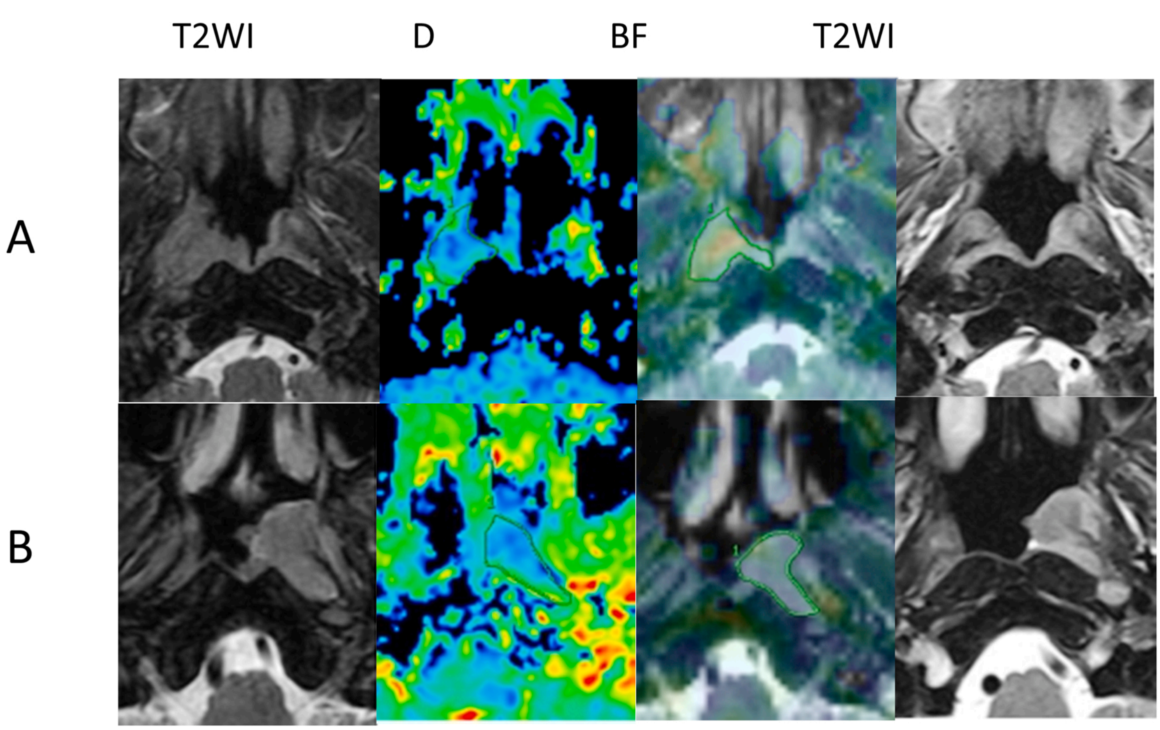

Fig. 1. A 59-year-old male patient with NPC who achieved CR. The sequence of images was pre-treatment T2WI, D, BF, and post-treatment T2WI images. D= 0.777 × 10^{-3} mm^2/s , BF_{avg}= 69 $mL/_{min}/100$ g , BF_{max}= 111 $mL/_{min}/100$ g. The T2WI showed that the tumor disappeared completely(A). A 45-year-old male patient with NPC who was evaluated as PR. The sequence of images was pre-treatment T2WI, D, BF, and post-treatment T2WI images. D= 0.83 × 10^{-3} mm^2/s, BF_{avg}= 37 $mL/_{min}/100$ g, BF_{max}= 56 $mL/_{min}/100$ g. The T2WI after treatment showed that the tumor had shrunk part of the tumor on the right side of the nasopharynx(B).

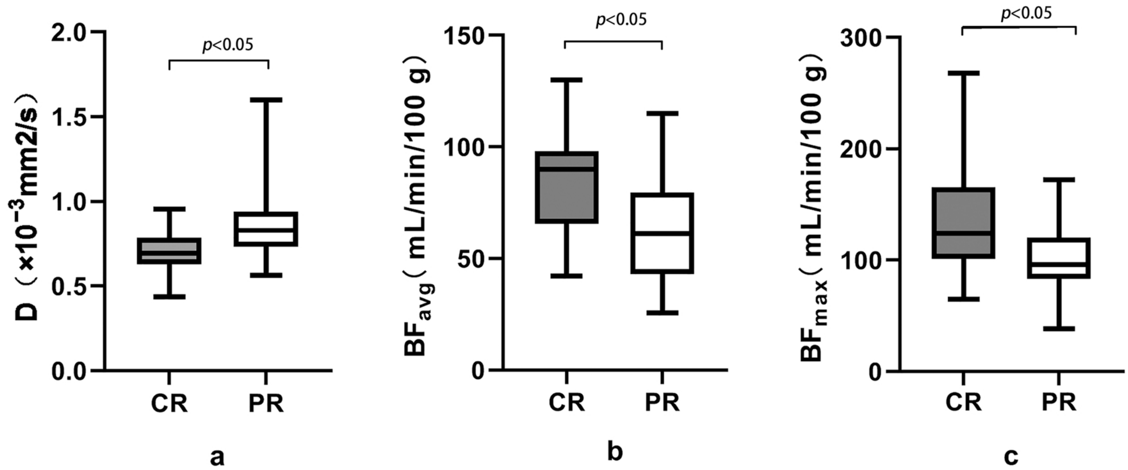

Fig. 2. Box diagram of different parameters in CR group and PR group. D value in the CR group was significantly lower than that in the PR group, while BFavg and BFmax in the CR group were significantly higher than those in the PR group.

Table 2
The differences in parameters of IVIM-DWI and 3D pCASL between the two groups before treatment (± s).

Parameters	CR	PR	Statistical value	*P*
D (× 10 − 3mm2/ s)	0.704 ± 0.126	0.849 ± 0.220	t = −2.581	0.014
D* (× 10 − 3mm2/ s)	12.696 ± 4.75	12.503 ± 4.785	t = 0.128	0.899
f	0.307 ± 0.063	0.294 ± 0.087	t = 0.549	0.586
BFavg (mL/min/ 100 g)	85.048 ± 23.111	62.253 ± 23.570	t = 3.086	0.004
BFmin (mL/min/ 100 g)	22.500 ± 17.969	19.132 ± 16.322	t = 0.618	0.54
BFmax (mL/min/ 100 g)	136.857 ± 52.407	99.421 ± 35.478	t = 2.617	0.013

BF_{max} also have better predictive efficiency. This suggests that IVIM-MRI and 3DpCASL can be used as potential indicators to predict the short-term efficacy of CRT in NPC.

IVIM-DWI is of great value in the evaluation of the treatment outcome and may become a non-invasive index in the evaluation of the response of NPC. IVIM-DWI is operated by a double exponential model, which can provide diffusion correlation and perfusion-related parameters, including D, D* , and *f*. Since the level of diffusion coefficient mainly depends on the proportion of intracellular and extracellular space in tissue [22], it is considered that D is negatively correlated with cell density and positively correlated with necrosis and cystic degeneration in tissue. The studys [8,10,11,14] showed that the D value of patients with good effect of induction chemotherapy, radiotherapy, and

Table 3
ROC curve analysis of D, BF_{avg}, and BF_{max} for predicting the efficacy for NPC after CRT.

Parameters	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificit (%)	*P*
D	0.777	0.73 (0.571–0.890)	0.762	0.682	0.013
BF_{avg}	85.75	0.75 (0.602–0.904)	0.571	0.895	0.006
BF_{max}	121	0.724 (0.566–0.883)	0.571	0.842	0.015

Table 4
Combined D, BF_{avg}, and BF_{max} to predict the efficacy for NPC after CRT.

Parameters	AUC (95% CI)	*P*
D+BFavg+BFmax	0.812 (0.682–0.942)	0.001

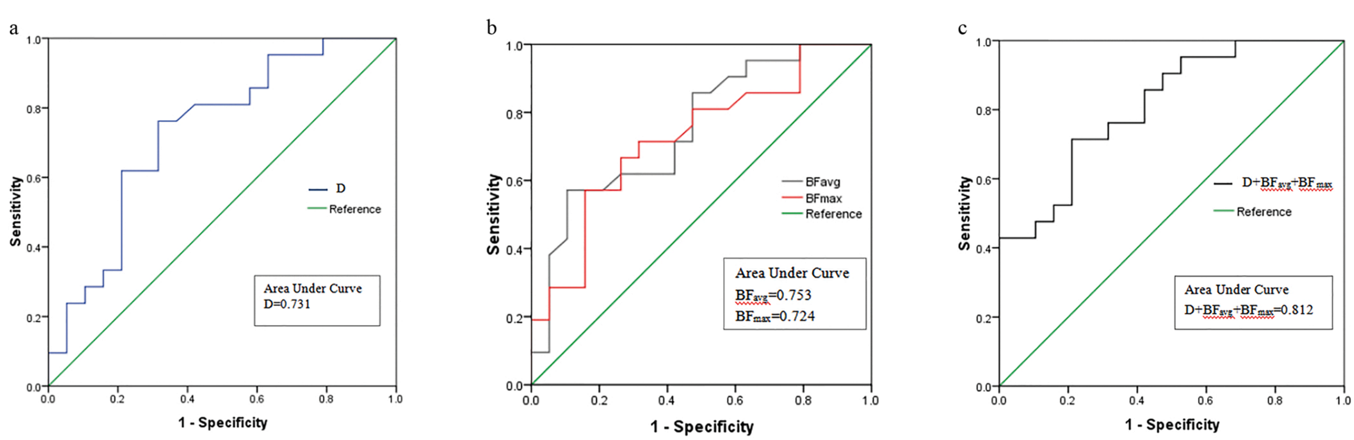

Fig. 3. ROC curves for D, Bfavg, and BFmax with respective areas under the curves in predicting the treatment outcome after CRT a: ROC curve of D value for predicting complete remission of NPC; b : ROC curve of BFavg and BFmax for predicting complete remission of NPC. c : ROC curve of D, BFavg and BFmax combined to predict the complete remission of NPC.

chemotherapy or neoadjuvant chemotherapy for NPC is significantly lower than that of patients with a poor clinical prognosis, which is consistent with the results of this study. This may be because a lower D value may mean less necrosis, higher cell density, and a higher degree of vascularization, which means richer perfusion and less hypoxia, resulting in a more significant reduction of tumor tissue and better therapeutic response after chemotherapy and or radiotherapy. Besides, the lower baseline D value was more sensitive to radiotherapy and chemotherapy in head and neck squamous cell carcinoma [23,24,25] and head and neck lymph node metastasis [26]. However, it is reported that the effectiveness of baseline D value in predicting the effectiveness of tumor treatment is controversial. Some studies have reported that higher D is more beneficial to radiotherapy for NPC [9] and cervical cancer [27], or that there is no correlation between D value and curative effect [13]. This may depend on the type of cancer, the method of treatment, the imaging scheme, and the criteria for evaluating the response. The pure diffusion parameter D value of this study has a good diagnostic and has a certain influence on predicting the early effect of treatment in NPC.

Both D* and *f* value are parameters related to perfusion. D* is proportional to the mean blood flow velocity and average capillary length [28], which mainly depends on the microvascular attenuation of the tissue [29]. *f* is the ratio of the volume of water in the capillary network that can be detected by MRI [28]. YU et al. [8] found that D* and f are of little help in predicting the early efficacy of induction and radiotherapy and chemotherapy in NPC. This is consistent with this study. However, only one previous IVIM-DWI study of NPC could show a correlation between D* and prognosis (low D* predicted a poor prognosis based on a short-term assessment of tumor size changes) [9], while most studies did not find a correlation [8,10,11]. In one study [14], low D* was a weak predictor of long-term prognosis (regional relapse-free survival) was poor. The low sensitivity and feasibility of perfusion-related parameters (D* and f) in predicting efficacy are since the measurement accuracy of perfusion-related parameters may be affected by repeatability, tissue characteristics under a magnetic field, and MRI examination. First, the cardiac cycle or pulsating blood flow in the head and neck may affect the repeatability of IVIM measurements, especially D* [30]. Thirdly, the measurement of value depends to a large extent on TE and T2 relaxation time [31]. A longer TE results in greater signal attenuation at a low b value, so the f value increases. Finally, the number of low b values used by IVIMDW-MRI may also affect the measurement accuracy of perfusion-related parameters.

3D pcASL technology is now widely used in the non-invasive measurement of tissue blood flow [32]. The application of head and neck tumors has certain reliability [33]. Unlike DCE-MRI, 3DpCASL can be performed non-invasively without a contrast medium, and its blood flow measurements may be more accurate because the tracer in asl diffuses more easily than the contrast medium (gadolinium chelate) in MRI perfusion [34]. In this study, it was found that there were significant differences in BF_{avg} and BF_{max} between the complete remission group and partial remission group, and had better diagnostic efficacy in predicting efficacy for NPC after CRT. A study [35] found that in the prediction of the treatment outcome of head and neck tumors with ASL, a higher BF value before treatment is better. Studies have shown that [36], ASL can predict the response of anti-angiogenic drugs in multiple myeloma early after the start of treatment. Besides, studies have reported that BF with a high baseline before treatment is sensitive to short-term antiangiogenic therapy for metastatic renal cell carcinoma [37], which is consistent with this study. Using DCE-MRI to evaluate the efficacy of laryngeal, hypopharyngeal, and cervical cancer in the study [38–40]], it was found that higher Ktrans perfusion parameters had better efficacy. The above can be understood as that when the blood with high perfusion, the blood with sufficient oxygen in the tumor at the same time, so it is sensitive to radiotherapy /chemotherapy. However, some studies [19,41] have suggested that higher BF_{max} before treatment has a higher risk of disease progression in predicting the efficacy of brain glioma or glioblastoma in children. This may be due to differences in the endpoints or treatment options of the study, so the results are inconsistent.

Perfusion-related parameters of IVIM-DWI have insignificance in predicting the short-term efficacy of NPC, but 3D pcASL perfusion parameters have better prediction performance. After the combination of D, BF_{avg}, and BF_{max}, the area under the curve for predicting the treatment outcome of NPC is increased, which indicates that prediction of short-term treatment outcome of NPC can use IVIM-DWI and 3DpcASL related parameters, and it is worth looking forward to the prospect.

Our research has some limitations. First of all, the sample is relatively small.,Secondly, susceptibility artifacts and movement problems (swallowing and coughing) lead to lesion distortion, so it is difficult to accurately determine the ROI on MR images. The imaging scheme needs to be further improved to reduce sensitivity artifacts. Thirdly, we did not extend our study to longer follow-up after treatment. Finally, only one post-label delay time (PLD) is set in this study, and whether the PLD is the best time needs further study.

4. Conclusion

The results of this study suggest that predicting the early efficacy of NPC can combine both of IVIM-DWI and 3DpcASL techniques. The pure diffusion coefficient D value of IVIM-DWI and the perfusion coefficient BFavg and BFmax value of 3DpcASL are helpful and can be used as potential imaging biomarkers to guide the treatment of patients with NPC.

Ethic statement

This study got approval from the research ethic committee of Guangxi Medical University Cancer Hospital and all patients participating in this study signed informed forms before examination.

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Conflict of interest

The authors of this manuscript declare no financial or other conflicts of interest with the publication of this work.

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