Nasopharyngeal carcinoma perfusion MRI
Comparison of arterial spin labeling and dynamic contrast-enhanced MRI

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Abstract
To investigate the feasibility of 3D arterial spin labeling (ASL) as an alternative to dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) for the qualitative and quantitative evaluation of nasopharyngeal carcinoma (NPC) perfusion.

Fifty-two newly diagnosed NPC patients underwent 3D ASL and DCE-MRI scans on a 3.0-T MRI system. The visual qualitative evaluation of the NPC perfusion level was scored from 0 to 3 (0 = no contrast to normal peripheral soft tissue, 3 = pronounced contrast to normal peripheral soft tissue). The visual evaluation of the NPC outline was scored from 0 to 2 (0 = very vague outline, 2 = clear outline). Comparisons of the ASL-derived blood flow (BF) with the DCE-MRI-derived positive enhancement integral, maximum slope of increase, maximum slope of decrease, and time to peak (TTP) were conducted between NPC and non-NPC areas with independent samples t-tests. The diagnostic performance of these parameters was assessed by receiver operating characteristic curve analysis. The correlations between ASL BF and DCE parameters were assessed by Spearman correlation analysis.

There was no difference in the visual scores of the NPC perfusion level between the 2 perfusion methods (P = .963). ASL had a lower visual score for describing the outline of NPC than DCE-MRI (P < .001). The ASL and DCE parameters of the NPC areas were significantly different from those of the non-NPC areas (P < .001). The ASL BF showed the largest area under the receiver operating characteristic curve (AUC) of 0.936 for identifying NPC. When all NPC and non-NPC areas were taken into account, significant correlations were observed between the ASL BF and the DCE parameters positive enhancement integral (r = 0.503, P < .001), maximum slope of increase (r = 0.616, P < .001), maximum slope of decrease (r = 0.380, P < .001), and TTP (r = -0.601, P < .001). 3D ASL could reveal the hyperperfusion of NPC in a qualitative and quantitative manner without using contrast agent. Additionally, the ASL BF correlated significantly with the semiquantitative DCE-MRI parameters.

Abbreviations: ASL = arterial spin labeling, AUC = area under the ROC curve, BF = blood flow, DCE = dynamic contrast-enhanced, MRI = magnetic resonance imaging, MSD = maximum slope of decrease, MSI = maximum slope of increase, NPC = nasopharyngeal carcinoma, PEI = positive enhancement integral, ROC = receiver-operating characteristic, TTP = time to peak.

Keywords: arterial spin labeling, dynamic contrast enhanced, magnetic resonance imaging, nasopharyngeal carcinoma, perfusion

1. Introduction
Nasopharyngeal carcinoma (NPC) is 1 of the most common head and neck malignant tumors in Southern China and Southeast Asia, with a reported incidence of 10–30/100,000 population per year. Conventional magnetic resonance imaging (MRI) has been regarded as the optimal imaging modality for NPC due to its excellent soft tissue contrast. Unfortunately, conventional MRI cannot provide information about tumor perfusion, which becomes increasingly important for precise tumor diagnosis and therapy. Dynamic contrast-enhanced MRI (DCE-MRI) has been widely used as a standard approach to evaluating tumor perfusion by providing biological markers reflecting tumor vascularity, permeability, and oxygenation and is useful in differentiating benign tumors from malignant tumors, predicting tumor grade and stage, monitoring therapeutic effect and assessing prognosis. Furthermore, a visual inspection can be directly performed due to the clear contrast between NPC and normal soft tissue on DCE-MRI perfusion maps. However, DCE-MRI cannot be performed without injecting exogenous contrast media, which may increase the risk of allergic reactions and nephrogenic systemic fibrosis especially in patients with significant renal insufficiency or those who need serial follow-ups.
for therapeutic effect monitoring. There is a need to develop a method that can be performed more safely to estimate NPC perfusion and be an alternative to DCE-MRI.

Arterial spin labeling (ASL) is a noninvasive MRI technique that utilizes magnetically labeled water protons in the blood as an endogenous contrast agent to achieve perfusion imaging and can avoid the issues associated with contrast media administration. This technique provides perfusion parameters by the pairwise subtraction of 2 images, 1 with magnetically “labeled” arterial blood water using radiofrequency irradiation and the other without labeling.[9] When first published in 1992, this perfusion method could only be performed in the rat brain to obtain a crude single-slice image.[10] Recent methodological advances and technical improvements rendered it possible to use 3D ASL to obtain whole-brain ASL data routinely in both the clinical and research settings. Previous studies of ASL have mainly focused on brain diseases,[11–18] such as neurodegenerative diseases, acute ischemic stroke, and brain tumors, but few have focused on NPC.[19]

The purpose of this study was to investigate the feasibility of 3D ASL as an alternative to DCE-MRI in the qualitative and quantitative evaluation of NPC perfusion.

2. Materials and methods

2.1. Patient population

This prospective study was approved by the ethics committee of the hospital. All recruited patients provided written informed consent. Between July 2016 and July 2018, 56 consecutive newly diagnosed (first episode) NPC patients were enrolled for MRI examinations. All recruited patients eligible for this study met the following criteria:

(1) biopsy-proven diagnosis of NPC;
(2) no history of prior chemotherapy, radiotherapy or other treatments;
(3) no contraindications to MR examinations; and
(4) no concurrent nasopharyngeal disease or other tumors.

Four patients were excluded from the study because of serious motion artifacts on their MR images. Finally, 52 patients (37 men, 15 women; mean age, 50 years; age range, 13–75 years) were included.

2.2. MRI protocols

MR imaging examinations of the whole nasopharynx were performed with a 3.0-T whole-body system (Discovery MR750; GE Medical Systems, Milwaukee, WI) utilizing an 8-channel head and neck phased array coil. The imaging protocol included the following:

(1) axial T1-weighted images (fast spin echo, FSE): repetition time/echo time (TR/TE) = 700/10 ms, number of excitations (NEX) = 2, bandwidth = 50 kHz, thickness = 6 mm, slice gap = 1 mm, field of view (FOV) = 28 cm, matrix = 288 x 192;
(2) axial T2-weighted images with fat suppression (fast recovery fast spin echo, FRFSE): TR/TE = 5000/70 ms, NEX = 3, bandwidth = 41.7 kHz, thickness = 6 mm, slice gap = 1 mm, FOV = 28 cm, matrix = 288 x 224;
(3) axial ASL (3D fast spin echo spiral-based pseudocontinuous pCASL sequence): TR/TE = 4500/10 ms, NEX = 3, bandwidth = 62.5 kHz, thickness = 4 mm, slice gap = 0 mm, FOV = 26 cm, PLD = 1525 ms; and
(4) axial DCE-MRI (3D liver acquisition with volume acceleration–extended volume, LAVA-XV): TR/TE = 4/1.8 ms, NEX = 0.7, bandwidth = 142.9 kHz, thickness = 4 mm, slice gap = -2 mm, FOV = 26 cm, matrix = 220 x 192, flip angle (FA) = 12°.

The total DCE-MRI scan time was approximately 280 s. Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA; Bayer Healthcare, Berlin, Germany) was administered at the second phase of the DCE-MRI protocol with a bolus dose of 0.1 mmol/kg of body weight through an antecubital vein at a rate of 2.0 mL/s by a power injector system, followed by a 20 mL saline flush at a rate of 2.0 mL/s.

2.3. Postprocessing and evaluation

All images were transferred to the Advantage Workstation, and Func tool software (ADW 4.6 version; GE Medical Systems, Milwaukee, WI) was used for postprocessing. The DCE-MRI parameters, including positive enhancement integral (PEI), maximum slope of increase (MSI), maximum slope of decrease (MSD), time to peak (TTP) and ASL parameter blood flow (BF), were calculated, and their corresponding pseudocolored maps were generated automatically.

The ASL images were corrected for motion, and the labeled images was pairwise subtracted from the unlabeled images and then averaged to generate the mean difference image (ΔM). Quantitative BF (f) maps were calculated based on the following equation[20]:

\[ f = \lambda \Delta M R_{1B}/2aM_0 [\exp(-w R_{1B}) - \exp(-(\tau + w)R_{1B})] \]

where \( R_{1B} \) (0.61 s\(^{-1}\) at 3 T) is the longitudinal relaxation rate of blood, \( M_0 \) is the equilibrium magnetization of brain tissue, \( \lambda \) (=0.8) is the tagging efficiency, \( \tau \) (=1.5 s) is the duration of the labeling pulse, \( w \) (=2 s) is the post labeling delay time, and \( \lambda \) (=0.9 g/mL) is the blood/tissue water partition coefficient.

PEI was obtained by calculating the area under the time intensity curve. MSI (or MSD) was calculated with the following formula: MSI or MSD = (SI2-SI1)/t, where SI2 and SI1 represent the signal intensity at 2 different time points in increasing (or decreasing) time intensity curve with the relative maximum ratio, respectively, and t represents the time interval between the 2 time points. TTP was defined as the time point when enhancement could be detected to the time when the maximum signal intensity appeared.

2.4. Visual scoring of NPC on the perfusion maps

Among these DCE-MRI perfusion maps, the PEI map was chosen to be compared with the ASL BF map because of its good reflection of the NPC perfusion level and high image quality. Visual scoring performed by between 2 radiologists (YR Zhao, MD and Y Lu, MD) with 15 and 10 years of experience in head and neck radiology, respectively, and based on a consensus, and the evaluation focused on the perfusion level and outline of NPC revealed on these maps. The visual evaluation of the NPC perfusion level was scored from 0 to 3, where 0 = no contrast to normal peripheral soft tissue, exhibiting as a blue region, 1 = mild contrast to normal peripheral soft tissue, shown as a green region, 2 = moderate contrast to normal peripheral soft tissue, shown as a yellow region, and 3 = pronounced contrast to normal peripheral soft tissue, shown as a red region. The visual
evaluation of the NPC outline was scored from 0 to 2, where 0 = very vague outline, with ill-defined boundaries, 1 = vague outline, with partial ill-defined boundaries, and 2 = clear outline, with well-defined boundaries.

### 2.5. Quantitative perfusion analysis

Regions of interest (ROIs), ranging from 146 to 1414 mm², were manually drawn by the 2 radiologists previously mentioned to cover as much of the tumor as possible on the maximum slice of the NPC while avoiding large vessels and areas of necrosis. Additionally, an oval region of interest, approximately 50 to 100 mm², was placed on the contralateral side of the tumor for a benign area analysis in each patient, except for 20 patients with diffuse lesions with bilateral invasion. The T2-weighted images and DCE images were used as references to assist in identifying the detailed anatomy of the nasopharynx (Fig. 1). A total of 52 NPC and 32 non-NPC areas were used in the analyses. All parameters were measured 3 times at the same site, and the average value was calculated.

### 2.6. Statistical analysis

Normality testing revealed that all parameters had an approximately normal distribution. Mann–Whitney U tests were used to compare the visual score on the perfusion level and outline of the NPC between the ASL and DCE perfusion maps. Independent sample t-tests were used to compare the perfusion values of BF, PEI, MSI, MSD, and TTP in the NPC and non-NPC areas. Receiver operating characteristic (ROC) curves were derived, and the respective cut-off values of each parameter were determined to accommodate the best diagnostic accuracy. The area under the ROC curve (AUC) was used to classify the diagnostic value of each parameter. Notably, $0.5 < \text{AUC} < 0.7$ indicated low accuracy, while $0.7 < \text{AUC} < 0.9$ indicated moderate accuracy, and $\text{AUC} > 0.9$ indicated high accuracy. The correlations between the perfusion parameters obtained with ASL and DCE were assessed using Spearman correlation analysis. All statistical analyses were performed using SPSS (version 21; IBM SPSS, Chicago, IL, USA). A $P$ value < 0.05 was considered statistically significant.

### 3. Results

#### 3.1. Visual scoring of NPC on the perfusion maps

On the BF and PEI maps, the total visual scores of the NPC perfusion level were 110 and 112, respectively (Fig. 2), and the visual scores were the same in 31 patients. There was no significant difference in the visual scores of the NPC perfusion level between the BF and PEI maps ($P = 0.963$).

The BF maps obtained a visual score of 38 for describing the outline of NPC, whereas the PEI maps obtained a score of 71 (Fig. 3). The visual evaluation of the NPC outline was significantly lower with BF maps than with PEI maps ($P < 0.001$).

#### 3.2. Quantitative perfusion analysis

The mean values of the ASL and DCE parameters between the NPC and non-NPC areas are shown in Table 1. Our data demonstrated that BF, PEI, MSI and MSD were significantly lower in the NPC areas compared to the non-NPC areas. Notably, the AUCs for BF, PEI, MSI, and MSD were >0.9, indicating high diagnostic accuracy. The correlations between the ASL and DCE parameters were assessed using Spearman correlation analysis, and the respective $R$ values were calculated.

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**Figure 1.** A 52-yr-old male with newly diagnosed nasopharyngeal carcinoma (NPC) invading the left pharyngeal recess. A region of interest (ROI) was manually drawn around the entire NPC area. An oval ROI was placed within the contralateral side of the non-NPC area. The NPC was shown as a remarkable pseudocolored region in contrast to the surrounding soft tissues on all arterial spin labeling (ASL) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameter maps. (A) T2-weighted images with fat suppression (T2WI-FS) image; (B) ASL blood flow (BF) map; (C) Combination of ASL BF map with a T2WI-FS image; (D) Enhanced T1WI image; (E) Positive enhancement integral (PEI) map; (F) Combination of the PEI map with an enhanced T1WI image. ASL = arterial spin labeling, BF = blood flow, NPC = nasopharyngeal carcinoma, PEI = positive enhancement integral, ROI = region of interest, T2WI-FS = T2-weighted images with fat suppression.
higher in NPC areas than in non-NPC areas \((P < 0.001)\), whereas TTP was significantly lower in NPC areas than in non-NPC areas \((P < 0.001)\). Based on the ROC curves (Fig. 4), the optimal cut-off values (with the respective AUC, sensitivity and specificity) are summarized in Table 2 and were as follows: BF = 42.85 ml/min/100g (0.936, 82.7%, 90.6%); PEI = 724.0 (0.787, 65.4%, 84.4%); MSI = 509.351/s (0.874, 78.8%, 65.6%); and TTP = 190.7s (0.883, 80.8%, 78.5%). On the basis of the AUCs, BF was the most powerful parameter, followed by TTP, MSI, PEI, and MSD.

When all NPC and non-NPC areas were taken into account, significant correlations were observed between BF and PEI \((r = 0.503, P < 0.001)\), MSI \((r = 0.616, P < 0.001)\), and TTP \((r = -0.601, P < 0.001)\). These results were summarized and represented by scatter plots as shown in Fig. 5.

4. Discussion

There are several advantages of applying 3D ASL for NPC, such as a high signal-to-noise ratio (SNR), immunity to field inhomogeneity, and few motion artifacts.\[18,19\] However, few studies have qualitatively or quantitatively assessed the perfusion of NPC. In our study, we first explored the effect of displaying NPC perfusion on a BF map and then compared the perfusion parameters obtained by ASL with those obtained by DCE-MRI, which are usually used to evaluate NPC.

Because of the high vascularity of NPC, hyperperfusion is an important feature. On pseudocolored maps of BF, the regions of NPC are shown in colors ranging from green to red, while normal soft tissues are shown in a blue color. In this study, the BF maps had high similarity with the PEI maps and could be readily applied to displaying NPC perfusion in routine clinical practice. Furthermore, there was no significant difference in the visual score of the NPC perfusion level between the BF and PEI maps. Because of the lower spatial resolution attributed to endogenous

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**Table 1**

| Parameters | NPC (n=53) | Non-NPC (n=33) | t  | P  |
|------------|------------|----------------|----|----|
| BF (ml/min/100 g) | 64.3±21.0  | 29.5±9.7      | 10.280 | <.001 |
| PEI | 725.9±152.6 | 621.4±147.7 | 5.061 |    |
| MSI (1/s) | 710.8±202.4 | 433.3±140.7 | 7.401 |    |
| MSD (1/s) | 70.0±28.6   | 43.9±22.8     | 4.601 |    |
| TTP (s) | 158.7±39.1  | 217.9±29.0    | -7.935 |    |

ASL = arterial spin labeling, BF = blood flow, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, MSI = maximum slope of decrease, NPC = nasopharyngeal carcinoma, PEI = positive enhancement integral, TTP = time to peak.

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contrast agents, the NPC outlines were vaguer on BF maps than on PEI maps. The combination of BF maps with T2WI-FS images could overcome this shortcoming, according to a previous study.\(^\text{[19]}\) Therefore, a BF map provides good contrast between the tumor and nontumor regions in the qualitative diagnosis of NPC.

DCE-MRI is the standard perfusion method applied outside the brain, including for the nasopharynx. Previous studies of DCE-MRI on NPC revealed that this method was promising for diagnosis and staging, therapeutic evaluations, and prognosis prediction.\(^\text{[21−23]}\) Semiquantitative and quantitative methods are the 2 main ways to assess hemodynamic information through DCE-MRI. Although not as accurate as the quantitative method, the semiquantitative method is more straightforward and more feasible in routine clinical practice. In addition, previous studies have demonstrated that semiquantitative perfusion parameters were highly correlated with quantitative parameters in characterizing NPC.\(^\text{[24]}\) Therefore, in our study, semiquantitative DCE-MRI parameters (PEI, MSI, MSD, and TTP) were compared with the ASL BF parameters of NPC.

DCE-MRI could yield multiparametric perfusion values, which have been widely used to investigate changes in vascular physiology at the tissue level. Unlike DCE-MRI, ASL could

### Table 2

| Parameters | Cut-off value | AUC (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-----------|---------------|--------------|----------------------|----------------------|
| BF (mL/min/100 g) | 42.85 | 0.936 (0.887–0.986) | 82.7 (69.2–91.3) | 90.6 (73.8–97.5) |
| PEI | 724.0 | 0.787 (0.682–0.894) | 65.4 (50.6–77.7) | 84.4 (66.5–94.1) |
| MSI (1/s) | 509.35 | 0.874 (0.802–0.947) | 82.7 (69.2–91.3) | 78.1 (59.6–90.1) |
| MSD (1/s) | 47.35 | 0.774 (0.672–0.877) | 78.8 (64.9–88.5) | 65.6 (46.8–80.8) |
| TTP (s) | 150.7 | 0.883 (0.808–0.957) | 80.8 (67.0–89.9) | 87.5 (70.1–95.9) |

ASL = arterial spin labeling, AUC = area under the receiver operating characteristic curve, BF = blood flow, CI = confidence interval, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, MSD = maximum slope of decrease, MSI = maximum slope of increase, PEI = positive enhancement integral, TTP = time to peak.

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**Figure 5.** Scatter plots showing the correlations between ASL (arterial spin labeling) and DCE-MRI (dynamic contrast-enhanced magnetic resonance imaging) parameters. NPC = nasopharyngeal carcinoma; BF = blood flow; PEI = positive enhancement integral; MSI = maximum slope of increase; MSD = maximum slope of decrease; TTP = time to peak.
only provide 1 parameter, BF, to evaluate the BF of tissues. In our study, the BF value was significantly higher in the NPC area than in the non-NPC area; this finding was similar to the results of the semiquantitative DCE-MRI parameters PEI, MSI and MSD and was contrary to TTP, which was significantly lower in NPC areas than in non-NPC areas, suggesting that the ASL BF could reflect the hypervascular property of NPC. Moreover, BF outperformed all other parameters and showed the highest AUC of 0.936 in identifying NPC areas from non-NPC areas; thus, ASL BF was the best indicator of diagnostic efficiency.

Compared to normal tissues, malignant tumors grow more rapidly. For growth, tumors rely on the transport of a large amount of nutrients and oxygen to the tumor site. This nutrient flow is facilitated by the growth of new blood vessels. In contrast to normal blood vessels, the newly generated blood vessels are larger in size and have incomplete vessel walls, leading to increased BF and increased vascular permeability. Therefore, the perfusion level of tumor tissue is significantly higher than that of normal tissue. ASL measures tumor BF, which reflects high perfusion, while the semiquantitative parameters of DCE-MRI provide information about perfusion and capillary permeability. Several previous studies[16–18] on brain tumors have demonstrated a positive linear correlation between ASL BF and dynamic susceptibility contrast (DSC), which is regarded as the gold standard for MR perfusion in brain diseases. Moreover, significant correlations between ASL BF and the quantitative parameters of DCE-MRI (Ktrans, Kep, and veu) were also observed in prostate cancers and clear cell renal cell carcinoma.[25,26] In our study of NPC, the highest positive and negative correlations were found between BF and MSI or TTP. Malignant tumors tend to have higher BF and MSI values and shorter TTP than normal tissues, suggesting that ASL BF can reflect the same tumor angiogenesis as DCE-MRI parameters. Thus, ASL may be helpful in further clinical research, such as in the differential diagnosis between malignant and benign tumors and in the monitoring and follow-up of tumor treatment.

There are several limitations of this study. First, the sample size was relatively small. Second, this study was not grouped by the pathological type or TNM stage of NPC. Third, this study only investigated the correlation between the parameters of 2 perfusion modalities, and a direct comparison between ASL BF and angiogenesis biomarkers was not available. And forth, both ASL and DCE map visual scoring are subjective evaluations of lesions, visual bias would be more likely to happen. Therefore, in the future, we will recruit more patients grouped by pathological type or TNM stage, and direct comparisons with the angiogenesis biomarkers of NPC will be available. In the future, we will recruit more patients grouped by pathological type or TNM stage, and direct comparisons with the angiogenesis biomarkers of NPC will be performed, and also, the ASL vs DCE-MRI map visual scoring should be further performed by blinded individual radiologist reading the films to eliminate visual bias as a confounding factor.

5. Conclusions

In conclusion, the present study demonstrated that 3D ASL could reveal the hyperperfusion of NPC. The ASL BF was significantly correlated with semiquantitative DCE-MRI parameters. As a noncontrast perfusion method, ASL can be used safely and repeatedly in NPC patients to avoid the adverse reactions from contrast agents that may occur during DCE-MRI, especially for patients who need intensive follow-up examinations during radiation therapy.

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