Original Article

Usefulness of Arterial Spin Labeling-Tumor Blood Flow and Dynamic Contrast-Enhanced Perfusion Techniques in Predicting Treatment Response of Nasopharyngeal Carcinoma

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Abstract

OBJECTIVES: To demonstrate the usefulness of arterial spin labeling (ASL)- tumor blood flow (TBF) and dynamic contrast enhancement (DCE) parameters in predicting the treatment response in patients with nasopharyngeal carcinoma (NPC) after 3-months of radiotherapy.

MATERIALS AND METHODS: Ten NPC patients who underwent magnetic resonance imaging (MRI) examinations with both ASL-TBF and DCE techniques before treatment and at the 3-month follow-up after radiotherapy were divided into complete-response (CR) and partial-response (PR) groups according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. The ASL-TBF and DCE parameters of the nasopharynx comprised TBF, Ktrans, IAUGC, Kep, and Ve were analyzed and compared between the two groups.

RESULTS: The CR group had a significantly higher pre-treatment Ve ratio (p = 0.038), a higher post-treatment TBF value (p = 0.038), and a higher post-treatment K trans value (p = 0.067) than the PR group.

CONCLUSION: The ASL-TBF and DCE techniques might be useful tools for the prediction of the treatment responses 3-months after radiotherapy in patients with NPC.

Keywords: arterial spin labeling; dynamic contrast enhancement; MR perfusion; nasopharyngeal carcinoma; perfusion

Primary malignancy of the nasopharynx is common in Thailand, being the second most frequently occurring head and neck cancer.[1] Patients usually consult a doctor when the condition is at its late stage due to its silent symptoms. The disease prognosis depends on the tissue pathology and the staging. The most prevalent pathology is non-keratinizing carcinoma undifferentiated type, WHO type 2B (35%); the second is non-keratinizing differentiated carcinoma, WHO type 2A (32%); the third is keratinizing squamous cell carcinoma, WHO type 1 (31%), while many other tissue subtypes account for the remaining 2% of cases.[2]

An endoscopic biopsy is necessary for the diagnosis of NPC with a 100% specificity and 100% positive predictive value.[3] According to the American Joint Committee on Cancer (AJCC), cross-sectional imaging in nasopharyngeal cancer is mandatory to complete the staging process. MRI often is the study of choice while the Computerized Tomography (CT) is an alternative.[4] MRI provides a better tissue contrast, and gives more detail of the anatomy or tumor involvement. Furthermore, MRI can also more accurately discriminate individual lymph nodes from direct tumor extensions and adjacent normal structures from metastatic lymph nodes.[5]

Dynamic susceptibility contrast (DSC) perfusion MR imaging—the standard method for measuring blood flow—has some limitations in the head and neck regions, including the nasopharynx, as these anatomical

areas are highly vulnerable to susceptibility artifacts. Two magnetic resonance-perfusion (MRP) techniques have recently been recently introduced: ASL and DCE. The ASL is a noninvasive MRI method of measuring perfusion using exogenous water molecules as tracers. Unlike DCE, ASL does not require the injection of gadolinium or any other exogenous contrast material. DCE imaging measures T1 changes in tissues over time after the bolus administration of gadolinium. The ASL and DCE parameters probably reflect tumor permeability and perfusion. Previous study by Fujima et al.[6] showed higher ASL-TBF value indicates a local control during the early pre-treatment period of NPC. DCE parameter difference was found in a short-term local control group compared to non-responder group of NPC after treatment.[7] The physiological processes of a tumor and the effects of its treatment may therefore be evaluated by these parameters.

Using both ASL and DCE for evaluation of treatment response in cases of NPC are new and not well known yet. This study was set out to explore the usefulness of ASL and DCE in predicting the treatment response in our cases of NPC.

Materials and Methods

This prospective study was approved by our institutional review board. Informed consent was obtained from all patients prior to MRI acquisition. Fifteen consecutive patients were collected from June 2019 to Mach 2020. Ten patients with primary NPC underwent MRI examinations before, and 3-months after, their radiotherapy treatment. Patients under the age of eighteen years were precluded from study entry; 5 patients who were lost to follow-up and had no post-treatment imaging were also excluded.

The 10 patients who were eventually enrolled comprised 6 males (60%) and 4 females (40%). All were newly diagnosed, with nine having the nonkeratinizing, undifferentiated subtype, and one with adenoid cystic carcinoma. The tumors were staged according to the tumor, node, metastasis (TNM) staging of Nasopharyngeal Carcinoma (AJCC 8). The local staging was T1 (n = 1), T2 (n = 4), T3 (n = 2), T4 (n = 3), N3 (n = 2), N2 (n = 7), and N0 (n = 1), and all were M0 (n = 10)

The 10 patients received radiotherapy as their primary treatment, with some given concurrent chemoradiation. Before commencing the radiotherapy, a conventional MRI scan with ASL and DCE techniques of the nasopharynx was performed. Three months after the radiation treatment, a second MRI scan with ASL and DCE techniques was performed.

Imaging Techniques

Routine MRI of nasopharynx was performed using a 1.5 Tesla MR scanner (GE Healthcare, Optima MR450W) with a 16-channel neurovascular coil. Post contrast-enhanced T1WI was obtained for each tumor delineation to determine the tumor region of interest. An example of tumor delineation is shown in Figure 1.

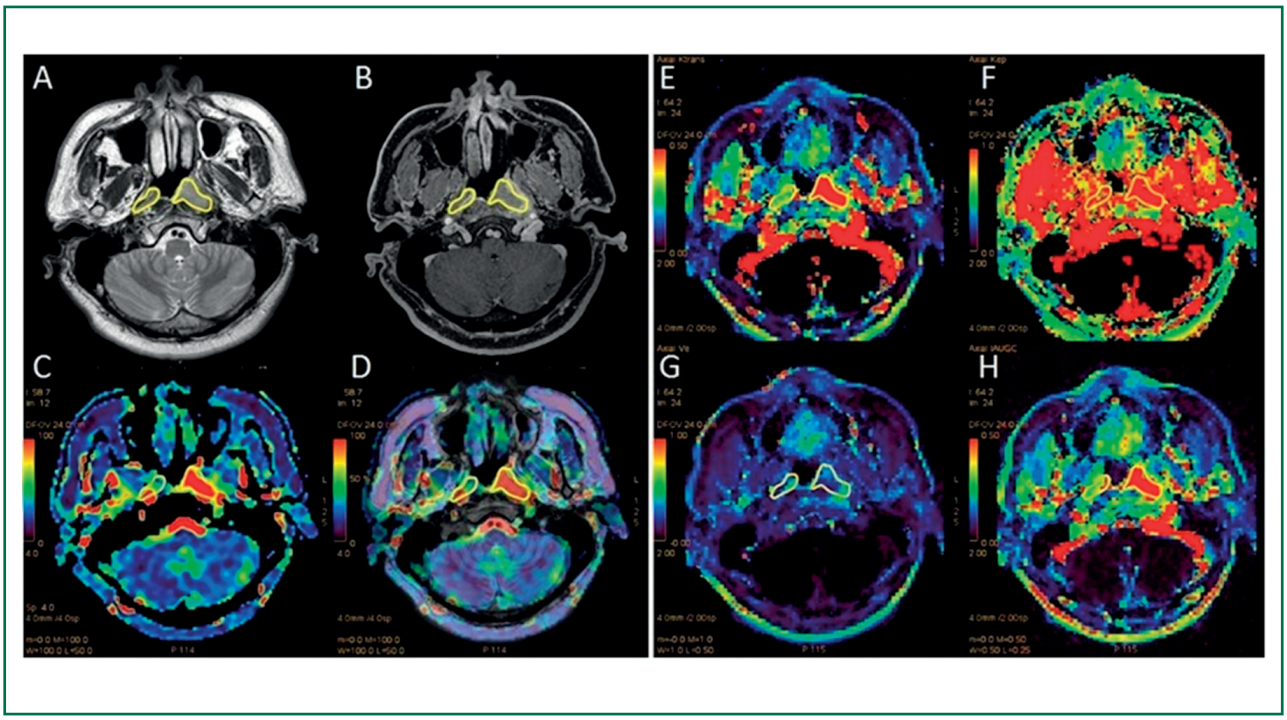

Figure 1: An example of tumor delineation of left NPC and normal right nasopharynx.

A = T2WI; B = T1WI/GD/FS; C = 3D ASL; D = T2WI/3D ASL-FUSION; E = K^{trans}; F = K_{ep}; G = V_e; and H = IAUGC

Acquisition of pseudo-continuous ASL (pcASL) was performed using a 3D spiral fast-spin-echo based sequence. The pcASL sequence used a post-label delay of 1525 ms, TR of 4554 ms, TE of 10.7 ms, FOV of 24 x 24 cm, matrix of 80 x 80 pixels, 30 slices, and slice thickness of 4 mm, with a total scan time of 4.24 minutes.

Acquisition of DCE perfusion was performed using an axial T1 DCE LAVA sequence. The DCE sequence used a TR of 4.4 ms, TE of 1.5 ms, flip angle of 12 degrees, dynamic duration of 6 s, 48 dynamic phases, FOV of 24 x 24 cm, matrix of 180x40 pixels, 30 slices, and slice thickness of 4 mm, with a total scan time of 5.02 minutes.

Criteria of Response

For the imaging analyses, the investigators defined the pre-treatment and post-treatment primary tumors based on freehand drawings along the entire margins of the enhanced areas of the primary tumors, as shown in axial post-gadolinium T1WI images. The responses to the therapy were assessed using Revised RECIST guideline version 1.1 (Table 1).[8] For all target lesions in the pre- and post-treatment imaging, calculations and comparisons were made of the sums of the longest diameter for the primary tumor and the minimal transverse diameter of the nodal lesions. Overall response is assessed in Table 2.

As none of the patients in our study had a stable or progressive disease, we classified them into two groups: "partial response" (PR) and "complete response" (CR).

Statistical Analysis

The Mann–Whitney U test was used to determine statistically significant differences in the values of the ASL-TBF and DCE parameters of the complete- and partial-response groups following treatment. All statistical analyses were performed using IBM SPSS Statistics for Macintosh (version 21; IBM Corp., Armonk, N.Y., USA), and a probability (p) value of < 0.05 was deemed statistically significant.

Table 1: Response criteria (RECIST guideline version 1.1): evaluation of target lesions

Response	Description
Complete response (CR)	• Disappearance of all target lesions. • Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial response (PR)	• At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	• At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). • In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered a progression.)
Stable disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest-sum diameters while on study.

Table 2: Timepoint response: patients with target (+/– non-target) disease (RECIST guideline version 1.1)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR= partial response; SD = stable disease

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Results

Of the ten patients, imaging revealed that four (40%) demonstrated a complete response to the radiation treatment, whereas the remainder (60%) had a partial response. Stable or progressive disease was not observed in any of the patients. Histological proof that none of the six PR patients had residual malignancy was obtained through post-treatment biopsies. There was just fibrosis with necrotic debris or acute/chronic inflammation.

The mean age of the CR group was 49.5 ± 6.1 years, which was noticeably lower than that for the PR group (56.8 ± 14.4 years). Nevertheless, the difference was not statistically significant (p = 0.352).

Table 3 summarizes the means and standard deviations of the ASL-TBF and DCE parameters for each group. Figure 2 graphically illustrates each parameter in the pre-treatment and post-treatment imaging for the CR and PR groups. A graph for each parameter value ratio in the pre-treatment and post-treatment imaging is presented by CR and PR group in Figure 3. Figures 4 and 5 demonstrated cases of no residual tumor and residual tumor at the 3-month follow up.

Compared with the PR group, the Mann–Whitney U test indicated that the CR group had a significantly higher pre-treatment V_e ratio (p = 0.038), a higher post-treatment TBF value (p = 0.038), and a higher post-treatment K trans value (p = 0.067). The other parameters did not reveal any significant differences.

Table 1: Summary of mean ASL and DCE parameters of the lesions, parameter differences of the lesions in pre- and post- treatment imaging, parameter ratios of the lesions, and the contralateral normal side and parameter differences of the lesions and the contralateral normal side in each group (CR VS PR)

pcASL (TBF)		CR (n = 4)	PR (n = 6)	*P*
Lesion				
	Pre-treatment (ml/100g/min)	81.362 ± 21.0975	69.240 ± 34.224	0.257
	Post-treatment (ml/100g/min)	78.497 ± 15.570	51.608 ± 13.286	0.038
Lesion difference				
Lesion (pre-treatment)/ lesion (post-treatment)	(ml/100g/min)	2.865 ± 28.333	17.631 ± 39.143	0.610
Ratio				
Lesion/normal (contralateral)	Pre-treatment	2.343 ± 0.685	1.573 ± 0.594	0.171
Lesion/normal (contralateral)	Post-treatment	1.340 ± 0.278	1.263 ± 0.381	0.914
Difference				
Lesion/normal (contralateral)	Pre-treatment (ml/100g/min)	45.615 ± 17.842	23.006 ± 29.185	1.000
Lesion/normal (contralateral)	Post-treatment (ml/100g/min)	19.735 ± 15.892	8.805 ± 16.991	0.476

K^{trans}		CR (n = 4)	PR (n = 6)	*P*
Lesion				
	Pre-treatment (min-1)	0.598 ± 0.240	0.588 ± 0.293	0.914
	Post-treatment (min-1)	0.183 ± 0.043	0.107 ± 0.060	0.067
Lesion difference				
Lesion (pre-treatment) - lesion (post-treatment)	(min-1)	0.414 ± 0.272	0.481 ± 0.319	0.914
Ratio				
Lesion/normal (contralateral)	Pre-treatment	1.599 ± 0.480	1.821 ± 0.503	0.610
Lesion/normal (contralateral)	Post-treatment	1.049 ± 0.337	0.706 ± 0.610	0.257
Difference				
Lesion - normal (contralateral)	Pre-treatment (min-1)	0.225 ± 0.208	0.256 ± 0.177	0.914
Lesion - normal (contralateral)	Post-treatment (min-1)	0.002 ± 0.053	-0.160 ± 0.318	0.352

IAUGC		CR (n = 4)	PR (n = 6)	*P*
Lesion				
	Pre-treatment (mmol.s)	0.592 ± 0.214	0.608 ± 0.268	0.076
	Post-treatment (mmol.s)	0.270 ± 0.056	0.154 ± 0.091	0.024
Lesion difference				
Lesion (pre-treatment) - lesion (post-treatment)	(mmol.s)	0.321 ± 0.258	0.453 ± 0.266	0.610
Ratio				
Lesion/normal (contralateral)	Pre-treatment	1.656 ± 0.446	1.948 ± 0.638	0.476
Lesion/normal (contralateral)	Post-treatment	1.097 ± 0.254	0.925 ± 0.632	0.476
Difference				
Lesion - normal (contralateral)	Pre-treatment (mmol.s)	0.234 ± 0.169	0.269 ± 0.123	1.000
Lesion - normal (contralateral)	Post-treatment (mmol.s)	0.015 ± 0.057	-0.030 ± 0.119	0.476

K_{ep}		CR (n = 4)	PR (n = 6)	*P*
Lesion				
	Pre-treatment (min-1)	0.764 ± 0.193	0.813 ± 0.291	0.719
	Post-treatment (min-1)	0.326 ± 0.098	0.291 ± 0.125	0.710
Lesion difference				
Lesion (pre-treatment) - lesion (post-treatment)	(min-1)	0.438 ± 0.277	0.521 ± 0.347	0.257
Ratio				
Lesion/normal (contralateral)	Pre-treatment	1.676 ± 0.723	1.837 ± 0.797	0.914
Lesion/normal (contralateral)	Post-treatment	1.202 ± 0.395	1.056 ± 0.423	0.914
Difference				
Lesion - normal (contralateral)	Pre-treatment (min−1)	0.216 ± 0.368	0.308 ± 0.135	0.914
Lesion - normal (contralateral)	Post-treatment (min−1)	-0.085 ± 0.162	-0.079 ± 0.120	0.914

V_e		CR (n = 4)	PR (n = 6)	*P*
Lesion				
	Pre-treatment	0.803 ± 0.146	0.750 ± 0.238	0.476
	Post-treatment	0.619 ± 0.074	0.444 ± 0.170	0.114
Lesion difference				
Lesion (pre-treatment) - lesion (post-treatment)		0.183 ± 0.135	0.306 ± 0.125	0.762
Ratio				
Lesion/normal (contralateral)	Pre-treatment	3.126 ± 1.204	1.437 ± 0.591	0.038
Lesion/normal (contralateral)	Post-treatment	1.505 ± 0.611	1.208 ± 0.511	0.114
Difference				
Lesion - normal (contralateral)	Pre-treatment	0.515 ± 0.227	0.207 ± 0.273	0.114
Lesion - normal (contralateral)	Post-treatment	0.175 ± 0.153	0.065 ± 0.172	0.114

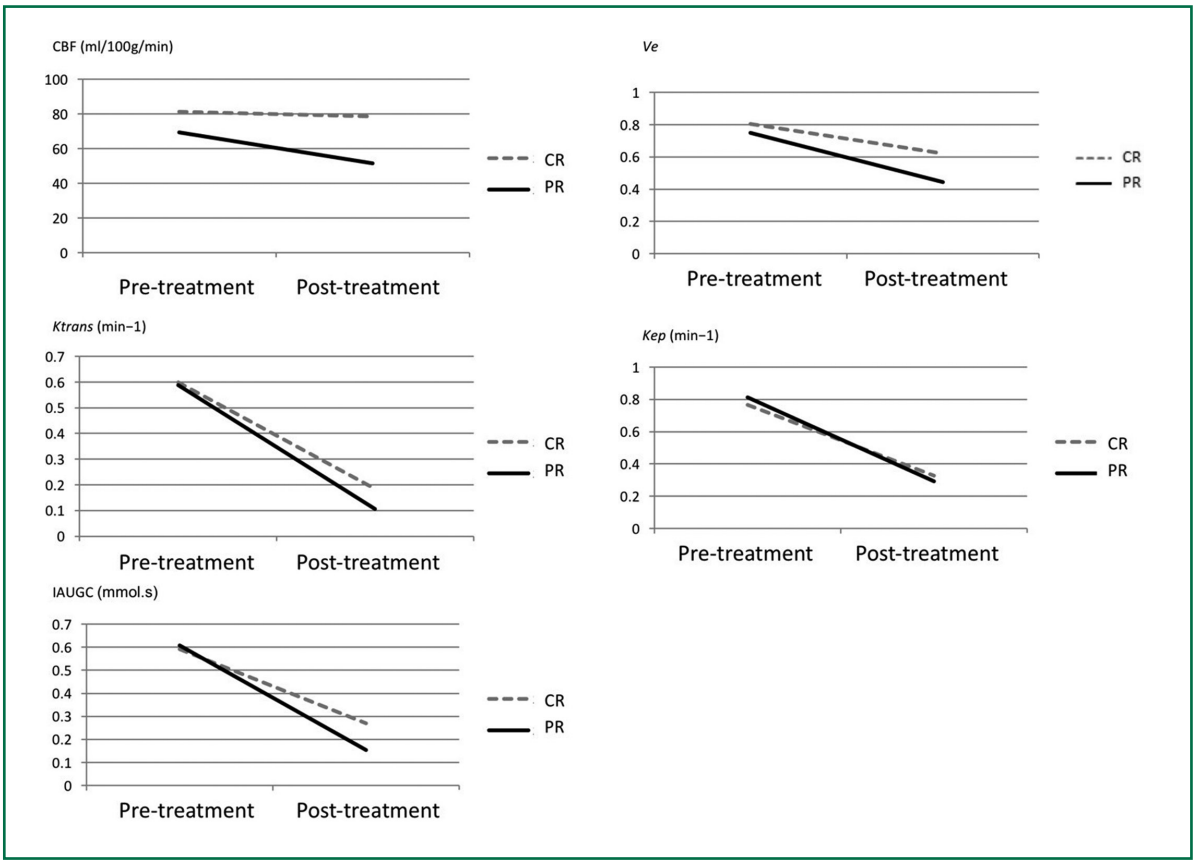

Figure 2: Graphs of each parameter for the CR and PR groups in the pre-treatment and post-treatment imaging.

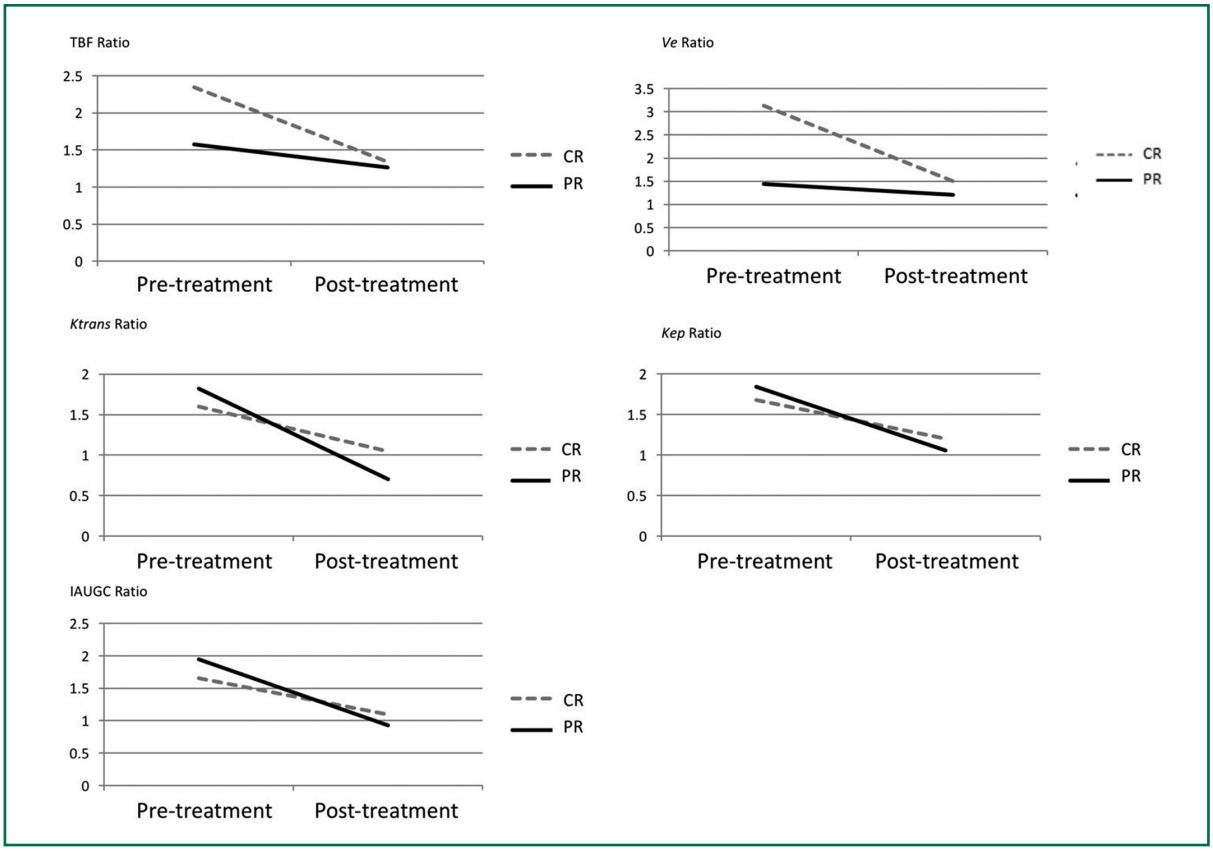

Figure 3: Graphs presenting the ratios of each parameter for the CR and PR groups in the pre-treatment and post-treatment imaging.

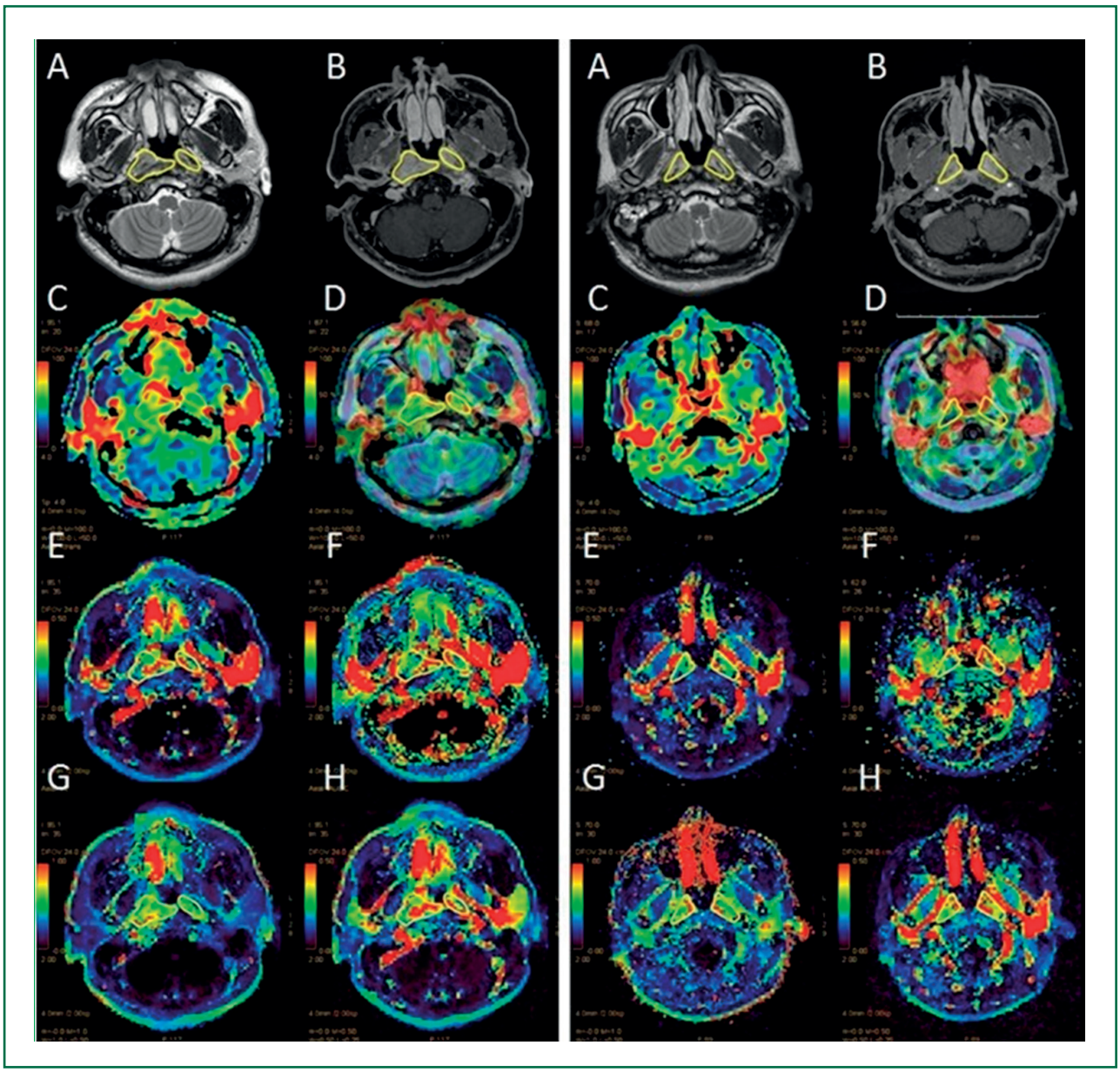

Figure 4A: Pre-treatment images of right nasopharyngeal cancer in the CR group

Figure 4B: Post-treatment images of right nasopharyngeal cancer 3-months after radiotherapy reveal no gross mass.

A = T2WI; B = T1WI/GD/FS; C = 3D ASL; D = T2WI/ASL FUSION; E = K^{trans}; F = K_{ep}; G = V_e; and H = IAUGC

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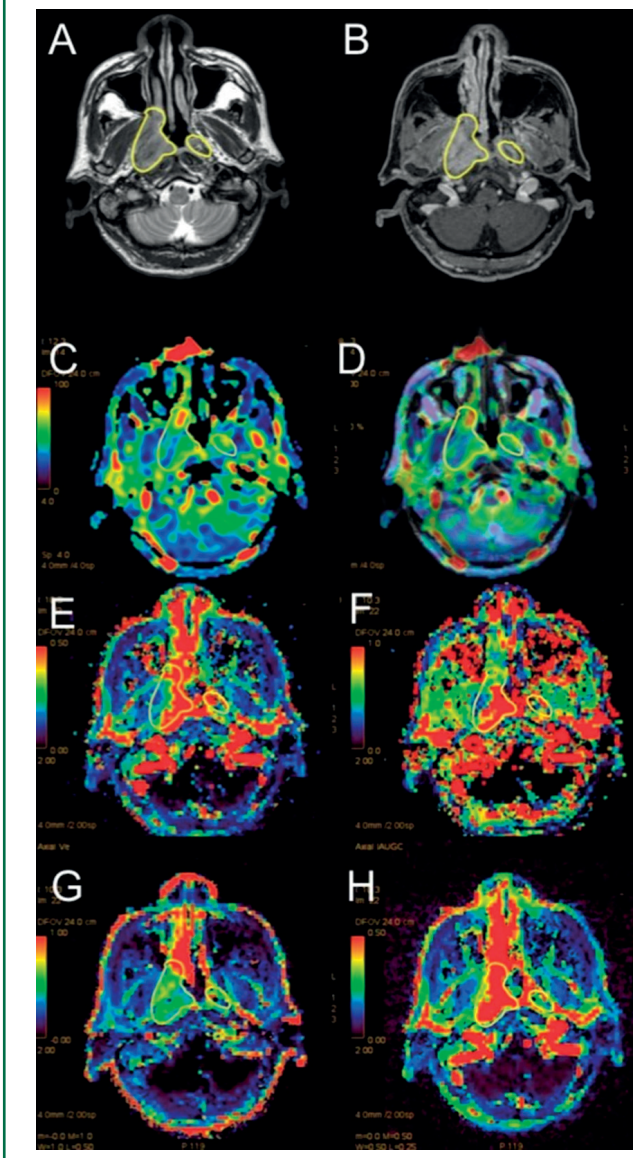

Figure 5A: Pre-treatment images of right nasopharyngeal cancer in the PR group.

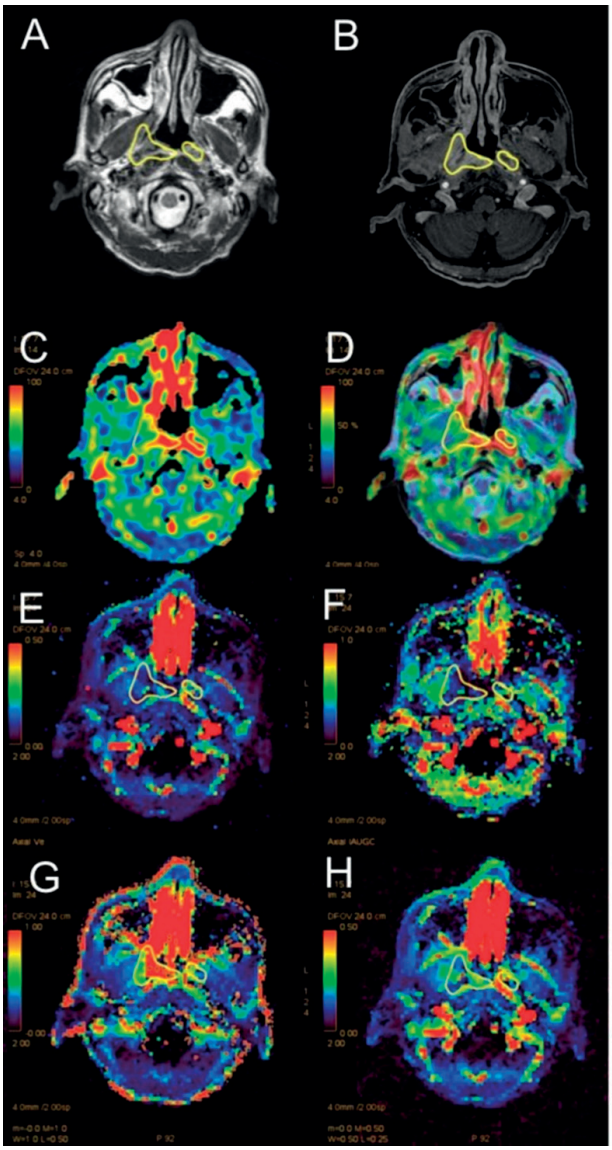

Figure 5B: Post-treatment images of right nasopharyngeal cancer 3-months after radiotherapy reveals a residual enhancing lesion at right nasopharynx.

A = T2WI; B = T1WI/GD/FS; C = 3D ASL; D = T2WI/ASL FUSION; E = K^{trans}; F = K_{ep}; G = V_e; and H = IAUGC

Discussion

ASL determines absolute blood flow by subtraction of labeled blood from the control data without a gadolinium injection, while the DCE imaging measures the T1 changes in the tissue over time after the bolus administration of gadolinium. There are many parameters of DCE, such as K^{trans}, V_e, K_{ep}, and IAUGC (Initial Area Under The Gadolinium Curve). K^{trans} determines the rate of gadolinium influx from plasma into the extravascular extracellular space (EES), which reflects the sum of the blood flow and capillary leakage. Ve refers to the fractional volume of the EES, and it reflects the space available for the accumulation of gadolinium within the tissue interstitium. K_{ep} is the time constant for gadolinium reflux from the EES into the vascular system; it is given by the ratio between the first two parameters ($K_{ep} = K^{trans}/V_e$). IAUGC measures the amount of contrast agent delivered to and retained by the tumor in a given period.[9] The physiological processes of a tumor and the effects of its treatment may therefore be evaluated by these parameters.

Four out of the ten patients (40%) in this study achieved a complete response to the radiotherapy, and the six others (60%) experienced a partial response. Moreover, none of our patients had a stable disease or a progressive disease. These results indicate that the treatment had a high efficacy.

Razek et al.[10] reported that the mean DSC of malignant tumors was significantly higher than that of benign lesions. The researchers also found that a combination of decreased ADC and increased DSC values can differentiate recurrent head-neck cancers (ADC 0.94 ± 0.16 x 10-3 mm^2/s, and DSC% 30.9% ± 5.16%; $p = 0.001$) from post-radiation changes (ADC 1.37 ± 0.12 x 10-3 mm^2/s, and DSC% 12.1% ± 3.06%; $p = 0.001$).[11] Despite these findings, DSC in head and neck cancers is still an unexplored area of research. Consequently, the current study included ASL-TBF and DCE techniques as they are less affected by susceptibility artifacts.

Work by Lin et al.[12] showed that there is significant correlation between TBF (ASL PLD 1500 ms) K^{trans} and K_{ep} in the assessment of perfusion in pre-treatment NPC. As these ASL and DCE parameters are comparable, they could be promising tools for the prediction of treatment response. Consequently, our study utilized both ASL-TBF and DCE techniques.

Our exploratory analysis revealed a decrease in all ASL-TBF and DCE parameters after radiotherapy. This agrees with work by Liao et al.,[13] which showed that the Ktrans value and Kep value of NPC were significantly decreased after the completion of radiotherapy.

On the other hand, our CR results did not show the larger parameter differences found by Zheng et al.[7] Their research revealed a significantly larger K^{trans} difference and K_{ep} difference after treatment in short-term local control (3 days and 40 days), compared with the non-responder group. By contrast, our post-treatment K^{trans} value for the CR group was still higher than that for the PR group. Unlike the study of Zheng and colleagues,[7] however, our study had a 3-month follow-up, and there was a tendency for the values of all parameters to decrease over this extended period. Although Hou J et al. [14] found no significant correlation between DCE-MRI parameters and the treatment response or failure in NPC patients 6-months after chemoradiotherapy.

Our investigation demonstrated the same results as Fujima et al.[6] They suggested that higher pre-treatment TBF values indicate a local control as TBF 81.362 ± 21.0975 ml/100g/min for the CR group, compared with 69.240 ± 34.224 ml/100g/min for the PR group during the early pre-treatment period (mean 19.1 Gy of 70 Gy). Furthermore, a study in Thailand by Tuntiyatorn et al.[15] revealed that elevated permeability, blood flow, and blood volume levels tended to demonstrate a positive correlation with the degree of primary tumor volume reduction within 3-months of the completion of radiotherapy. These values tended to be higher for their "complete response" group than for their "non-response" group, which corresponds with our results. We believe that tumors with a higher level of perfusion and permeability are likely to be better oxygenated and therefore more sensitive to radiation. The pre-treatment TBF, K^{trans} , and Ve values for our CR group were higher than those for the PR group, but without statistical significance. Still, there were significant differences in the pre-treatment V_e ratios ($p = 0.038$), post-treatment TBF values ($p = 0.038$), and post-treatment K^{trans} values ($p = 0.067$). The increase in the V_e ratio might indicate that the increase in the extravascular, extracellular space was higher in the CR group than the PR group, possibly because of a loosening of tissue due to tumor shrinkage. In contrast with the work by Tuntiyatorn and colleagues,[15] in which decreased TBF and Ktrans were found in the CR group, our study revealed increased post-treatment TBF and Ktrans levels. As this might have been the result of temporary angiogenesis secondary to inflammatory process after the radiation treatment, long-term follow-up is needed.

Songsaeng et al.[16] also demonstrated that, based on perfusion CT parameters two years after radiotherapy, a local recurrence/residual group showed statistically significant higher blood flow, blood volume, and permeability-surface values than a nonlocal recurrence/residual group. If there is a focal increased perfusion parameter which might reflect local recurrence, we must therefore be careful to correlate with the clinical contexts and obtain a tissue biopsy when indicated. In our study, all patients in the PR group underwent a tissue biopsy; however, none of the biopsies revealed a definite recurrent tumor.

We also used T2WI/ASL fusion images to delineate the NPC volume along with T1WI/GD/FS, as done by Lin et al.[17] Their research demonstrated that the utilization of T2WI-FS/ASL fusion images can overcome the limitations of a poor anatomy definition to evaluate the tumor extent. When combined with T1WI/GD/FS, the delineation of the NPC volume is more evident than using T1WI/GD/FS alone.

Furthermore, we did not correlate the parameters with the clinical stage due to the small number of patients. Zheng et al.[18] had previously demonstrated that both K^{trans} and K_{ep} of pre-treatment NPC showed moderate negative correlations with the clinical stage, T stage, and N stage, whereas V_e showed a moderate positive correlation with those stages.

One limitation of our study was the small number of patients. There might also have been confounding factors for the treatment results of each patient due to the different tumors, nodes, and metastatic staging, including variations in the treatments and disease prognoses. Although we followed up at 3-months, which is quite a short period, we plan to continue our work and assess the treatment responses over a follow-up period of 1–2 years. We assessed only the primary tumor and did not assess the associated cervical lymph node. A future study could also focus on the lymph node, which might demonstrate changes.

Conclusion

Changes in various ASL and DCE parameters might reflect different physiological processes. The higher pre-treatment V_e ratios and the higher post-treatment ASL-TBF and K^{trans} values suggest that they are promising tools for differentiating between complete and partial responses to radiation therapy.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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