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FULL PAPER

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for pretreatment prediction of neoadjuvant chemotherapy response in locally advanced hypopharyngeal cancer

¹WEI GUO, MD, ²YA ZHANG, MD, ²DEHONG LUO, MD, ¹HUISHU YUAN, MD and On behalf of

¹Department of Radiology, Peking University Third Hospital, Beijing, 100191, China

²Department of Diagnostic Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Address correspondence to: Mr Dehong Luo

E-mail: cjr_luodehong@163.com

The authors Dehong Luo and Huishu Yuan contributed equally to the work.

Objective:

The aim of this study was to predict response to neoadjuvant chemotherapy (NAC) in patients with locally advanced hypopharyngeal cancer by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Methods:

A retrospective study enrolled 46 diagnosed locally advanced hypopharyngeal cancer. DCE-MRI were performed prior to and after two cycles of NAC. The volume transfer constant (K^{trans}), extracellular extravascular volume fraction (V_e), and plasma volume fraction (K_{ep}) were computed from primary tumors. DCE-MRI parameters were used to measure tumor response according to the Response Evaluation Criteria in Solid Tumors criteria (RECIST).

Results :

After 2 NAC cycles, 30 out of 46 patients were categorized into the responder group, whereas the other 16 were categorized into non-responder group. Compared with the pretreatment value, the post-treatment K^{trans} and K_{ep} was significantly lower ($P < 0.05$), but no significant change in V_e ($P > 0.05$). Compared with non-responders,

a notably higher pretreatment K^{trans} , K_{ep} , lower post-treatment K^{trans} , higher ΔK^{trans} and ΔK_{ep} were observed in responders (all $P < 0.05$). While the pretreatment V_e , post-treatment V_e , and ΔV_e did not differ significantly ($P > 0.05$) between the two groups. The receiver operating characteristic curve analysis revealed that pretreatment K^{trans} of 0.202/min is the most optimal cut-off in predicting response to chemotherapy, resulting in an AUC of 0.837 and corresponding sensitivity and specificity of 76.7%, and 81.1%, respectively.

Conclusion:

DCE-MRI especially pretreatment K^{trans} can potentially predict the treatment response to neoadjuvant chemotherapy for hypopharyngeal cancer.

Advances in knowledge:

Few studies of DCE-MRI on hypopharyngeal cancer treated with chemoradiation reported. The results demonstrate that DCE-MRI especially pretreatment K^{trans} may be more potential value in predicting the treatment response to neoadjuvant chemotherapy for hypopharyngeal cancer.

INTRODUCTION

Hypopharyngeal cancer constitutes less than 5% of all malignancies in the head and neck tumors.¹ Nearly 80% of hypopharyngeal cancer arise from pyriform sinus, whereas the other 20% arise from the posterior pharyngeal wall and the post-cricoid region.² Due to high rates of regional relapse and distant metastasis, the overall survival of hypopharyngeal cancer is unfavorable.² The local recurrent rate and distant metastasis might be reduced by

neoadjuvant chemotherapy (NAC).^{3–5} Although NAC is not a conventional treatment regimen for patients with locally advanced hypopharyngeal cancer, it may serve as a prognostic tool with potential to evaluate early treatment response. Chemoradiotherapy resistance is the main cause of tumor recurrence.² Thus, it is necessary to elucidate reliable predictive imaging biomarkers for treatment outcomes, and to avoid continuation of ineffective treatment and

Table 1. DCE in predicting HNSCC tumor response to CRT

Study	Tumor site	AJCC stage	No. patients	Assessed	Tracer kinetic models	Correlation with DCE-MRI parameters
Ng et al. ⁸	OH	II-IVB	58	Primary tumor	Quantitative (Tofts model)	Higher pretreatment K^{trans} in local control group than in local failure group
Kim et al. ⁹	L,OC,OP	IV	33	Largest lymph node metastasis	Quantitative (SSM)	Lower pretreatment K^{trans} in PR group than in CR group
Chawla et al. ¹¹	OP,L,NP,HP,UKP	II-IVB	57	Largest lymph node metastasis	Quantitative (SSM)	Lower pretreatment K^{trans} correlated with shorter DFS

CRT, chemoradiotherapy; DFS, disease-free survival; HP, hypopharynx; L, larynx; NP, nasopharynx; OC, oral cavity; OH, oropharynx and hypopharynx; OP, oropharynx; SSM, shutter speed model (based on the Tofts model); UKP, unknown primary.

guide adaptation of therapy based on response.⁶ These imaging biomarkers may help in stratifying patients who would benefit from chemoradiation therapy from those who would not. For non-responders, initial treatment strategies should be adjusted. So, it is meaningful to assess the treatment response of NAC to optimize an individual therapeutic regimen.

Dynamic contrast-enhanced MRI (DCE-MRI) is a functional imaging technique that allows measuring tumor microvasculature.⁷ Recently, predictive DCE-MRI imaging to assess tumor hypoxia or tumor perfusion prior to therapy in various tumor types, including head and neck tumors have shown favorable outcomes for HNSCC with high blood perfusion.⁸⁻¹⁸ To our knowledge, few studies of DCE-MRI on hypopharyngeal cancer treated with chemoradiation reported.¹⁹⁻²¹ The present study was therefore designed to evaluate the potential of DCE-MRI parameters (K^{trans} , K_{ep} , and V_e) in predicting the local treatment response of neoadjuvant chemotherapy in locally advanced hypopharyngeal cancer.

Figure 1. A 67-year-old male with left pyriform sinus carcinoma with good response to neoadjuvant chemotherapy. (a) Transverse T_2 weighted imaging. (b) Transverse post-contrast enhanced T_1 weighted imaging. (c-e) The pretreatment K^{trans} , K_{ep} , and V_e values were 0.312/min, 0.397/min and 0.786 in responder, respectively. (f) Transverse T_2 weighted imaging show that the mass disappeared completely after two cycle NAC. NAC, neoadjuvant chemotherapy.

METHODS AND MATERIALS

Patients

Theretrospective study was approved by the institutional review board, and the requirement for informed consent was waived. The inclusion criteria were a confirmed diagnosis of N2M0 or N3M0 squamous cell carcinoma (SCC), clinically staged as the Stage III or IV according to the seventh edition of American Joint Committee on Cancer Classification (AJCC),²² and have received two whole cycles of NAC. The exclusion criteria were severe image artifact and the maximum diameter of primary lesions <1.0 cm. The study group composed of 46 patients (44 males and 2 females; mean age 57.32 ± 12.11 years) between March 2017 and October 2018. At initial presentation, the location of the primary tumors was pyriform sinus ($n = 37$), posterior pharyngeal wall ($n = 6$), and the post-cricoid region ($n = 3$).

Neoadjuvant chemotherapy regimen included paclitaxel (270 mg/m² of body-surface area, for Day 1), followed by intravenous cisplatin (40 mg/m², for days 1–2). Response was evaluated approximately 3 weeks after the second cycle of chemotherapy. Patients were classified as responders, or non-responders according to the RECIST Criteria.²³

MR protocol

Head and neck MRI exam was conducted on a 3.0 T scanner (GE Healthcare, Discovery 750, USA, Milwaukee, Wis) equipped with an 8-channel neurovascular phased-array coil. All the enrolled subjects received the following conventional MRI sequences: axial T_1 weighted imaging with fast spin echo (Ax T_1 WI-FSE): repetition time/echo time (TR/TE) = 660/9.3 ms, field of view (FOV) = 260×260 mm², reconstruction matrix = 960×960, slice number = 30, slice thickness/gap = 4/0.4 mm; axial T_2 weighted imaging with fast spin echo (Ax T_2 WI-FSE): TR/TE = 5760/88.3 ms, FOV = 260×260 mm², reconstruction matrix = 960×960, slice number = 30, slice thickness/gap = 4/0.4 mm. DCE-MRI was performed using LAVA-XV sequence (liver acquisition with volume acceleration-extended volume). To minimize the inflow effect from carotid arteries, a spatial saturation slab was implanted below the acquired region. The DCE-MRI parameters were: TR/TE of 2.8/1.3 ms, FOV of 26 cm², 108 × 128 matrix, temporal resolution = 7 s/dynamic, slice thickness/gap = 4.2/0 mm, FA of 15°, and receiver bandwidth of 510 Hz/pixel. This sequence was repeated 60 times and total scan time was approximately 420 s.

Table 2. MR protocol

MR sequences	TR/TE	FOV	Matrix	Thickness/gap	Temporal resolution	Phase	TA
Ax T1WI-FSE	660/9.3 ms	260 × 260 mm ²	960 × 960	4/0.4 mm	-	-	123 s
Ax T2WI-FSE	5760/88.3 ms	260 × 260 mm ²	960 × 960	4/0.4 mm	-	-	89 s
Ax LAVA-XV	2.8/1.3 ms	26 cm ²	108 × 128	4.2/0 mm	7 s/dynamic	60	420 s
Ax FSPGR	295/2.86 ms	260 × 260 mm ²	960 × 960	4/0.4 mm	-	-	117 s

ET, echo time; FOV, field of view; FSPGR, fast spoiled gradient-echo; LAVA-XV, liver acquisition with volume acceleration-extended volume; RT, repetition time; TA, acquisition time.

Before the contrast media injection, the mask series with three different flip angles (*i.e.* 5°, 10° and 15°) were performed. While the imaging continued, Gadodiamide injection (Omniscan, GE Healthcare Ireland) was intravenously injected at a dose of 0.1 mmol/kg of body weight with a rate of 2.0 ml s⁻¹, followed by a 20 ml saline flush with a power injector.

Patients were instructed to take codeine for oral administration before the MRI scanning in order to relieve cough-induced motion artifacts. Following the DCE-MRI scan, post-contrast enhanced anatomical *T*₁ weighted images were acquired as a part of the routine clinical examination. All patients underwent two MRI studies, first study was prior to any treatment at the baseline and second study was performed within 3 weeks after completion of two cycles (42 days) neoadjuvant chemotherapy.

Image and data analysis

DCE-MRI data were processed using GenIQ software installed on GE advanced workstation (GE Healthcare, Milwaukee, WI), on basis of two-compartment pharmacokinetic model proposed by Tofts et al.²⁴ The arterial input function (AIF) and T1-mapping

were automatically calculated by the software and determined from the following equations²⁴:

$$\{d C_t/dt = K^{trans}C_p - K_{ep}C_t \quad (1)$$

$$C_t(t) = K^{trans} [C_p(t) \otimes e^{-(Kt)}] \quad (2)$$

$K_{ep} = K^{trans}/V_e$ (3) where $d C_t/dt$ is the integration of concentration with time, K^{trans} as the volume transfer constant of the contrast agent from Vascular space (*vs*) to Extravascular extra-cellular space (EES), C_p as the plasma tracer concentration, K_{ep} as the rate transfer constant of the contrast agent from EES to *vs*, C_t as the concentration of contrast agent in the tissue, $\otimes$ as the calculation of convolution, and V_e as the volume of EES per unit volume of the contrast agent in the tissue}.

DCE-derived parameters were calculated and measured blindly by two independent radiologists with 10 year experience in head and neck imaging. The ROIs were drawn encompassing the visually solid portion of the primary tumors while avoiding necrotic,

Table 3. General characteristics of the study patients (*n* = 46)

Parameters	Responders	Non-responders	<i>P</i>
	(<i>n</i> = 30)	(<i>n</i> = 16)	
Age(years)	55.27 ± 13.02	56.18 ± 10.33	0.8704
Sex(<i>n</i> ,%)			
Male	(28,60.9)	(16,34.8)	0.2373
Female	(2, 4.3)	(0, 0.0)	
Subsites(<i>n</i> ,%)			0.4621
Pyiform sinus	(25,54.3)	(12,26.1)	
Posterior pharyngeal	(3,6.5)	(3,6.5)	
post-cricoid region	(2, 4.3)	(1,2.2)	
Tumor maximum diameter	3.02 ± 1.64 cm	2.83 ± 1.20 cm	0.3372
Stage(<i>n</i> ,%)			0.5271
III	(5,10.9)	(3,6.5)	
IVA	(14,30.4)	(7,15.2)	
IVB	(11,23.9)	(6,13.0)	
$K^{trans}(\text{min}^{-1})$	0.261 ± 0.070	0.178 ± 0.359	0
K_{ep}	0.392 ± 0.089	0.323 ± 0.070	0.01
V_e	0.707 ± 0.298	0.574 ± 0.161	0.105

Table 4. Neoadjuvant chemotherapy response correlation with DCE-MRI parameters in hypopharyngeal cancer

Group	Parameters		
	$K^{trans} (/min)$	$K_{ep} (/min)$	V_e
Responders($n = 30$)	0.179 ± 0.055	0.291 ± 0.076	0.663 ± 0.314
Non-responders($n = 16$)	0.147 ± 0.030	0.267 ± 0.081	0.610 ± 0.250
t	2.131	0.962	0.585
P	0.039	0.341	0.562
Pretreatment($n = 46$)	0.232 ± 0.072	0.368 ± 0.089	0.660 ± 0.264
Post-treatment($n = 46$)	0.168 ± 0.050	0.282 ± 0.077	0.645 ± 0.291
t	7.952	9.202	0.433
P	0.000	0.000	0.667

K_{ep} , the rate transferconstant of the contrast agent from EES to VS; K^{trans} , the volume transfer constant of the contrast agent from Vascular space (VS) to Extra-vascular extracellularspace (EES); V_e , the volume of EES per unitvolume of the contrast agent in the tissue.

p -value for the comparison of DCE-MRI values was calculated using unpaired Student's t test or paired Student's t test.

cystic, and hemorrhagic areas. We delineated three ROIs in each tumor on one slice and the average value of all parameters over all three ROIs was used for analysis, and the results showed only average values.

Statistical analysis

The data were analyzed using SPSS (v. 20.0; IBM SPSS; Chicago, IL), with a 2-tailed probability value, a $p < 0.05$ was considered statistically significant. Kolmogorov–Smirnov tests were used to assess the nature of data distributions.

The statistical method of unpaired t test, paired t test and the receiver operating characteristic (ROC) curve analysis were done for estimating predictive capability of DCE-MRI parameters.

RESULTS

Between March 2017 and October 2018, a total of 46 patients of locally advanced hypopharyngeal cancer were enrolled. Based on the RECIST criteria, after two NAC cycles, 30 out of 46 patients were categorized into the responder group (2 female and 28 male; mean age 56.18 ± 10.33 years; tumor site: 25 pyriform sinus, 3 posterior pharyngeal wall, 2 post-cricoid region, Figure 1, Table 1) whereas the other 16 were categorized into non-responder group (0 female and 16 male; mean age 56.18 ± 10.33 years; tumor site: 12 pyriform sinus, 3 posterior pharyngeal wall, 1 post-cricoid region, Table 1). All of our 46 patients had advanced stage disease: for responders, 5 (10.9 %) were Stage III, 14 (30.4 %) in Stage IVA and 11 (23.9%) in Stage IVB; for

Table 5. Changes of DCE-MRI values between before and after treatment

Group	Parameters		
	$\Delta K^{trans} (/min)$	$\Delta K_{ep} (/min)$	ΔV_e
Responders($n = 30$)	0.082 ± 0.057	0.102 ± 0.066	0.107 ± 0.203
Non-responders($n = 16$)	0.031 ± 0.030	0.056 ± 0.045	0.063 ± 0.110
t	3.349	2.485	0.795
P	0.002	0.017	0.431

p -value for the comparison of means was calculated using unpaired Student's t test.

Table 6. The predictive values of DCE-MRI for differentiation of responders from non-responders

Parameters	Cut-off	AUC	Sensitivity	Specificity	Youden index
Pre- K^{trans}	0.202	0.837 (95%CI, 0.708 ~ 0.944)	76.7	81.1	0.578
Pre- K_{ep}	0.348	0.745 (95%CI, 0.593 ~ 0.896)	66.7	75	0.417
Post- K^{trans}	0.173	0.696 (95%CI, 0.546 ~ 0.845)	63.3	75	0.383
ΔK^{trans}	0.045	0.826 (95%CI, 0.713 ~ 0.962)	63.3	83.5	0.468
ΔK_{ep}	0.091	0.725 (95%CI, 0.575 ~ 0.875)	53.3	87.5	0.408

AUC, area under curve; K^{ep} , (/min); K^{trans} , (/min).

Sensitivity: % Specificity: % Youden index : Sensitivity+ Specificity-1.

Figure 2. ROC curves for differentiation of responders from non-responders based on the DCE-MRI values. ROC, receiver operating characteristic; DCE, dynamic contrast-enhanced.

non-responders, 3 (6.5 %) were Stage III, 7 (15.2 %) in Stage IVA and 6 (13.0%) in Stage IVB. For primary tumors, the pretreatment K^{trans} and K_{ep} value in responders was significantly higher than in non-responders ($p = 0.000, 0.010$; Table 1), whereas the pretreatment V_e had no significant changes ($p = 0.105$; Table 1).

For primary tumors, the post-treatment K^{trans} in responders was significantly lower than in non-responders ($p = 0.039$, Table 2), whereas the post-treatment K_{ep} and V_e between them had no significant changes ($p = 0.341, 0.562$; Table 2). For primary tumors, the K^{trans} and K_{ep} in post-treatment group was significantly lower than in pretreatment group ($p = 0.000, 0.000$; Table 3), whereas the V_e had no significant changes ($p = 0.667$; Table 3). For primary tumors, the ΔK^{trans} and ΔK_{ep} in responders was significantly higher than in non-responders ($p = 0.002, 0.017$; Table 4), whereas the ΔV_e had no significant changes ($p = 0.431$; Table 4). The ROC curve analysis revealed that pretreatment K^{trans} of 0.202/min is the most optimal cutoff in predicting response to chemotherapy, resulting in an AUC of 0.837 and corresponding sensitivity and specificity of 76.7%, and 81.1%, respectively (Tables 5 and 6; Figure 2).

DISCUSSION

Our study showed that the post-treatment K^{trans} and K_{ep} was significantly lower than the pretreatment value, however no significant change in post-treatment V_e was observed. Compared with non-responders, the higher pretreatment K^{trans} , K_{ep} and lower post-treatment K^{trans} , and higher ΔK^{trans} , ΔK_{ep} were observed in responders, but no significant change in ΔV_e . The ROC analysis revealed that pretreatment K^{trans} was the most optimal DCE-MRI parameter for predicting responders. It can best classify patients when the cut-off was 0.202/min, achieving an AUC of 0.837 and sensitivity of 76.7 and specificity of 81.1%.

The two-compartment model of Tofts has been widely adapted in DCE-MRI, which gives rise to three quantitative parameters including V_e , K^{trans} , and K_{ep} .²⁴ K^{trans} and K_{ep} are the main perfusion parameter which are dominated by tumor blood flow and micro-vascular permeability.²⁴ In the current study, patients with disease responsive to NAC had significantly higher pretreatment K^{trans} and K_{ep} than non-responders. We also observed higher ΔK^{trans} and ΔK_{ep} values from primary tumors of responders in comparison with non-responders. Our results and those of earlier published reports support the notion that tumors with a high perfusion status might closely better to a good response.^{25–32} Lowe et al²⁹ reported that high pretreatment tumor perfusion evaluated using pretreatment DCE-MRI imaging in HNSCC predicts a good response to neoadjuvant chemotherapy. Kim et al⁹ reported that a higher pretreatment K^{trans} in primary cancer may predict good treatment response in patients with HNSCC underwent chemoradiation, which both agreed with our results. In addition, DCE-MRI parameters can also be confounded by tumor's heterogeneity, observation window in the early chemotherapy period, and tumors therapy regimens, which can affect the result.

V_e reflects the EES, which is balanced in both size and shape to provide adequate supply of nutrients and oxygen to the tissue under normal physiological condition.²⁴ In contrast, tumor tissues have a large interstitial space, higher collagen concentration, higher interstitial fluid pressure.²⁷ This study didn't reveal a significant difference in V_e between responders and non-responders in an agreement of some previous studies.^{15,18} In contrast, other studies have reported a favorable outcome for chemotherapy-treated osteosarcoma patients.¹⁷ Collectively, these studies imply that V_e may not be a reliable biomarker in patients with hypopharyngeal cancer who underwent NAC.

Our study has limitations that need to be mentioned. First, our study mainly evaluated the short-term response rather than the long-term survival outcomes. Second, the sample size of this study was relatively small. In addition, the intrinsic limitations of DCE-MRI in head and neck imaging were still challenging. Although patients were instructed to take codeine for oral administration before the MRI scanning in order to relieve cough-induced motion artifacts. Finally, individual AIF values was quite difficult to measure, which may have affected the pharmacokinetic parameters.

CONCLUSION

DCE-MRI parameters enabled identification of non-responders at higher risk for treatment failure-thus allowing timely shifts in treatment strategies. Pretreatment K^{trans} , and K_{ep} were significant in predicting responders. The DCE-MRI parameters, especially pretreatment K^{trans} show promise as a imaging biomarker in predicting the NAC response for locally advanced hypopharyngeal carcinoma.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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