RESEARCH ARTICLE

Dynamic Contrast-enhanced Magnetic Resonance Imaging for Differentiating Between Primary Tumor, Metastatic Node and Normal Tissue in Head and Neck Cancer

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Abstract: Objective: To study the difference of the Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) parameters among the primary tumor, metastatic node and peripheral normal tissue of head and neck cancer.

Materials and Methods: Consecutive newly-diagnosed head and neck cancer patients with nodal metastasis between December 2010 and July 2013 were recruited, and 25 patients (8 females; 24-63, mean 43±11 years old) were enrolled. DCE-MRI was performed in the primary tumor region including the regional lymph nodes on a 3.0-T MRI system. Three quantitative parameters: \( K^{\text{trans}} \) (volume transfer constant), \( v_e \) (volume fraction of extravascular extracellular space) and \( k_{ep} \) (the rate constant of contrast transfer) were calculated for the largest node. A repeated-measure ANOVA with a Greenhouse-Geisser correction and post hoc tests using the Bonferroni correction were used to evaluate the differences in \( K^{\text{trans}} \), \( v_e \) and \( k_{ep} \) among primary tumors, metastatic nodes and normal tissue.

Results: The values of both \( K^{\text{trans}} \) and \( v_e \) of normal tissue differed significantly from those of nodes (both \( P < 0.001 \)) and primary tumors (both \( P < 0.001 \)) respectively, while no significant differences of \( K^{\text{trans}} \) and \( v_e \) were observed between nodes and primary tumors (\( P = 0.075 \) and 0.365 respectively). The \( k_{ep} \) values of primary tumors were significantly different from those of nodes (\( P = 0.001 \)) and normal tissue (\( P = 0.002 \)), while no significant differences between nodes and normal tissue (\( P > 0.999 \)).

Conclusion: The DCE-MRI parameters were different in the tumors, metastatic nodes and normal tissue in head and neck cancer. These findings may be useful in the characterization of head and neck cancer.

Keywords: Head and neck cancer, dynamic contrast-enhanced magnetic resonance imaging, primary tumor, nodal metastasis, normal tissue, quantitative analysis.

1. INTRODUCTION

Head and neck cancer, especially nasopharyngeal carcinoma, is an aggressive cancer type commonly found in Southern China. Regardless of the status of the primary lesion, nodal metastasis is a significant prognostic factor for survival [1]. Hence the accurate detection and characterization of primary tumor and metastatic nodes are of paramount importance in patient management. The gold standard for nodal metastasis has been pathologic verification of needle biopsies and/or long-lasting clinical or radiographic follow-up of suspected nodes [2]. However, needle biopsy is unable to provide the information of the whole node, while follow-up requires a long period, and more importantly, would delay the possible treatment before confirmation of metastasis. Thus, radiographic imaging is able to provide useful information as it can diagnose metastatic nodes and differentiate the primary tumor and metastatic node from normal tissues.

As a kind of Magnetic Resonance Imaging (MRI), Dynamic Contrast-Enhanced MRI (DCE-MRI) may play a key role as a useful biomarker in the studies of cancer. The three
quantitative parameters $K_{trans}$, $v_e$ and $k_p$ derived by DCE-MRI are frequently used. $K_{trans}$ (in minute$^{-1}$) is the volume transfer constant of contrast agent from blood plasma to Extravascular Extracellular Space (EES) reflecting both blood plasma flow and permeability; $v_e$ is the volume of EES per unit volume of tissue and $k_p$ (in minute$^{-1}$) is the flux rate constant of contrast agent from EES to plasma and equal to $K_{trans} / v_e$ [3]. Studies have found DCE-MRI to be useful in differentiating diseased nodes from normal nodes in Head and Neck Squamous Cell Cancer (HNSCC), breast cancer, and cervical cancer [4-6]. In breast cancer, it was found that the 100% increase of DCE-MRI signal intensity in nodes has an accuracy of 83% in differentiating axillary Lymph Node (LN) metastases [7]. In such studies, in the malignant nodes the microvascular permeability and the extravascular extracellular space could be increased. However, no studies have been performed about the differentiation between tumor, metastatic node and normal tissue in head and neck cancer.

It has been shown that DCE-MRI by semi-quantitative and quantitative methods is useful in characterizing the neovasculature and permeability of Nasopharyngeal Carcinoma (NPC) [8]. In this study, the perfusion parameters were found to be higher in high stage tumors. However, it is still unclear whether and how DCE-MRI can differentiate between primary tumor, metastatic nodes and normal tissue. Studies have been performed to investigate the usefulness of several imaging techniques, Including Intravoxel Incoherent Motion Imaging (IVIM), Diffusion Weighted Imaging (DWI), and Computed Tomography (CT) perfusion for nodal characterization in head and neck cancer [9-11]. However in these studies only the difference between primary tumor and metastatic nodes, or between normal and metastatic nodes, were studied. In the present project, we aimed to study the difference of DCE-MRI parameters between primary tumor, metastatic nodes and normal tissue. We hypothesized that the DCE-MRI parameters in nodes and in primary tumor are higher than those in normal tissue.

2. MATERIALS AND METHODS

2.1. Patients

This study was approved by the local Institutional Review Board. All consecutive newly-diagnosed head and neck cancer patients between December 2010 and July 2013 were included. Twenty-five patients (8 females; 24–63, mean 43±11 years old) were enrolled. Written informed consent was obtained for each patient before the MRI scan. TNM staging was performed according to the American Joint Committee on Cancer (AJCC) staging system [12].

2.2. MRI Acquisition

DCE-MRI was performed in the primary tumor region including the loco-regional LNs on a 3.0-T system (Magnetom Trio, Siemens) by using a fast 3D spoiled gradient-echo sequence. Imaging parameters were: reconstructed FOV = 260 × 260 mm², 20 axial sections, section thickness = 3 mm, FA = 20°, TR/TE = 5.0/4.2 ms. This data-acquisition scheme resulted in a temporal resolution of 4.5 seconds in 4.5 minutes (60 time points) with full spatial resolution of 256 × 256. A single dose of gadodiamide (Gd-DTPA) (Omniscan; Nycomed, Oslo, Norway) at a concentration of 0.1 mmol/kg body weight was injected at the rate of 1 mL/s into the antecubital vein, followed by a saline flush with a power injector (Spectris; Medrad, Indiana, Pennsylvania) at 8th scan. Baseline images were acquired with FA of 5°, 10° and 15° for quantitative analysis of DCE-MRI images. Contrast-Enhanced MRI and T2W-MRI were performed as for routine practice, and used for the following analysis in our study. After DCE-MRI scan, contrast-enhanced MRI were performed with: acquired matrix = (305–335) × (304–332), reconstructed FOV = 220–240 mm, section thickness = 2–3 mm, FA = 10°, TR/TE = 4.7–5.0/2.4–2.5 ms. T2W-MRI were performed with an Inversion Recovery sequence and these parameters: acquired matrix = (210–230) × (260–280), reconstructed FOV = 220–240 mm, section thickness = 3 mm, FA = 90°, TR/TE = 4900–5900/60 ms, number of average = 2.

2.3. ROI Drawing

For each patient, the head and neck cancer tumor boundary was identified in the relevant consecutive slices of the DCE-MRI images and a series of two-dimensional Regions of Interest (ROI) were extracted that included the whole tumor using the software ImageJ (NIH, Bethesda, MD, USA). The largest metastatic node within the scanned region in each patient identified by a neuroradiologist (J Jiang) on conventional anatomical MR images (T1-weighted, T2-weighted, and post-contrast T2-weighted) was taken to be representative of all the metastatic nodes [13-15]. The node boundary was then identified in the relevant consecutive slices of the DCE-MRI images and a series of two-dimensional ROI were contoured in ImageJ. The ROIs on the normal longus capitis muscle were delineated adjacent to both sides of the NPC lesions, and were used for comparison with the tumor and metastatic nodes. This is because the perfusion characteristics of this muscle are similar to the non-tumoral tissue in this region, however an ROI is hard to be drawn within this small region. The criteria for ROI drawing of normal longus capitis muscle were the hypointensity on T2W images and obvious enhancement on contrast-enhanced T1W images. For the ROI drawing of normal tissue, the areas with hyperintensity on T2W images and/or obvious enhancement on contrast-enhanced T1W images indicate tumor invasion, and hence were avoided when the ROIs were delineated. The ROIs of a typical case is shown in Fig. (1).

2.4. Statistical Analysis

The gold standard for nodal metastases in our cohort was clinical and radiographic follow-up of suspected nodes lasting for at least 2 years [16]. The parametric maps of $K_{trans}$, $v_e$ and $k_p$ were calculated from the acquired DCE-MRI images according to Huang et al. [8]. The whole procedure of calculating parametric maps of $K_{trans}$, $v_e$ and $k_p$ were performed using the software dcemri S4 (http://cran.r-project.org/web/packages/dcemriS4/) developed by Whitcher et al. [17], according to the standard Tofts-Kety model [3]. We directly calculated the arterial input function from the DCE-MRI images of the carotid artery, and if in some patients the individual AIF could not be differentiated clearly, the population AIF acquired from other patients was used [8].

The normality of the DCE-MRI parameters distribution in our cohort was checked using the Shapiro–Wilk test.
repeated-measure ANOVA with a Greenhouse-Geisser correction and post hoc tests using the Bonferroni correction were used to evaluate the difference in \( K_{\text{trans}} \), \( v_e \) and \( k_e \) among primary tumors, metastatic nodes and normal tissue. All statistical analyses were performed using SPSS 20 (SPSS Inc, Chicago, IL, USA), and \( P < 0.05 \) was considered statistically significant.

### 3. RESULTS

The cohort characteristics of this study are shown in Table 1. There were 10 patients with nasopharyngeal carcinoma, 8 with oropharynx cancer, 3 with cancer in the tongue base, and 4 with cancer of the larynx.

![Fig. (1). The ROIs drawn in the MRI images of a typical case for: A, the primary tumor; B, a metastatic node; C, the normal longus capitis muscle.](image)

Table 1. Patient demographic data and tumor characteristics (n=25).

| No. | Age (years) | Sex | AJCC Stage | Metastatic Node | Primary Tumor | Normal Tissue |
|-----|-------------|-----|------------|----------------|--------------|--------------|
|     |             |     |            | \( K_{\text{trans}} \) | \( v_e \) | \( k_e \) | \( K_{\text{trans}} \) | \( v_e \) | \( k_e \) | \( K_{\text{trans}} \) | \( v_e \) | \( k_e \) |
| 1   | 40          | F   | 4          | 0.699          | 0.237        | 0.103        | 0.214          | 0.283        | 0.762        | 0.357          | 0.078        | 0.229        |
| 2   | 31          | M   | 4          | 0.175          | 0.419        | 0.132        | 0.207          | 0.283        | 0.847        | 0.100          | 0.294        | 0.158        |
| 3   | 46          | M   | 3          | 0.245          | 0.348        | 0.539        | 0.213          | 0.341        | 0.626        | 0.109          | 0.158        | 0.516        |
| 4   | 43          | F   | 4          | 0.324          | 0.460        | 0.369        | 0.254          | 0.375        | 0.473        | 0.061          | 0.104        | 0.645        |
| 5   | 61          | M   | 4          | 0.445          | 0.459        | 0.526        | 0.240          | 0.247        | 1.055        | 0.247          | 0.478        | 0.218        |
| 6   | 58          | M   | 3          | 0.210          | 0.222        | 1.042        | 0.180          | 0.248        | 0.854        | 0.124          | 0.159        | 0.588        |
| 7   | 55          | F   | 3          | 0.249          | 0.432        | 0.623        | 0.175          | 0.256        | 0.786        | 0.096          | 0.221        | 0.510        |
| 8   | 50          | M   | 2          | 0.257          | 0.302        | 0.661        | 0.164          | 0.265        | 0.671        | 0.143          | 0.133        | 0.485        |
| 9   | 36          | F   | 3          | 0.236          | 0.365        | 0.666        | 0.185          | 0.273        | 0.762        | 0.140          | 0.157        | 0.535        |
| 10  | 26          | M   | 3          | 0.429          | 0.597        | 0.527        | 0.266          | 0.406        | 0.629        | 0.211          | 0.205        | 0.464        |
| 11  | 45          | F   | 3          | 0.459          | 0.602        | 0.291        | 0.280          | 0.321        | 0.946        | 0.256          | 0.289        | 0.309        |
| 12  | 45          | M   | 4          | 0.607          | 0.623        | 0.416        | 0.476          | 0.492        | 0.445        | 0.224          | 0.495        | 0.310        |
| 13  | 38          | M   | 3          | 0.324          | 0.526        | 0.518        | 0.390          | 0.509        | 0.699        | 0.268          | 0.475        | 0.215        |
| 14  | 45          | F   | 4          | 0.293          | 0.376        | 0.312        | 0.300          | 0.395        | 0.625        | 0.025          | 0.047        | 0.675        |
| 15  | 28          | M   | 4          | 0.311          | 0.328        | 0.635        | 0.298          | 0.415        | 0.587        | 0.281          | 0.406        | 0.320        |
| 16  | 46          | M   | 3          | 0.274          | 0.372        | 0.594        | 0.202          | 0.274        | 0.731        | 0.065          | 0.120        | 0.495        |
| 17  | 25          | M   | 3          | 0.338          | 0.322        | 0.381        | 0.251          | 0.411        | 0.297        | 0.053          | 0.059        | 0.742        |
| 18  | 40          | M   | 4          | 0.328          | 0.380        | 0.507        | 0.314          | 0.368        | 0.640        | 0.138          | 0.229        | 0.634        |
| 19  | 44          | F   | 3          | 0.312          | 0.391        | 0.299        | 0.263          | 0.318        | 0.650        | 0.094          | 0.069        | 0.481        |
| 20  | 35          | M   | 3          | 0.256          | 0.384        | 0.311        | 0.283          | 0.439        | 0.565        | 0.117          | 0.242        | 0.290        |
| 21  | 60          | F   | 4          | 0.478          | 0.419        | 0.215        | 0.278          | 0.351        | 0.596        | 0.186          | 0.107        | 0.191        |
| 22  | 47          | M   | 4          | 0.316          | 0.549        | 0.384        | 0.284          | 0.429        | 0.500        | 0.239          | 0.510        | 0.234        |
| 23  | 64          | M   | 3          | 0.234          | 0.332        | 0.318        | 0.308          | 0.436        | 0.538        | 0.258          | 0.353        | 0.282        |
| 24  | 52          | M   | 4          | 0.165          | 0.344        | 0.319        | 0.307          | 0.356        | 0.371        | 0.087          | 0.137        | 0.522        |
| 25  | 43          | M   | 3          | 0.331          | 0.410        | 0.427        | 0.252          | 0.344        | 0.620        | 0.158          | 0.231        | 0.418        |

Age (years), patient age at diagnosis; M, male; F, female; AJCC stage, tumor stage evaluated according to AJCC staging system. AJCC, American Joint Committee on Cancer.
The mean $K_{\text{trans}}$ values of primary tumors, nodes and normal tissue were $0.251\pm 0.066$ min$^{-1}$, $0.332\pm 0.149$ min$^{-1}$, $0.159\pm 0.087$ min$^{-1}$ respectively; the mean $v_e$ values were $0.344\pm 0.081$, $0.408\pm 0.124$ and $0.229\pm 0.146$ respectively; and the mean $k_{ep}$ values were $0.621\pm 0.195$ min$^{-1}$, $0.429\pm 0.206$ min$^{-1}$ and $0.420\pm 0.170$ min$^{-1}$ respectively. As shown in Fig. (2), $K_{\text{trans}}$, $v_e$ and $k_{ep}$ differed among different tissue types. Both $K_{\text{trans}}$ and $v_e$ of normal tissue differed significantly from those of metastatic nodes (both $P < 0.001$) and primary tumors (both $P < 0.001$), while no significant differences of $K_{\text{trans}}$ and $v_e$ were observed between metastatic nodes and primary tumors ($P = 0.075$ and 0.365 respectively). The $k_{ep}$ values of primary tumors were significantly different from those of node ($P = 0.001$) and normal tissue ($P = 0.002$), however no significant differences between those of nodes and normal tissue ($P > 0.999$).

4. DISCUSSION

Studies have been performed to investigate the role of DCE-MRI in differentiating the primary tumors and nodal status from benign tissue in some cancer types. The slopes derived from Time-Intensity Curves (TICs) from DCE-MRI were found to be significantly greater compared to the benign lesions in the tumors of the tongue [18]. Wendel found that in DCE-MRI the mean Time To Peak (TTP) was 27 s (range 18-36 s, SD 9 s) for benign and 21 s (range 18-27 s, SD 5 s) for malignant LNs, and the relative signal change with respect to the reference tissue was significantly higher for LNs with than for those without metastases [19]. In thyroid tumors, the thyroid carcinoma showed significantly lower slope of the rising part of TIC and higher TTP than the benign lesions [20]. In minor salivary gland tumors in the oral cavity, it was also found that the TTP was significantly different between the benign and malignant tumors [21]. By converting the TIC patterns into a color-coded map, it was found that DCE-MRI of head and neck tumors was able to distinguish all 21 primary tumors and 15 metastatic nodes from normal structures [22]. All these studies have justified the role of DCE-MRI in the differentiating diagnosis of cancer. However, none of these publications was related to the role of DCE-MRI quantitative parameters in differentiating the tumor and nodal metastasis from normal tissues of head and neck cancer. We in this study by applying the quantitative analysis of contract concentration curves, calculated the perfusion parameters, and analyzed the role of differentiating among the three tissue types.

In the present study, the $K_{\text{trans}}$ of the tumors and metastatic nodes was significantly higher than that of normal tissue, which is consistent with the results of Chang et al. [23] and Li et al. [24]. Chang et al. reported that $K_{\text{trans}}$ in esophageal adenocarcinoma was higher than in benign tissue, while Li et al. found that $K_{\text{trans}}$ calculated by a shutter-speed model provided the most useful biomarkers for malignant/benign prostate tissue discrimination. Lowry et al. [25] also have a similar finding that $K_{\text{trans}}$ in prostate tumor was increased compared to the peripheral normal tissue. The explanation is, $K_{\text{trans}}$ is a rate constant measuring the contrast transfer between the intravascular space and the interstitial space within the tissue of interest. With cancer-related angiogenesis, the contrast within tumor blood vessels may exhibit increased permeability thereby allowing a more rapid transfer, when compared to benign tissue, and hence a higher $K_{\text{trans}}$ value in tumor or metastatic nodes.

The $v_e$ of tumor was significantly higher compared to the normal tissue, consistent with the results by Lowry et al. [25], who found that $v_e$ in prostate tumor was increased compared to the peripheral normal tissue. $v_e$ is the measurement of volume of EES per unit volume of tissue, and reflects the available space for contrast permeability. Parallel to the increase of $K_{\text{trans}}$ value in tumor and metastatic nodes, our results indicated that the increase of $v_e$ reflects the increase of contrast permeability in tumor and metastatic nodes compared to healthy tissue in head and neck cancer.

Similar to Li et al. [24], Lowry et al. [25] and Kiessling et al. [26], we found that the $k_{ep}$ of tumor was significantly higher compared to the normal tissue. According to Li et al., $k_{ep}$ was also useful in discriminating malignant prostate tumor from benign prostate tissue. Lowry et al. found that the fast exchange limit model revealed increased mean $k_{ep}$ in tumor compared to the peripheral normal tissue. Kiessling et al. reported that $k_{ep}$ of prostate tumors were significantly higher than peripheral non-affected prostate tissue. $k_{ep}$ is a complex parameter depending on the underlying physiology such as blood flow and permeability surface area product. Compared to benign tissues, the microvessel density and
vessel permeability of tumors are relatively high, and hence may result in a higher $k_{ep}$. The $k_{ep}$ showed no significant differences between the tumor and the nodes, which may be because it is calculated as $K^{\text{trans}} / v_e$, and the increase of $K^{\text{trans}}$ may be compensated by the increase of $v_e$.

To summarize, all the results about $K^{\text{trans}}$, $v_e$, and $k_{ep}$ may show that, for our head and neck cancer cohort, the perfusion and vascular permeability in the metastatic LNs were increased, together with the primary tumors. These findings may further indicate that to characterize the head and neck cancer the studies focused on the nodes (but not only on primary tumors) should be performed. Our results in the present study may have some indications for the management of head and neck cancer patients. It has been reported that, the LN status is a key prognostic factor for head and neck cancer patients.

Our study may have some limitations. Firstly, for each patient, we only selected the largest node in the DCE-MRI scan region. These selection criteria may not be sufficient enough to reflect the status of all nodes. Since some other metastatic nodes were too small to be analyzed, we followed the methodology in the literature and analyzed the largest one only. Secondly, error may be caused by the ROI selection of normal tissue which can be a bit ambiguous among different researchers. However, according to the histological characteristics of head and neck cancer, it was believed that the normal longus capitis muscle be the best choice for comparison. Finally, the sample size was small, thus the statistical power may not be high enough. A large sample would provide more reliable results to verify our findings.

CONCLUSION

Significant differences of $K^{\text{trans}}$, $v_e$, and $k_{ep}$ were observed among the primary tumors, metastatic nodes and normal tissue. We hence concluded that these DCE-MRI parameters may help to differentiate the tumors/metastatic nodes from normal tissue in head and neck cancer. Further studies with bigger cohort are required for validating our findings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board. TNM staging was performed according to the American Joint Committee on Cancer (AJCC) staging system.

HUMAN AND ANIMAL RIGHTS

No animal were used in this study. Reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consent was obtained for each patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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