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Pretreatment Diffusion-Weighted and Dynamic Contrast-Enhanced MRI for Prediction of Local Treatment Response in Squamous Cell Carcinomas of the Head and Neck

Sanjeev Chawla¹, Sungheon Kim^{1,2}, Lawrence Dougherty¹, Sumei Wang¹, Laurie A. Loevner¹, Harry Quon^{3,4}, and Harish Poptani¹

¹Department of Radiology, University of Pennsylvania, 423 Guardian Dr, B6 Blockley Hall, Philadelphia, PA 19104

³Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA

Abstract

OBJECTIVE—The objective of our study was to predict response to chemoradiation therapy in patients with head and neck squamous cell carcinoma (HNSCC) by combined use of diffusion-weighted imaging (DWI) and high-spatial-resolution, high-temporal-resolution dynamic contrast-enhanced MRI (DCE-MRI) parameters from primary tumors and metastatic nodes.

SUBJECTS AND METHODS—Thirty-two patients underwent pretreatment DWI and DCE-MRI using a modified radial imaging sequence. Postprocessing of data included motion-correction algorithms to reduce motion artifacts. The median apparent diffusion coefficient (ADC), volume transfer constant (K^{trans}), extracellular extravascular volume fraction (v_e), and plasma volume fraction (v_p) were computed from primary tumors and nodal masses. The quality of the DCE-MRI maps was estimated using a threshold median chi-square value of 0.10 or less. Multivariate logistic regression and receiver operating characteristic curve analyses were used to determine the best model to discriminate responders from nonresponders.

RESULTS—Acceptable χ^2 values were observed from 84% of primary tumors and 100% of nodal masses. Five patients with unsatisfactory DCE-MRI data were excluded and DCE-MRI data for three patients who died of unrelated causes were censored from analysis. The median follow-up for the remaining patients ($n = 24$) was 23.72 months. When ADC and DCE-MRI parameters (K^{trans} , v_e , v_p) from both primary tumors and nodal masses were incorporated into multivariate logistic regression analyses, a considerably higher discriminative accuracy (area under the curve [AUC] = 0.85) with a sensitivity of 81.3% and specificity of 75% was observed in differentiating responders ($n = 16$) from nonresponders ($n = 8$).

CONCLUSION—The combined use of DWI and DCE-MRI parameters from both primary tumors and nodal masses may aid in prediction of response to chemoradiation therapy in patients with HNSCC.

Keywords

diffusion-weighted imaging; dynamic contrast-enhanced MRI; metastatic lymph nodes; primary tumors; squamous cell carcinomas of head and neck

Head and neck squamous cell carcinomas (HNSCCs) are among the most common neoplasms of the upper aerodigestive tract in humans. Accurate assessment of the extent and location of primary tumors and nodal masses at the time of diagnosis is crucial for selection of the appropriate treatment regimen. Radiation therapy and concurrent or induction chemotherapy is the standard of care for nonresectable HNSCCs. However, not all patients with HNSCC respond to chemoradiation therapy. Thus, it is important to develop prognostic imaging biomarkers that can accurately predict treatment outcome before initiation of treatment. These imaging biomarkers may help in stratifying patients who would benefit from chemoradiation therapy from those who would not. For patients with nonresponsive disease, alternative treatment strategies such as upfront neck surgery and novel treatment modalities that include monoclonal antibodies, molecular inhibitors, gene therapy, and photodynamic therapy can be individually tailored to improve survival and quality of life [1]. If the outcome can be predicted before the treatment, patients with nonresponsive disease could also be spared from the unnecessary economic burden and toxic side effects associated with chemoradiation therapy.

Standard clinical imaging modalities such as CT, MRI, and ^{18}F -FDG PET studies are typically used to predict treatment response in HNSCC patients. However, these techniques lack sensitivity and specificity in evaluating treatment response, which limits the use of these modalities for response prediction [2, 3]. Because of increased incidences of false-positives immediately after chemoradiation therapy, follow-up FDG PET is recommended only if performed 12 weeks after the completion of radiation therapy [2], which may lead to a lost opportunity for alternative treatments in patients with nonresponsive disease. The 12-week duration might result in complication risks with neck surgery due to the development of soft-tissue fibrosis and impaired wound healing.

Recently, advanced MRI methods including diffusion-weighted imaging (DWI) and perfusion-weighted MRI have been used in the evaluation of treatment response [4–11] and in the prediction of survival [12]. Unfortunately, most of these studies have focused only on the metastatic cervical lymph nodes [6, 7, 12–14] because the nodal region is less susceptible to motion-induced artifacts. However, treatment outcome in patients with HNSCC is dependent on the biology and microenvironment of both the primary tumors and the metastatic nodes. Primary tumors with an adverse microenvironment exhibit an increased probability of metastatic dissemination and growth at secondary sites and patients with these tumors show poor prognosis [15].

The current study was thus performed to evaluate the potential utility of multivariate analysis of DWI- and dynamic contrast-enhanced MRI (DCE-MRI) derived parameters from both primary tumors and meta-static nodes in predicting local treatment response to chemoradiation therapy in patients with HNSCC.

Subjects and Methods

Patients

Written informed consent was obtained from each patient for this HIPAA-compliant and institutional review board–approved study. The inclusion criteria were a previous CT or MRI examination indicating the presence of HNSCC, which had to be confirmed by biopsy, and both the primary tumor and the metastatic cervical lymph node occurred at the same anatomic level of neck. The reasons for exclusion from the study were previous treatment with chemotherapy or radiation therapy, presence of cancer other than HNSCC, and plan for upfront surgery. The study group was composed of 32 patients (26 men and six women; mean age $\pm$ SD, 57.82 ± 11.10 years). At initial presentation, the location of the primary

tumors was the base of the tongue (66%) followed by tonsil (19%), larynx (6%), oropharynx (6%), and vallecula (3%). Disease in the majority of patients was staged as T2 tumor (50%) and N2 nodal mass (72%).

All patients received chemoradiation therapy; the radiation therapy regimen included a total dosage of 7040 cGy that was given in 32 fractions at a daily dose of 220 cGy per fraction over a course of 44 days. The chemotherapy regimen was variable and included either concurrent chemotherapy alone ($n = 18$) or induction chemotherapy followed by concurrent chemotherapy ($n = 14$). Patients receiving induction chemotherapy were treated with 1–3 cycles of cisplatin (75 mg/m²), docetaxel (75 mg/m²), and 5-fluorouracil (1000 mg/m²) or eight cycles of cetuximab (400 mg), paclitaxel (90 mg), and carboplatin (155.1–239.8 mg). Patients treated with concurrent chemotherapy were treated either with cisplatin (100 mg/m²) or with cetuximab (400 mg/m²) 3–7 days before radiation therapy. During radiation therapy cetuximab was given weekly at 250 mg/m² on days 1, 8, 15, 22, 29, 36, and 43 of the radiation treatment.

MRI Data Acquisition

All patients underwent MRI before chemoradiation therapy. A 1.5-T scanner (Sonata, Siemens Healthcare) ($n = 15$) or a 3-T scanner (Trio, Siemens Healthcare) ($n = 17$) was used along with a neck array coil or a neurovascular coil. The diagnostic imaging protocol included axial T2-weighted images (TR/TE = 4000/131, FOV = 260 × 260 mm², matrix size = 384 × 512, slice thickness = 5 mm, flip angle [FA] = 120°, bandwidth = 130 Hz, number of excitations [NEX] = 1) and axial T1-weighted images (TR/TE = 600/10, FOV = 260 × 260 mm², matrix size = 384 × 512, slice thickness = 5 mm, FA = 90°, bandwidth = 130 Hz, NEX = 1). Eight axial slices with an FOV of 260 × 260 mm² and slice thickness of 5 mm were selected to cover the tumor at the primary site and the largest metastatic cervical lymph node.

DW images were acquired in the axial orientation using a fat-suppressed pulsed spin-echo echo-planar imaging sequence (TR/TE = 4000/89) with three b values—0, 500, and 1000 s/mm²—to generate trace diffusion maps. Other sequence parameters were as follows: bandwidth, 1500 Hz/pixel; FOV, 260 × 260 mm²; matrix size, 128 × 128; number of slices, 8; slice thickness, 5 mm; interslice gap, 0 mm; NEX, 8; number of signals acquired, 4; and acquisition time, 1 minute 58 seconds.

DCE-MRI was performed using the methods described previously [7, 16]. Briefly, a modified 3D spoiled gradient-recalled sequence was used to acquire the radial imaging data. The radial imaging protocol included eight angle-interleaved subframe images from the full-echo radial dataset. Typical imaging parameters for the DCE-MRI protocol included eight axial slices of 5 mm thickness each. Other parameters were a TR/TE of 5.0/4.2, FOV of 26 cm², 256 readout points and projections, 256 projections (32 projections/subframe, 8 subframes), FA of 20°, and receiver bandwidth of 510 Hz/pixel. A frequency-selective fat-saturation pulse was applied once every 8 excitations to suppress the signal from fat. In addition, a spatial saturation pulse was used once every 32 excitations to minimize the effect of inflow while keeping the scan time as short as possible. When these optimized parameters were used, the scan time of full-resolution data was about 20 seconds with an effective temporal resolution of 2.5 seconds for each subframe image. A k-space-weighted image contrast (KWIC) algorithm [16] was used to generate images with full spatial resolution of 256 × 256.

Before contrast injection, baseline images were obtained for 1 minute. While the imaging continued, a single dose of gadolinium diethylenetriaminepentaacetic acid (gadodiamide) (Omniscan, GE Healthcare) was injected into the antecubital vein at a rate of 1 mL/s (0.1

mmol/kg of body weight) followed by a saline flush with a power injector. Scanning was continued for another 9 minutes to characterize the contrast enhancement kinetics.

Image Processing

Before data analysis, a motion-correction algorithm was used on the raw DCE image data to correct for any in-plane rotational motion artifacts caused by voluntary and involuntary motion using a self-navigated autocorrection method [17]. Individual DW images with different b values were coregistered to the reference T2-weighted image ($b = 0 \text{ s/mm}^2$) to account for any motion during the acquisition of the DWI data using the method described earlier [6]. In addition, the T1-weighted, contrast-enhanced T1-weighted, DCE-MRI, and DW images were coregistered to spin-echo T2-weighted images using a two-step nonrigid image registration technique [6]. The first step involved a 3D registration with affine transformation to minimize global misalignment. Subsequently, each slice was coregistered using a 2D nonrigid registration with second-order discrete sine bases for both x - and y -axes.

Regions of interest (ROIs) were drawn by an experienced neuroradiologist who was blinded to treatment outcome. The ROIs were drawn on all imaging sections encompassing the solid-appearing portion of the primary tumors and nodal masses while avoiding necrotic, cystic, and hemorrhagic areas as well as surrounding blood vessels.

Pixel-by-pixel apparent diffusion coefficient (ADC) maps were computed by a single exponential fit using the DWI signal intensity–b value curves. Median ADC values were computed from the primary tumors as well as the largest metastatic nodal mass using the same ROIs as described earlier. All image processing procedures were performed using in-house–developed interactive data language (IDL) routines (IDL, version 6.3, Exelis Visual Information Solutions).

Pharmacokinetic analysis of the DCE-MRI data were performed on a pixel-by-pixel basis from the selected ROIs of the primary tumor and metastatic node using the extended generalized kinetic model (GKM) model [16]. The parameter estimation was performed using Simplex algorithm provided in IDL. Based on Bayesian information criteria, a goodness of fit for the GKM was used to determine the quality of the fit by constructing χ^2 maps and measuring the median χ^2 values. The median χ^2 values were measured by the averaged normalized sum of squared differences between observed and expected values from the selected ROIs from primary tumors and nodal masses using the following equation:

$$\chi^2 = \frac{1}{N} \sum_{i=1}^N \frac{(S_i - P_i)^2}{P_i},$$

where N is the number of measured data points, S_i is the observed signal, and P_i is the predicted signal. The chi-square test was used to evaluate the null hypothesis stating that the measured curve was consistent with the theoretic model curve. A good fit was represented by lower median χ^2 values. Based on our data distribution, median χ^2 values of 0.10 or less were considered acceptable and corresponding DCE-MRI–derived parameters were included. Median pretreatment volume transfer constant (K^{trans}), extracellular extravascular volume fraction (v_e), and plasma volume fraction (v_p) values were computed from the primary tumor and the largest metastatic nodal mass.

Data Analysis

Clinical assessment was used as the endpoint to evaluate response to chemoradiation therapy, and it was measured from the end date of chemoradiation therapy. This duration was measured as the difference in time (in months) from the date of death (due to any cause) or the date of last contact for surviving patients. Patients were retrospectively categorized into two groups: responders (patients with no evidence of disease) and nonresponders (those who died of HNSCC or had residual disease or disease relapse) on the basis of clinical evaluation by the treating radiation oncologist using the information from clinical evaluation as well as radiologic, nuclear medicine, and histologic reports.

Kolmogorov-Smirnov tests were used to assess the nature of data distributions. Because the MRI data did not depart from gaussian distribution, independent-sample Student *t* tests were performed to look for differences in ADC values and DCE-MRI parameters (K^{trans} , v_e , v_p) from primary tumors and nodal masses between responders and nonresponders. A probability (*p*) of < 0.05 was considered significant. Univariate receiver operating characteristic (ROC) curve analyses were performed only for significantly different ($p < 0.05$) parameters between the two groups. Multivariate logistic regression and ROC analyses were also used to ascertain the best discriminatory model to differentiate responders from nonresponders. ROC curves based on sensitivity and specificity pairs, in terms of true-positive fraction (equivalent to sensitivity) versus false-positive fraction (equivalent to $1 - \text{specificity}$), were constructed. Area under the ROC curve (AUC) at 95% CI determined the accuracy. A Bonferroni correction was applied for analyzing the multivariate data involving eight parameters (i.e., ADC and DCE-MRI [K^{trans} , v_e , and v_p] from both primary tumors and nodal masses) using a *p* value of $0.05 / 8 = 0.00625$ to distinguish two groups of patients. Leave-one-out cross-validation tests were also applied to evaluate the robustness and accuracy of logistic regression models. All data analyses were performed using a statistical tool (SPSS, version 15.0, SPSS) for Microsoft Windows.

To assess the bias introduced by the different treatment regimen (concurrent chemotherapy only and induction chemotherapy followed by concurrent chemotherapy), we performed an analysis of a subgroup of patients who underwent concurrent chemotherapy only ($n = 18$). Of these 18 patients, 13 patients were responders and five, nonresponders. Independent-sample Student *t* tests were performed to look for differences in ADC values and DCE-MRI parameters from primary tumors and nodal masses between responders and nonresponders. Multivariate logistic regression and ROC analyses were also used to ascertain the best discriminatory model to distinguish between responders and nonresponders.

Results

Representative coregistered pretreatment anatomic MR images, ADC maps, and color-coded pharmacokinetic parametric K^{trans} , v_p , and v_e maps from a responder patient and a nonresponder patient are shown in Figures 1 and 2, respectively.

DCE-MRI-derived parametric maps were fitted satisfactorily with an acceptable median χ^2 value of 0.10 or less from all the nodal masses. However, five primary masses had a χ^2 value of more than 0.10 and these patients were excluded from the data analysis. Of the remaining 27 patients who had good-quality DCE-MRI data, three (11.11%) patients died of diseases unrelated to HNSCC and the data for those cases were censored. The final data analysis was performed of 24 patients. Of those 24 patients, 18 underwent concurrent chemoradiation therapy only and six patients underwent induction chemotherapy followed by concurrent chemoradiation therapy. The median follow-up for the 24 patients (including both alive and dead patients) was 23.72 months (range, 2.37–49.90 months). Of these patients, three died of HNSCC and five exhibited locoregional disease relapses; these eight

patients were collectively considered nonresponders. The remaining 16 patients were considered responders.

The average ADC, K^{trans} , v_e , and v_p values from the primary tumors are shown in Figure 3, and the corresponding values from the nodal masses are shown in Figure 4. Among the primary tumors, higher K^{trans} (mean $\pm$ standard error [SE], 0.32 ± 0.07 vs 0.27 ± 0.09 min^{-1}) (Fig. 3B) and higher v_p (0.08 ± 0.02 vs 0.05 ± 0.01) (Fig. 3D) values were observed in responders in comparison with nonresponders. The responders also exhibited lower ADC ($0.82 \pm 0.07 \times 10^{-3}$ mm^2/s vs $0.89 \times 10^{-3} \pm 0.09 \times 10^{-3}$ mm^2/s ; Fig. 3A) and lower v_e (0.27 ± 0.06 vs 0.36 ± 0.08 ; Fig. 3C) values than nonresponders. However, none of the parameters was significantly different between the two groups ($p > 0.05$).

Significantly higher K^{trans} values (0.20 ± 0.04 min^{-1} vs 0.15 ± 0.02 min^{-1} ; $p = 0.015$) (Fig. 4B) were observed from the nodal masses of responders relative to those of nonresponders. Similar to the primary tumors, the nodes of the responder group also exhibited higher v_p values (0.09 ± 0.02 vs 0.06 ± 0.02) (Fig. 4D). Similarly, lower ADC ($0.94 \times 10^{-3} \pm 0.08 \times 10^{-3}$ mm^2/s vs $1.11 \times 10^{-3} \pm 0.10 \times 10^{-3}$ mm^2/s) (Fig. 4A) and lower v_e (0.40 ± 0.05 vs 0.43 ± 0.09) (Fig. 4C) values were observed in the nodes of responders in comparison with those of the nonresponder group. However, these values were not significantly different ($p > 0.05$).

A univariate ROC analysis of K^{trans} from the nodes provided a sensitivity of 44% and specificity of 87.5% with an AUC of 0.56 ($p > 0.05$). When all MRI parameters including ADC and DCE-MRI parameters (K^{trans} , v_e , and v_p) from the primary tumors were combined, a moderate accuracy (AUC = 0.69) (Fig. 5) with a sensitivity of 67.2% and specificity of 75% was observed ($p > 0.05$). Similarly, multivariate logistic regression analyses from only nodal masses resulted in a moderate accuracy (AUC = 0.70) (Fig. 5) with a sensitivity of 69% and specificity of 75% ($p > 0.05$). However, when ADC and DCE-MRI parameters from both the primary tumors and nodal masses were incorporated into the multivariate logistic regression analyses, a considerable improvement in the performance of the model was observed. A substantially higher discriminative accuracy (AUC = 0.85; Fig. 5) with a sensitivity of 81.3% and specificity of 75% was observed in differentiating responders from nonresponders.

When the Bonferroni correction was used, none of the individual parameters from primary tumors and nodal masses was significantly different between the two groups of patients. However, the multivariate logistic regression model involving ADC and DCE-MRI parameters from both locations showed significant difference ($p = 0.006$) in differentiating responders from nonresponders. Leave-one-out cross-validation tests revealed that 75% of patients were correctly classified as responders and nonresponders involving all the parameters from both locations.

When an analysis of a subgroup of patients who underwent only concurrent chemoradiation therapy was performed, a discriminatory accuracy (AUC = 0.84) similar to that obtained from the analysis of all patients (AUC = 0.85) was observed when ADC and DCE-MRI parameters from both the primary tumors and nodal masses were incorporated into the multivariate logistic regression analyses. However, the sensitivity was 61.5% and specificity was 100% in distinguishing between responders and nonresponders.

Discussion

We report the utility of DWI and DCE-MRI of the primary tumors and the metastatic nodes in predicting response to chemoradiation therapy in patients with HNSCC. In patients with HNSCC, clinical response is evaluated using the overall disease status, which includes local

response from the primary tumor as well as from the metastatic neck node. Thus our approach of combining the analyses of both the primary tumor and the metastatic node is more clinically relevant than approaches described in previously published advanced MRI studies that focused primarily on analysis of the metastatic node [6, 7, 12, 13]. Because both primary tumors and nodal masses are potent risk factors for prediction of treatment failure and survival in patients with HNSCC [18], evaluation of both lesions should be used to predict treatment outcome. Inclusion of ADC and DCE-MRI parameters (K^{trans} , v_e , and v_p) from primary tumors and nodal masses yielded an AUC of 0.85 and correct classification of 75% in differentiating responders from nonresponders. These results suggest that diffusion and perfusion parameters from two tumor sites may be synergistic interacting factors in the logistic regression analysis and that this interaction might be greater than what would be expected from individual sites or individual measurement parameters.

DWI studies of HNSCC have suggested that ADC can be used as a potential marker for prediction of treatment response and long-term survival [6, 11, 19]. These results are consistent with the hypothesis that a high pretreatment ADC value may be indicative of micronecrosis and, consequently, of increased resistance to treatment and poor prognosis in these patients. Although our results are similar to those of earlier studies in the literature, we did not find a significant difference in ADC values between responders and nonresponders. Histologic observations have revealed that HNSCCs are very heterogeneous in nature, with marked variations in proliferation and cellular differentiation in different regions of the tumors [20], and that this heterogeneity greatly influences the clinical course of the disease [21]. We believe that a nonsignificant difference in ADC values between the two groups of patients in our study might be because of higher intratumor heterogeneity of the relatively smaller cohort of patients or differences in the clinical follow-up times (median, ≈ 24 months) in the current study in comparison with previously published studies that used much shorter response assessment times of 3–12 months from the end of chemoradiation therapy [6, 8].

DCE-MRI provides a perfusion parameter K^{trans} that reflects a combination of tumor blood flow and microvascular permeability. In the current study, patients with disease responsive to chemoradiation therapy had significantly higher pretreatment K^{trans} values from nodal masses than patients with a partial response or no response. This result is in agreement with previous studies that have reported HNSCC patients exhibiting elevated pretreatment tumor blood flow, increased blood volume, and higher K^{trans} values showed improved response to chemoradiation therapy and prolonged survival [7, 12, 22]. We also observed higher K^{trans} values from primary tumors of responders in comparison with nonresponders; however, the difference was not significant. Our results and those of earlier published reports support the notion that tumors with relatively higher blood flow are associated with increased oxygenation levels resulting in better access to chemotherapeutic drugs and radiosensitivity [23]. On the other hand, tumor hypoxia adversely influences treatment response and enhances chemoresistance by impeding delivery of therapeutic agents [24]. In a recent DCE-MRI study [25], an inverse correlation was observed between presurgical tumor perfusion parameters and hypoxia in patients with HNSCC; this finding suggests that high tumor blood flow and volume are associated with low levels of hypoxia.

In addition to K^{trans} , pharmacokinetic analysis of DCE-MRI data provides two other perfusion parameters: v_e and v_p . The v_e parameter reflects the extravascular extracellular space, which consists of interstitial fluid and connective tissue arranged in a supportive frame structure and is restricted by blood vessel walls and cell plasma membranes. In normal tissues, the extracellular space is balanced in size and shape to ensure adequate supply of nutrients and oxygen to the tissue. However, the composition of the extracellular space of neoplastic tissues is significantly different from that of most normal tissues. In

general, the tumor extracellular space is characterized by a large interstitial space, higher collagen concentration, higher interstitial fluid pressure, and higher effective interstitial diffusion coefficient of macromolecules compared with normal tissues [26]. Although the v_e and v_p parameters are physiologically important, previous studies of different cancers [27, 28] and the current study failed to show a significant difference in v_e and v_p values between responders and nonresponders. However, a recent study indicated the importance of v_e and v_p as prognostic biomarkers of clinical outcome in patients with osteosarcoma who underwent chemotherapy [29]. Collectively these studies imply that v_e and v_p may not be considered to be reliable as independent parameters. However, given the inherently different physiologic information that v_e and v_p provide and the trend in the differences between responders and nonresponders, we believe these parameters may play a complementary role in the overall prediction of treatment response when used in conjunction with other parameters.

A multiparametric data analysis approach allows us to exploit the unique strengths of different imaging techniques. Previously, investigators have reported that the combination of DWI and DCE-MRI could improve diagnostic accuracy and decision making in the characterization of breast lesions [30]. Thus, we believe that a combined analysis of DCE-MRI parameters (K^{trans} , v_e , and v_p) and ADC from both primary tumors and nodal masses may be a better approach to obtain greater discrimination accuracy for differentiating responders from nonresponders as has been observed in the current study.

DCE-MRI-derived parametric maps of primary tumors are vulnerable to severe image distortion caused by motion- and susceptibility-induced artifacts that may result in inaccurate pixel-by-pixel maps unless offline postprocessing motion-correction algorithms are applied to the imaging data. Although DCE-MRI parameters from primary tumors have been reported as being helpful for predicting and monitoring treatment response in patients with HNSCC [4, 5], the quality of the data and potential errors in fitting the parametric maps could not be ascertained from those studies because the authors did not report these values. In the current study, we used the goodness of fit as a criterion for DCE-MRI data quality. Acceptable χ^2 values were observed from 84% of primary tumors and from 100% of nodal masses. The relatively high quality of the data in our study was possible because we used a robust modified radial imaging scheme along with a KWIC filtering reconstruction scheme [31]. This method is inherently less sensitive to motion-induced artifacts and also provides high-spatial-resolution, high-temporal-resolution DCE-MRI data. In addition, we used a self-navigated autocorrection method to correct for in-plane rotational motion artifacts caused by voluntary and involuntary motion. This method results in substantial motion correction with a relative error of less than 5% [17]. However despite these efforts, data from five patients were discarded because of severe motion artifacts that led to poor fitting of the DCE-MRI data. A dropout rate of about 17% occurred from primary tumors primarily because of motion from swallowing and coughing. We believe that more stringent acquisition and postprocessing tools would be needed in the future to reduce the dropout rate further.

The evaluation of treatment efficacy and incidences of adverse effects after chemoradiation therapy are dependent on the time to follow-up and thus are different for patients who undergo short-term follow-up than for those who are followed up for longer periods [32]. However, earlier studies have evaluated the prognostic value of DCE-MRI [5, 7, 14] and DWI [6, 8] in predicting treatment response with relatively shorter follow-up periods in HNSCC. In the current study, we used a long-term follow-up period (median = 23.72 months) to assess the prognostic significance of DWI and DCE-MRI in predicting therapeutic response to chemoradiation therapy, and we believe that these results have greater clinical significance in the management of HNSCC patients.

In the current study, data from patients scanned on 1.5- and 3-T MR systems were combined. In addition, investigators have reported that ADC values from submandibular glands were not significantly different when healthy volunteers underwent DWI within 1 hour on MR systems of both field strengths [6], suggesting that ADC values are independent of field strength. A strong correlation for ADC values between 1.5 and 3 T has also been observed from the parotid glands of healthy volunteers [33]. For DCE-MRI data, differences in magnetic field were accounted for by using the published relaxivity values at the two field strengths and by using individually measured T1 relaxation times while computing the DCE-MRI parameters. Because DCE-MRI data were acquired using a modified radial imaging sequence with a temporal resolution of 2.5 seconds in the current study, this sequence allowed us to acquire data from only eight central slices with a slice thickness of 5 mm covering the primary tumor and largest metastatic cervical lymph node with a nodal mass as the epicenter from each patient. However, a recent development of a 3D golden angle radial scheme allows more coverage of tissues of interest while acquiring the DCE-MRI data with high temporal resolution [34]. We believe that this newer scheme will allow us to acquire DCE-MRI data with greater tissue coverage encompassing both primary tumors and nodal masses in all the patients. This scheme will also help in excluding only the motion-corrupted image slices from a particular set of images, thus permitting us to make use of the remaining good-quality image slices for data analysis.

The results of our study should be treated with caution because these findings are from a relatively smaller number of patients ($n = 24$). Further studies of a larger cohort may be necessary to confirm our findings. Another limitation of the current study was that the chemotherapy doses and regimens were different among patients because assessment of treatment strategy was based on curative intent. These differences in treatment regimens may have played a confounding role in differentiating responders from nonresponders. To account for these differences, we performed an analysis of a subgroup of patients who underwent only chemoradiation therapy. The discriminatory accuracy for this subgroup of patients was similar to that of the entire patient group. These findings suggest that the differences in treatment regimens did not have an influence in distinguishing between responders and nonresponders in our cohort of patients. Using DCE-MRI and PET, some studies [10] have shown a relationship between the vascular and metabolic characteristics of HNSCC and have suggested that a combined approach of PET and MRI may provide a better assessment of tumor microenvironment. Although some of our patients also underwent FDG PET before the commencement of chemoradiation therapy, different patient orientations during the two imaging examinations (PET and MRI) precluded us from performing a comparative analysis in predicting treatment response. To address the issue of image coregistration, the use of combined MRI/PET systems would be the best alternative in future studies [35]. Despite these shortcomings, our study shows that patients exhibiting complete response to chemoradiation therapy can be separated from nonresponders.

In conclusion, our preliminary data suggest that high-spatial-resolution, high-temporal-resolution ADC maps and DCE-MRI parametric maps may be obtained of both primary tumors and nodal masses. A multiparametric approach to analyze pretreatment DWI and DCE-MRI of primary tumors and nodal masses is promising in accurately predicting local treatment response to chemoradiation therapy in HNSCC. However, further studies of a larger patient population are required to confirm these findings.

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Fig. 1.

Images obtained before chemoradiation therapy in 61-year-old man with head and neck squamous cell carcinoma that are representative of patients in responder group.

A, Axial T2-weighted image shows heterogeneous hyperintense primary tumor (*green arrow*) and nodal mass (*white arrow*) at level IIa of neck.

B, Masses shown in **A** exhibit heterogeneous enhancement on contrast-enhanced T1-weighted image.

C–F, Coregistered and corresponding apparent diffusion coefficient map (**C**) and color-coded dynamic contrast-enhanced MRI-derived volume transfer constant (K^{trans}) (**D**), extracellular extravascular volume fraction (v_e) (**E**), and plasma volume fraction (v_p) (**F**) maps are shown.

Fig. 2.

Images obtained before chemoradiation therapy in 64-year-old man with head and neck squamous cell carcinoma that are representative of patients in nonresponder group.

A, Axial T2-weighted image shows heterogeneous hyperintense primary tumor (*green arrow*) and nodal mass (*white arrow*) at levels II and III of neck.

B, Masses shown in **A** exhibit heterogeneous enhancement on contrast-enhanced T1-weighted image.

C–F, Coregistered and corresponding apparent diffusion coefficient map (**C**) and color-coded dynamic contrast-enhanced MRI-derived volume transfer constant (K^{trans}) (**D**), extracellular extravascular volume fraction (v_e) (**E**), and plasma volume fraction (v_p) (**F**) maps are shown.

Fig. 3.

Bar graphs show values obtained from primary tumors of responders and of partial responders and nonresponders. Bars represent mean values and error bars represent standard errors.

A–D, Distributions of apparent diffusion coefficient (ADC) (**A**), volume transfer constant (K^{trans}) (**B**), extracellular extravascular volume fraction (v_e) (**C**), and plasma volume fraction (v_p) (**D**) values are shown.

Fig. 4.

Bar graphs show values obtained from metastatic nodal masses of responders and of partial responders and nonresponders. Bars represent mean values and error bars represent standard errors. Asterisk indicates significant difference ($p < 0.05$) between two groups of patients. **A–D**, Distributions of apparent diffusion coefficient (ADC) (**A**), volume transfer constant (K^{trans}) (**B**), extracellular extravascular volume fraction (v_e) (**C**), and plasma volume fraction (v_p) (**D**) values are shown.

Fig. 5. Receiver operating characteristic (ROC) curves for dynamic contrast-enhanced MRI (DCE-MRI) parameters (volume transfer constant [K^{trans}], extracellular extravascular volume fraction [v_e], and plasma volume fraction [v_p]) and apparent diffusion coefficient (ADC) values from only primary tumors exhibiting area under ROC curve (AUC) of 0.69 (*dotted line*) and only nodal masses exhibiting AUC of 0.70 (*dashed line*). Incorporation of DCE-MRI parameters and ADC values from both primary tumors and nodal masses into multivariate logistic regression model provided best discriminatory accuracy (AUC = 0.85, *solid line*) in distinguishing between responders and nonresponders with sensitivity of 81.3% and specificity of 75% ($p = 0.006$).