DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING AS A PREDICTOR OF OUTCOME IN HEAD-AND-NECK SQUAMOUS CELL CARCINOMA PATIENTS WITH NODAL METASTASES

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Purpose: Dynamic contrast-enhanced MRI (DCE-MRI) can provide information regarding tumor perfusion and permeability and has shown prognostic value in certain tumors types. The goal of this study was to assess the prognostic value of pretreatment DCE-MRI in head and neck squamous cell carcinoma (HNSCC) patients with nodal disease undergoing chemoradiation therapy or surgery.

Methods and Materials: Seventy-four patients with histologically proven squamous cell carcinoma and neck nodal metastases were eligible for the study. Pretreatment DCE-MRI was performed on a 1.5T MRI. Clinical follow-up was a minimum of 12 months. DCE-MRI data were analyzed using the Tofts model. DCE-MRI parameters were related to treatment outcome (progression-free survival [PFS] and overall survival [OS]). Patients were grouped as no evidence of disease (NED), alive with disease (AWD), dead with disease (DOD), or dead of other causes (DOC). Prognostic significance was assessed using the log-rank test for single variables and Cox proportional hazards regression for combinations of variables.

Results: At last clinical follow-up, for Stage III, all 12 patients were NED. For Stage IV, 43 patients were NED, 4 were AWD, 11 were DOD, and 4 were DOC. Ktrans is volume transfer constant. In a stepwise Cox regression, skewness of Ktrans (volume transfer constant) was the strongest predictor for Stage IV patients (PFS and OS: \( p < 0.001 \)).

Conclusion: Our study shows that skewness of Ktrans was the strongest predictor of PFS and OS in Stage IV HNSCC patients with nodal disease. This study suggests an important role for pretreatment DCE-MRI parameter Ktrans as a predictor of outcome in these patients. © 2012 Elsevier Inc.

Dynamic contrast enhanced MRI (DCE-MRI), Head and neck squamous cell carcinoma (HNSCC), Volume transfer constant (Ktrans).

INTRODUCTION

The American Cancer Society estimated that in 2010 approximately 49,260 new cases of oral cavity, pharyngeal, and laryngeal cancers would be diagnosed and that 11,480 deaths would occur from these cancers in the United States (1). Treatment for advanced (Stage III or IV) head and neck squamous cell carcinoma (HNSCC) usually consists of combined chemoradiation therapy or complete surgical resection followed by adjuvant chemotherapy and/or radiation therapy (2–5). Despite advances in the treatment options available, the overall survival rate of HNSCC patients with advanced disease has not improved substantially over the past decade (6). Thus, an a priori predictor of outcome could prove extremely valuable by allowing oncologists to intervene with alternative therapies if necessary.

Reported tumor-based prognostic factors for locoregional control of HNSCC include the presence and extent of nodal metastases, T-stage, tumor size, human papilloma virus (HPV) tumor positivity, and other biological markers (7–10). In advanced HNSCC, the T stage and nodal disease at initial presentation are the most important predictors of outcome (8). The use of individual and combined markers to predict outcome in HNSCC has shown conflicting results. For example, various investigators have
recorded different degrees of correlation between tumor suppressor gene p53 status and outcome (11–13). Epidermal growth factor receptor (EGFR) overexpression has been shown to correlate strongly with advanced tumor stage, shorter disease-free survival, and overall survival in HNSCC (14). Recently, HPV-positive HNSCC has been shown to respond to treatment better than non-HPV-positive HNSCC (15). Preliminary evidence supports the potential role of such biomarkers in disease management, but their value needs to be tested in prospective validation studies (7).

Noninvasive measurement of tumor perfusion and permeability using gadopentetate dimeglumine (Gd-DTPA)-based dynamic contrast-enhanced MRI (DCE-MRI) has shown promise in predicting treatment response and outcome in selected tumors (16–21). DCE-MRI involves assessing changes in signal intensity over time. With proper quantitative analysis, the data may provide parameters reflecting tumor-vessel permeability, tumor perfusion, and extracellular-extravascular volume fraction (22–25). Studies have suggested that DCE-MRI parameters such as K\text{trans} (volume transfer constant) and primary tumor blood volume (BV) may predict early response in HNSCC patients treated with chemoradiation (20, 26). This study aimed to assess the prognostic value of pretreatment DCE-MRI parameters in HNSCC patients with nodal disease undergoing chemoradiation therapy or surgery.

METHODS AND MATERIALS

Patient selection

The institutional review board (IRB) granted a waiver of informed consent for this retrospective study that included 74 patients with histologically proven squamous cell carcinoma (SCC) and neck nodal metastases. Their clinical characteristics are listed in Table 1. Of 74 patients, 61 had primary treatment with chemoradiation and 13 underwent surgery (Table 1). Patients received treatment as per standard guidelines (4, 5, 27, 28) (see Table 2 for details).

DCE-MRI methodology

All patients had a baseline DCE-MRI performed before surgery or chemoradiation therapy (mean 16 ± 11 days). MR images were acquired on a 1.5-Tesla Excite scanner (General Electric, Milwaukee, WI) with a four-channel neurovascular phased-array coil for signal reception and a body coil for transmission. The MR imaging protocol for the neck survey included rapid scout images, multiplanar (axial, coronal, and sagittal) T2-weighted images and neurradiologist identified the largest lymph node in the neck region for DCE-MRI study. DCE-MRI data acquisition and analysis have been described previously (29, 30). DCE-MRI images were acquired using a fast multiphase spoiled gradient echo sequence. Antecubital vein catheters delivered a bolus of 0.1 mmol/kg Gd-DTPA (Magnevist; Berlex Laboratories, Wayne, NJ) at 2 cc/s, followed by saline flush using an MR-compatible programmable power injector (Spectris; Medrad, Indianola, PA). The entire node was covered contiguously with 5- to 7-mm thick slices, zero gap, yielding 3–6 slices with 3.75–7.5 sec temporal resolution. Acquisition parameters were as follows: repetition time = 9 msec, echo time = 2 msec, 30° flip angle (\(\alpha\)), two excitations, 15.63-kHz receive bandwidth, field

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemoradiation therapy (n = 61)</th>
<th>Surgery (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–69, n (%)</td>
<td>55 (90)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>≥70, n (%)</td>
<td>6 (10)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Range</td>
<td>38–83</td>
<td>41–79</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (87)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (13)</td>
<td>3 (23)</td>
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<td>KPS (%), Median</td>
<td>90</td>
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<td>Range</td>
<td>80–100</td>
<td>90–100</td>
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<td>Alcohol consumption, n (%)</td>
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<td>2 (15)</td>
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<td></td>
</tr>
<tr>
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<td>42 (69)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>No</td>
<td>19 (31)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Clinical stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10 (16)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>IV</td>
<td>51 (84)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Primary tumor location, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>61 (100)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>0</td>
<td>4 (31)</td>
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<tr>
<td>Unknown primary</td>
<td>0</td>
<td>6 (46)</td>
</tr>
<tr>
<td>HPV status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16 (26)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Negative</td>
<td>21 (34)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Unknown</td>
<td>24 (40)</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>

Abbreviations: HPV = human papilloma virus; KPS = karnofsky performance status.

of view = 18–20 cm, 256 × 128 matrix that was zero filled to 256 × 256 during image reconstruction, and 40–80 time course data points collected.

All DCE-MRI analyses were conducted by an investigator blinded to patient identity, treatment group, scan date, and patient outcome. DCE-MRI data were analyzed with IDL 5.4 (Research Systems, Boulder, CO). For the tumor tissue time course data, regions of interest (ROIs) were manually drawn by the same neuroradiologist who outlined the contrast-enhanced lymph nodes for signal intensity measurements. All the slices containing the tumor were outlined and analyzed. Quantitative DCE-MRI analyses of the tumor tissue time course data were performed using the Tofts model (24). For functional analysis of tissue microcirculation, Tofts et al. (24) proposed, in a consensus paper, kinetic parameters to describe tumor and tissue permeability using a two compartment (i.e., blood
plasma and extravascular extracellular space [EES]) model. A population-based arterial input function was used (29). The data were fit to the Tofts model to determine the kinetic parameters $K_{\text{trans}}$ (the volume transfer constant between the plasma and the EES in min$^{-1}$), $v_e$ (the volume fraction of the EES, which is dimensionless), and $k_{ep}$ (the rate constant describing the contrast transfer between the EES and plasma in min$^{-1}$, which equals the ratio $K_{\text{trans}}/v_e$). DCE-MRI analyses of each ROI were done on a pixel-by-pixel basis. Histogram analysis was done for all pixels within the ROI, which yielded median, standard deviation, and skewness. Histograms were normalized to the total number of tumor voxels to allow direct comparison between patients. The standard deviation (SD) describes the width of the distribution and is indicative of the tumor heterogeneity (31). The skewness characterizes the asymmetry of the distribution.

**Patient assessment**

A complete medical history was obtained, and clinical tumor assessment was performed before treatment. Clinical follow-up to detect distant metastases or local failure included clinical evaluation and imaging studies. Planned clinical disease evaluation was performed approximately 1–3 months during the first year and included imaging as clinically indicated but was not routine. Local-regional control was assessed at approximately 3 months after completion of treatment. All patients alive had a minimum of 1 year of clinical follow-up (range, 13–64 months, median 40 months). Data was censored at the time of last follow-up. The primary end points calculated were progression-free survival (PFS) and overall survival (OS), consistent with published literature (5). Each patient’s status on last follow-up was classified as no evidence of disease (NED), alive with disease (AWD), dead with disease (DOD), or dead of other causes (DOC) (32).

**Human papilloma virus in situ hybridization**

Assays were performed on 4-μm whole sections of a paraffin-embedded tissue specimens. Tissue for 48 of 74 patients was available for HPV staining. Staining was performed on an automated stainer using INFORM HPV III family 16 probe (Ventana Medical Systems, Tucson AZ) according to the manufacturer’s instructions. The probe has affinities to HPV genotypes 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, and 66. Adequate positive and negative control slides were included in each batch. An HPV-positive tumor was defined as a tumor for which there was specific staining of tumor-cell nuclei for HPV in the analysis.

**Statistical analysis**

There were three data types per patient: outcomes (PFS and OS), potential prognostic variables (demographic and clinical variables that may influence outcome), and DCE-MRI parameters ($K_{\text{trans}}$, $v_e$, and $k_{ep}$). The distributions of the DCE-MRI parameters for the ROIs were summarized as median, mean, standard deviation, and skewness. Relationships between DCE-MRI parameters and prognostic variables were assessed by Spearman correlation coefficients for numeric variables and $r$ test or analysis of variance for categorical variables. T-stage was treated as a numeric variable (1, 2, 3, 4, assigning 2.5 for unknown T stage). N Stage III was combined with N Stage II because there were only two cases of Stage III. Survival analyses were done for PFS and OS using the Kaplan-Meier method to compute survival curves, the log-rank test to assess univariate statistical significance of prognostic variables, and Cox proportional hazards regression to assess statistical significance of combinations of prognostic variables. Significant prognostic factors were determined, and the prognostic significance of DCE-MRI parameters was assessed using Cox regression to adjust for significant prognostic factors. Subset analysis was done for Stage IV patients and patients who received chemoradiation as primary treatment. Results were considered to be statistically significant with a $p$ value $<0.05$. Statistical computations were performed using SAS version 9.2 (SAS Institute, Cary, NC).

**RESULTS**

All 12 clinical Stage III patients were NED at last clinical follow-up. Of the clinical Stage IV patients, 43 were NED, 4 were AWD, 11 were DOD, and 4 were DOC at last clinical follow-up. The average pretreatment values for the median, standard deviation, and skewness of $K_{\text{trans}}$, $v_e$, and $k_{ep}$ for Stage III and Stage IV patients are provided in Table 3. Figure 1 shows representative pretreatment DCE-MRI data. Figure 2 shows representative case of HPV positive and negative staining. Patterns of failure were reviewed. Among 61 patients who received chemoradiation as primary treatment, the initial site of failure was distant for 8 patients and simultaneous distant and locoregional failure for 2 patients. No patient in the chemoradiation cohort had only locoregional disease as the first site of failure. Five patients underwent neck surgery within 4 months of completion of chemoradiation, but this is not considered locoregional failure, because neck dissection is part of multimodality locoregional therapy. All 13 patients who underwent surgery as primary treatment were further treated with chemoradiation or radiation alone. Seven patients received radiation, and six received chemoradiation postsurgery. Patterns of failures showed that one patient had regional failure and two patients had distant failure.

The pretreatment DCE-MRI parameters appeared to give information independent of demographic and clinical because they were not, in general, significantly related to prognostic factors. Correlation coefficients with T Stage, age, and nodal size were very small in most cases ($-0.1 < r < 0.1$), and the few in the ranges $-0.3 < r < -0.2$ or $0.2 < r < 0.3$ were not statistically significant after adjusting for multiple statistical significance testing. Similarly, DCE-MRI parameters did not differ significantly according to categorical variables such as sex, type of treatment, or risk factors such as smoking history. These results were not shown because they were ancillary and not significant. Age was partially confounded with sex, because women were on average significantly older than men in this study sample. Because both could not be entered in the same Cox regression analysis, age was given preference in regression analyses, and thus replacing with sex would yield similar results.

**Prognostic factors for survival**

Univariate survival analyses of PFS and OS showed significant prognostic value for T stage (numeric): $p = 0.004$ (PFS), $p = 0.010$ (OS); N stage (1vs 2/3): $p = 0.028$ (PFS) and $p = 0.050$ (OS); clinical stage (III vs. IV): $p = 0.034$ (PFS) and $p = 0.056$ (OS); age: $p = 0.008$ (PFS) and $p = 0.013$ (OS); sex: $p = 0.008$ (PFS) and $p = 0.009$ (OS); and
Table 3. Pretreatment values (mean/SEM) of dynamic contrast-enhanced MRI parameters in neck nodal metastases of Stage III (n = 12) and Stage IV (n = 58)* patients who had NED.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Median ( \text{K}_{\text{trans}} )</th>
<th>Median ( \text{v}_e )</th>
<th>Median ( \text{k}_{\text{ep}} )</th>
<th>Skewness of ( \text{K}_{\text{trans}} )</th>
<th>Skewness of ( \text{v}_e )</th>
<th>Skewness of ( \text{k}_{\text{ep}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III: NED (n = 12)</td>
<td>0.31 ± 0.03</td>
<td>0.56 ± 0.01</td>
<td>0.63 ± 0.04</td>
<td>3.45 ± 1.26</td>
<td>1.17 ± 0.19</td>
<td>0.73 ± 0.13</td>
</tr>
<tr>
<td>Stage IV: NED (n = 43)</td>
<td>0.26 ± 0.02</td>
<td>0.50 ± 0.02</td>
<td>0.60 ± 0.04</td>
<td>3.65 ± 0.60</td>
<td>0.17 ± 0.02</td>
<td>0.23 ± 0.02</td>
</tr>
<tr>
<td>Stage IV: AWD (n = 4)</td>
<td>0.26 ± 0.02</td>
<td>0.50 ± 0.02</td>
<td>0.60 ± 0.04</td>
<td>3.65 ± 0.60</td>
<td>0.17 ± 0.02</td>
<td>0.23 ± 0.02</td>
</tr>
<tr>
<td>Stage IV: DOD (n = 11)</td>
<td>0.19 ± 0.03</td>
<td>0.52 ± 0.08</td>
<td>0.47 ± 0.05</td>
<td>1.63 ± 0.51</td>
<td>0.11 ± 0.22</td>
<td>0.71 ± 0.26</td>
</tr>
</tbody>
</table>

Abbreviations: AWD = alive with disease; DOD = dead with disease; \( \text{K}_{\text{trans}} \) = rate constant describing the contrast transfer between the EES and plasma in min\(^{-1}\); \( \text{v}_e \) = volume fraction of the extravascular extracellular space; SEM = Standard Error of the Mean.

* The mean/SEM for patients dead of other causes is not included.

The data in this study indicate that lower skewness (i.e., less asymmetry in the distribution) of \( \text{K}_{\text{trans}} \) may be predictive of better outcome in HNSCC patients with Stage IV nodal disease. There is overwhelming evidence that tumors are heterogeneously perfused (33). Imaging vascular heterogeneity by DCE-MRI has been shown to be useful for understanding tumor biology and predicting outcome (34). Jackson et al. (34) reported that tumor heterogeneity is better reflected by the distribution of the DCE-MRI parameter values than by their mean or median. Studies in gliomas, breast, and rectal cancers have shown that tumor heterogeneity measures, such as the upper part of the distribution (95th percentile) or the skewness of the distribution, of DCE-MRI parameter values correlate with overall survival, tumor grade, or radiation treatment outcome (35–38). Tumor heterogeneity in HNSCC has been attributed in part to treatment (chemoradiation vs surgery): \( p = 0.210 \) (PFS) and \( p = 0.039 \) (OS). Disease site, tobacco history, and alcohol addiction were nonsignificant. There was no difference in survival between HPV-positive and HPV-negative patients; the 26 patients (35%) without HPV data had slightly better survival than patients with HPV data, suggesting that high-risk patients had tissue available for assay. Locoregional control was achieved in all but two patients, so this variable was not considered further. In Cox regression analysis, only T stage and either age or sex had a jointly significant relationship to PFS or OS.

**DCE-MRI parameters and survival**

Cox regression analyses of the additive value of DCE-MRI parameters for predicting survival, adjusting for the two primary prognostic factors of T stage and age, showed the following: significant for PFS were skewness of \( \text{K}_{\text{trans}} \) (\( p = 0.011 \)), SD \( \text{v}_e \) (\( p = 0.043 \)), and, marginally, median \( \text{K}_{\text{trans}} \) (\( p = 0.060 \)). The latter two did not add significant prognostic value to skewness of \( \text{K}_{\text{trans}} \). Significant predictors of OS were mean \( \text{v}_e \) (\( p = 0.007 \)), skewness of \( \text{K}_{\text{trans}} \) (\( p = 0.012 \)), and, marginally, median \( \text{K}_{\text{trans}} \) (\( p = 0.067 \)) or SD \( \text{K}_{\text{trans}} \) (\( p = 0.068 \)). The latter three did not add significant prognostic value to mean \( \text{v}_e \).

**Subset analyses**

Survival analyses based on 61 of 74 patients who received chemoradiation as primary treatment yielded similar results to analyses based on the full sample. Analysis was also performed on the subset comprising 62 Stage IV patients, because the 12 Stage III patients experienced 100% PFS during the follow-up period. Cox regression results showed similar results for both PFS and OS: more skewness of \( \text{K}_{\text{trans}} \) (\( p < 0.0001 \) PFS, \( p < 0.001 \) OS), higher T stage (\( p = 0.004 \) PFS, \( p = 0.009 \) OS), and older age (\( p = 0.028 \) PFS, \( p = 0.042 \) OS) were jointly associated with shortened OS. Figure 3A and 3B shows Kaplan-Meier survival curves for skewness of \( \text{K}_{\text{trans}} \).

**DISCUSSION**

The data in this study indicate that lower skewness (i.e., less asymmetry in the distribution) of \( \text{K}_{\text{trans}} \) may be predictive of better outcome in HNSCC patients with Stage IV nodal disease. There is overwhelming evidence that tumors are heterogeneously perfused (33). Imaging vascular heterogeneity by DCE-MRI has been shown to be useful for understanding tumor biology and predicting outcome (34). Jackson et al. (34) reported that tumor heterogeneity is better reflected by the distribution of the DCE-MRI parameter values than by their mean or median. Studies in gliomas, breast, and rectal cancers have shown that tumor heterogeneity measures, such as the upper part of the distribution (95th percentile) or the skewness of the distribution, of DCE-MRI parameter values correlate with overall survival, tumor grade, or radiation treatment outcome (35–38). Tumor heterogeneity in HNSCC has been attributed in part to...
regions of hypoxia and necrosis within the tumor (39). In a study of 28 HNSCC patients with Stage IV disease, Brizel et al. (40) found that tumor hypoxia (measured by pO\(_2\)) adversely affected prognosis. Recently, in a study of 13 patients, our group showed that hypoxic metastatic neck lymph nodes were poorly perfused (i.e., had significantly lower \(k_{ep}\) and \(K^{\text{trans}}\) values) compared with nonhypoxic nodes. Additionally, hypoxic nodes had a more asymmetric

Fig. 1. (A) Magnetic resonance image illustrating left neck lymph node (with arrow) of patient who continued to have no evidence of disease for 57 months after concurrent chemoradiation therapy (male, aged 56 years, primary tonsil cancer). (B) A corresponding postcontrast axial image extracted from the dynamic contrast-enhanced MRI scan, on which the color, calculated parametric \(K^{\text{trans}}\) map of the node is overlaid. (C) Magnetic resonance image illustrating right neck lymph node (with arrow) of patient who died 5 months after surgery due to distant recurrence (male, aged 56 years, primary base of tongue cancer). (D) A corresponding postcontrast axial MR image extracted from the dynamic contrast-enhanced MRI scan, on which the color, calculated parametric \(K^{\text{trans}}\) map of the node is overlaid. The heterogeneity of the necrotic node can be appreciated in the \(K^{\text{trans}}\) map.

Fig. 2. (A) Positive human papilloma virus in situ hybridization on a tumor from a patient who received chemoradiation and continued to have no evidence of disease at 30 months (female, aged 79 years, primary oropharynx cancer). (B) Negative human papilloma virus tumor from a patient who received chemoradiation and died of disease after 27 months of treatment (male, aged 52 years, primary oropharynx cancer).
distribution of \( k_{ep} \) values than did nonhypoxic nodes (30). These 13 patients were also included in the present study.

In advanced HNSCC, tumor stage and neck node involvement are widely recognized as negative prognostic factors (8, 41, 42). Our results have shown that in Cox regression analysis, only T stage and either age or sex had a jointly significant relationship to PFS or OS. The present study examined imaging measurements from neck nodal metastases only. The primary endpoints of the analysis in this study were PFS (including assessment of all tumor sites) and OS, rather than just disease progression at the primary site. Our results show that information about tumor vascularity from a priori DCE-MRI may help in stratifying HNSCC patients with Stage IV nodal disease for risk-adjusted treatment selection.

DCE-MRI parameters have shown promise as early markers of response in HN cancers (20, 26). Cao, et al. (26) performed quantification of blood volume and blood flow from DCE-MRI data before therapy and 2 weeks after initiation of chemoradiation in 14 HNSCC patients; they found that an increase in available primary tumor blood volume during RT was associated with locoregional control. The median follow-up for the 10 surviving patients in their study was 9.7 months (range, 5.3–27 months) (26). In a cohort of 33 HNSCC patients who were treated with chemoradiation, Kim et al. (20) found that the average pretreatment \( K^{\text{trans}} \) value of the complete response group was significantly higher \( (p = 0.001) \) than that of the partial response group at 6-month follow-up. Our study has a larger number of patients \( (n = 74 \text{ patients}) \) and longer clinical follow-up (minimum 1 year).

The use of functional imaging (with CT, PET, or MRI) is gaining acceptance in the management of patients with HN cancers (43). DCE-MRI measures changes in signal intensity, whereas perfusion CT measures changes in tissue attenuation during a dynamic contrast infusion (43). In a study of 105 HNSCC patients who underwent perfusion CT followed by radiotherapy, Hermans et al. (44) showed that patients with lower median perfusion values had a significantly higher local failure rate \( (p <0.05) \). The results confirmed the hypothesis that less-perfused tumors respond poorly to radiotherapy. Consistent with this hypothesis, we found that the skewness of the perfusion parameter \( K^{\text{trans}} \) was higher in Stage IV patients who had heterogeneous, poorly perfused tumors and died of disease thereafter.

A few studies have shown that \(^{18}\)F-fluorodeoxyglucose uptake intensity in HNSCC has some prognostic value (45–47). These studies have used the maximum standardized uptake value \( (\text{SU}V_{\text{max}}) \) as a predictor of outcome. Perfusion CT and PET, unlike DCE-MRI, use ionizing radiation, which has known risks. Efforts have been initiated by the National Cancer Institute Cancer Imaging Program to develop DCE-MRI as a mainstay of diagnostic imaging that can provide quantitative data for use in multicenter clinical trials (48). DCE-MRI is rapidly gaining acceptance as a tool for early assessment of therapeutic response in clinical trials (18). In a Phase II study of HNSCC patients treated with sunitinib, a significant decrease in \( K^{\text{trans}} \) was seen in three of the four patients who received DCE-MRI monitoring (21).

Our study has a few limitations. First, the study design was retrospective, and the patients were not consecutive. Second, patients received different treatments; however, this reflects daily practice at our center. Thirdly, we had HPV status on 48 (65%) patients; it would have been better if we had the data for the whole population, particularly given that the oropharynx was the predominant primary site. Finally, our study included no direct pathological validation of heterogeneity (necrosis). Future prospective validation studies are necessary to confirm our findings in a larger patient population, and known predictors that were not significant in this study should be pursued.

**CONCLUSION**

Skewness of \( K^{\text{trans}} \) was a strong predictor of progression-free survival and overall survival in HNSCC patients with Stage IV nodal disease. This finding suggests an important role for this pretreatment DCE-MRI parameter as a predictor of outcome in HNSCC patients with advanced disease.
REFERENCES