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ORIGINAL RESEARCH

Prediction of Locoregional Control in Head and Neck Squamous Cell Carcinoma with Serial CT Perfusion during Radiotherapy

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BACKGROUND AND PURPOSE: Tumor hypoxia is a known factor of radioresistance in HNSCC. CTP is a noninvasive method of measuring tumor perfusion in vivo. The purpose of our study was to determine serial changes in tumor perfusion in HNSCC during a course of RT by using CTP and to correlate tumor perfusion measurements to LRC.

MATERIALS AND METHODS: A prospective study was performed in 15 patients with HNSCC receiving definitive RT who underwent serial CTP before RT; at weeks 2, 4, and 6 of RT; and 6 weeks after RT. The median follow-up was 28 months (range, 6–44 months). Thirteen patients achieved LRC, and 2 patients had LRF. Tumor perfusion parameters, including BF, BV, MTT, and CP, were obtained by using a deconvolution-based analysis.

RESULTS: Pretreatment tumor BF was significantly higher in patients who achieved LRC, 118.0 mL/100 g/min, compared with those with LRF, 53.4 mL/100 g/min ($P = .004$). Similarly, pretreatment CP was higher in patients with LRC, 16.6 mL/100 g/min, compared with those with LRF, 7.7 mL/100 g/min ($P = .02$). At week 2 of RT, tumor BF parameters showed a 27.5% increase versus an 18.1% decrease from pretreatment BF values ($P = .046$) in patients with LRC and LRF, respectively. A decrease in BF and BV was observed in both groups 6 weeks after RT compared with these values at baseline scanning.

CONCLUSIONS: An increase in tumor BF and CP by using CTP early during a course of RT predicts LRC in patients with HNSCC treated with RT.

ABBREVIATIONS: BF = blood flow; BV = blood volume; CP = capillary permeability surface product; CTP = CT perfusion; 3D-CRT = 3D radiotherapy; FDG = fluorodeoxyglucose; GTV = gross tumor volume; HNSCC = head and neck squamous cell carcinoma; IMRT = intensity-modulated radiation therapy; LRC = locoregional control; LRF = locoregional failure; M = metastasis; MTT = mean transit time; N = node; PET = positron-emission tomography; RT = radiotherapy; SCC = squamous cell carcinoma; SUV = standardized uptake value; T = tumor; VEGF = vascular endothelial growth factor

HEAD & NECK

ORIGINAL RESEARCH

HNSCC constitutes approximately 5% of all cancers, accounting for 35,720 new cases and 7600 deaths in the United States in 2009.[1] LRF occurs in approximately 50% of patients and continues to be a therapeutic challenge despite advances in RT, chemotherapy, and surgery. Improvements in radiologic imaging such as high-resolution CT, MR imaging, and FDG-PET, have significantly aided clinical diagnosis, staging, RT planning, and posttreatment surveillance. Despite improvements in imaging for staging and pretreatment planning, determining which patients will achieve LRC with RT or chemoradiotherapy without salvage surgery and early detection of tumor recurrence are difficult in the initial post-treatment period.

Tumor hypoxia has been a known factor contributing to radioresistance and poor survival rates in HNSCC.[2] Because neovascularity is an important feature of HNSCC,[3] a sufficient blood supply is vital for tumor support and rapid growth. Therefore, direct quantification of tumor oxygenation during the course of RT could be of potential prognostic value. CTP is a noninvasive method of measuring perfusion through tumor tissue, which can provide functional information about tumor vascularity in addition to conventional anatomic information by using physiologic parameters, such as BF, BV, MTT, and CP.[4] Thus, CTP may provide information for estimating tumor hypoxia and possible radioresistance or tumor oxygenation and improved radiosensitivity. Studies using CTP before therapy have shown altered perfusion parameters within malignant tissues of the head and neck before therapy.[5] Few data exist regarding serial CTP changes at various time points during RT and whether these parameters can predict the early response of HNSCC to RT.[6] The hypothesis is that if CTP measurements can quantify tumor perfusion, then areas of increased tumor perfusion may result in improved LRC in patients treated with RT as a result of improved oxygenation. Additionally serial CTP studies during RT may quan-

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tify a dynamic state of perfusion in the tumor in response to radiation.

Therefore, we conducted a prospective study examining CTP as a noninvasive method to measure regional tumor perfusion parameters of patients with HNSCC undergoing definitive RT, before, during, and after RT, and to determine whether CTP parameters during these time points correlate with LRC.

Materials and Methods

Patient Population and Treatment

The study protocol was approved by the institutional review board as a prospective single-arm study. Written informed consent was obtained from all patients before they entered the study. Fifteen patients undergoing RT with curative intent for HNSCC participated in the study between 2007 and 2008. All patients underwent staging workup, including initial evaluation with history and physical examination with a focused head and neck evaluation, panendoscopy and biopsy, renal function tests, CT, and FDG-PET/CT. Concurrent chemotherapy was also administered in patients with stages III and IV nonmetastatic disease. Patients received 6–7 weeks of radiation for a total dose of 70–72 Gy (median dose, 70 Gy) by using 3D-CRT in 2 patients and IMRT in 13 patients. Baseline CTP parameters were calculated as well as percentage change from baseline to weeks 2, 4, and 6 of RT and 6 weeks post-RT (corresponding to median radiation doses of 12.72, 33.92, 55.12, and 69.96 Gy, respectively). Renal function was assessed before each CTP, and the study scan was not obtained if the creatinine level was >1.5 mg/dL. Pretreatment tumor volumes of the primary and nodal disease were drawn by a single board-certified radiation oncologist on the contrast-enhanced CT scan with the aid of PET/CT to generate GTVs, which were used for radiation planning (Pinnacle3, Version 7.6; Philips Healthcare, Best, the Netherlands).

Evaluation of Treatment Response and LRC

LRC was measured from the end of radiation treatment to the date of local or regional relapse. Survival time was measured from the end of radiation therapy until death or last follow-up. The Kaplan-Meier product-limit method was used to estimate the probabilities of tumor control and survival rates.

A complete clinical response was defined as patients obtaining disappearance of the tumor by clinical examination and standard CT 3 months after completion of RT. Patients who had persistent disease after RT included those who achieved a partial response, defined as ≥50% shrinkage of tumor, or no response to therapy, ≤50% reduction in tumor. Patients were examined clinically at 6 weeks and 6–12 weeks thereafter. Post-RT imaging consisted of a CTP scan at 6 weeks and a FDG-PET/CT at 8–12 weeks posttreatment. FDG-PET/CT was used to assess clinical response (in addition to clinical examination at 3 months) as part of standard treatment care.

Patients with suspected disease persistence by clinical examination or imaging at 12 weeks post-RT underwent examination under anesthesia and biopsy and/or salvage surgery. If biopsy or salvage surgery did not reveal any pathologic evidence of residual cancer, then patients were classified as having LRC.

CTP Data Acquisition

A 64-multidetector row CT scanner (Lightspeed VCT; GE Healthcare, Milwaukee, Wisconsin) was used for all CTP data acquisitions. An initial noncontrast CT scan (5 mm thick, 120 kV, 125 mA) was obtained through the known primary and nodal site, which served as a localizer for the CTP scan. Eight contiguous 5-mm-thick sections, 4-cm craniocaudal coverage, were selected to cover the largest axial diameter of the primary and nodal tumor mass. Patients received a power injection of 40-mL nonionic iodinated contrast agent (4 mL/s, 350 mg/mL) (ioversol, Optiray 350; Mallinckrodt, St Louis, Missouri). At 5 seconds after the start of the intravenous contrast injection, a cine (continuous) acquisition was initiated by using the following parameters: 120 kV, 50 mA, 5 × 8 mm section coverage, 1-second rotation for a 50-second duration, followed by another 20-second acquisition beginning at 3 minutes after the start of the intravenous contrast injection. The 1-second images were reformatted at 0.5-second intervals, and the 5-mm sections were reformatted into 10-mm-thick sections. The cumulative radiation dose from the CTP scan was measured in a 16-cm head and neck phantom before enrolling patients. The radiation dose measured from the CTP scan was the CT dose index volume and dose-length product of 476.19 + 190.48 mGy and 1904.76 + 761.90 mGy/cm, respectively, for all CTP studies because we used a fixed protocol.

CTP Data Analysis

The CTP data were postprocessed by using a commercially available software package based on a deconvolution technique (Advantage Windows workstation, GE Healthcare) with a CTP3 software package.[4] A single neuroradiologist, who was aware of the primary tumor site, placed the regions of interest. The regions of interest were selected in available arterial input vessels by using the internal carotid artery to generate contrast-enhanced curves. The data were processed into maps that corresponded to MTT (seconds), BV (milliliters per 100 g), BF (milliliters per 100 g per minute), and CP (milliliters per 100 g per minute). Then, regions of interest were placed in the primary tumor site where the tumor cross-section was largest, to obtain CTP measurements. Perfusion parameters (BF, BV, MTT, and CP) were estimated via deconvolution-based calculations.[4]

Statistical Analysis

For each perfusion parameter, 2 measurements in the center of the tumor were recorded from each CTP map, and an average of the 2 values was obtained for each patient. Baseline CTP parameters were calculated as well as percentage change from baseline to weeks 2, 4, and 6 of RT and 6 weeks post-RT (corresponding to median radiation doses of 12.72, 33.92, 55.12, and 69.96 Gy, respectively).

Two-sided hypotheses were used for all tests, with a significance (α) level of .05. Mean baseline values and percentage change between patients who achieved LRC versus patients who did not achieve LRC were compared by using the independent-samples t test. LRC was measured from the end of RT to the date of local or regional relapse. Survival time was measured from the end of RT until death or last follow-up.

Results

Patient and Treatment Characteristics

The median age of the patients was 58 years (range, 45–68 years). There were 12 men and 3 women. All patients were smokers, with a median pack-year history of 38 (range, 10–100). All patients were staged according to the 2002 American Joint Committee on Cancer classification.[7] One patient presented with an unknown primary with nodal disease; CTP

Table 1: Patient and tumor characteristics of 15 patients with HNSCC undergoing serial CTP imaging during RT

Age (yr)	Sex	Primary Site	T	N	M	Overall Stage
46	M	Base of tongue	2	2c	0	IVa
68	M	L auricle	2	0	0	II
60	M	Oral tongue	4a	3	0	IVb
54	M	L tonsil	2	2c	0	IVa
59	F	Base of tongue	4a	2b	0	IVa
63	M	Nasopharynx	2	2	0	III
65	M	Larynx	2	0	0	II
63	M	Larynx	4a	0	0	IVa
45	M	Nasopharynx	4	1	0	IVa
48	F	L tonsil	2	2b	0	IVa
46	M	Nasopharynx	3	2c	0	IVa
57	M	R tonsil	2	2c	0	IVa
55	F	Larynx	3	0	0	III
61	M	L hypopharynx	3	0	0	III
50	M	Unknown primary	0	2b	0	IVa

Table 2: Mean tumor perfusion parameters for the whole patient cohort before, during, and after RT[a]

		During RT			
Parameter (mean value)	Baseline Prior to RT ($n = 15$)	Week 2 ($n = 15$)	Week 4 ($n = 14$)	Week 6 ($n = 11$)	6 Weeks Post-RT ($n = 12$)
BF (mL/100 g/min)	109.4 (65.3)	123.5 (73.7)	109.6 (94.6)	126.7 (146.0)	64.3 (54.3)
BV (mL/100 g)	5.5 (1.9)	5.8 (2.5)	4.9 (2.8)	5.9 (4.8)	3.9 (2.8)
MTT (s)	5.1 (2.5)	4.8 (2.4)	4.9 (4.4)	4.9 (2.4)	6.0 (2.5)
CP (mL/100 g/min)	15.4 (9.2)	20.0 (8.9)	20.5 (13.4)	10.6 (7.9)	14.6 (8.8)

[a] Data are presented as mean ± SD.

measurements of the nodal disease were performed. Patient and tumor characteristics are shown in Table 1.

Thirteen patients received IMRT for a total dose of 70 Gy in 33 fractions at 2.12 Gy per fraction by using a simultaneous integrated boost technique, and 2 patients received 3D-CRT, of which 1 patient received a concomitant boost technique to 72 Gy. All patients completed RT without any planned treatment breaks.

Fourteen patients underwent concurrent chemotherapy, of whom 13 received concurrent weekly cisplatin chemotherapy (30 mg/m^2) and 1 received weekly cetuximab (250 mg/m^2).

CTP Acquisition

All patients completed the baseline and week 2 of RT CTP studies. Fourteen of 15 patients completed CTP imaging at week 4 of RT, 11 of 15 patients completed the CTP scan at week 6 of RT (the CP parameter was not measurable for 1 patient at week 6 due to motion artifacts; $n = 10$), and 12 of 15 patients completed the CTP scan at 6 weeks post-RT (Table 2). During the course of the protocol, a total of 5 patients could not undergo all CTP scanning. Reasons included difficult intravenous access in 2 patients (resulting in omission of the CTP scans at weeks 4 and 6 during RT), contrast injection failure in 1 patient (omission of the CTP scan at 6 weeks post-RT), and the development of renal insufficiency during chemoradiotherapy (resulting in omission of the CTP scans at week 6 during RT and 6 weeks post-RT in 2 patients).

LRC and Survival

With a median follow-up of 28 months (range, 6–44 months), 13 patients achieved LRC and 2 patients had LRF at last follow-up. Four of 15 patients developed distant metastases. The actuarial LRC rate at 1 and 2 years was 87%. The freedom from distant metastases at 1 and 2 years was 93% and 68%, respectively. The overall survival rate at 1 and 2 years was 93% and 86%, respectively. The disease-free survival at 1 and 2 years was 80% and 58%, respectively.

Surgical Management of Persistent Disease and Pathologic Assessment of Treatment Response

Four of 15 patients underwent surgical salvage after RT, 2 of whom had histologically confirmed persistent disease after chemoradiation and underwent subsequent salvage surgery. Two patients with a partial clinical response of nodal disease at 12 weeks underwent subsequent salvage neck dissection; histopathologic specimens revealed a complete pathologic response.

Baseline CT Data and GTVs

At baseline, the mean tumor volume of the primary tumor was 39.46 ± 44.42 mL; 10 patients had nodal disease at presentation, with a mean nodal volume of 47.04 ± 58.71 mL. The mean primary tumor volume was 26.68 mL and 116.16 mL for patients with LRC and LRF, respectively ($P = .003$).

CTP Data Analysis

The mean values for BF, BV, CP, and MTT for the whole patient cohort at baseline; weeks 2, 4, and 6 of RT (median radiation doses of 12.72, 33.92, and 55.12 Gy, respectively); and 6 weeks after completion of RT (median dose, 69.96 Gy) are described in Table 2. The mean values for BF, BV, MTT, and CP according to their LRC status are described in Table 3.

BF measurements at baseline were significantly higher in patients who achieved LRC (118.0 mL/100 g/min) compared

Table 3: Tumor perfusion parameters by LRC status, before, during, and after RT[a]

Parameter	Locoregional Status	Baseline Prior to RT, LRF (n = 2); LRC (n = 13)	During RT (SD)			6 Weeks Post-RT, LRF (n = 2); LRC (n = 10)
			Week 2, LRF (n = 2); LRC (n = 13)	Week 4, LRF (n = 2); LRC (n = 12)	Week 6, LRF (n = 1); LRC (n = 10)	
BF (mL/100 g/min)	LRF	53.4 (1.8)	43.9 (9.9)	217.7 (243.8)	16.2 (NA)	28.4 (20.8)
	LRC	118.0 (66.1)	135.8 (71.5)	91.6 (51.9)	137.8 (149.0)	71.5 (56.6)
P value		.004	.0008	.598	NA	.122
BV (ml/100 g)	LRF	4.5 (1.9)	3.6 (1.1)	6.7 (6.2)	2.3 (NA)	3.2 (3.1)
	LRC	5.6 (2.0)	6.1 (2.5)	4.6 (2.2)	6.2 (4.9)	4.0 (2.8)
P value		.546	.081	.721	NA	.766
MTT (s)	LRF	6.4 (2.0)	7.2 (2.8)	3.5 (1.8)	11.1 (NA)	7.8 (2.2)
	LRC	4.9 (2.6)	4.4 (2.2)	5.1 (4.7)	4.2 (1.3)	5.7 (2.5)
P value		.461	.379	.438	NA	.381
CP (mL/100 g/min)	LRF	7.7 (2.3)	6.6 (5.6)	29.5 (28.5)	4.4 (NA)	9.9 (9.2)
	LRC	16.6 (9.3)	22.0 (7.5)	19.0 (11.1)	11.3 (8.1)	15.6 (8.9)
P value		.02	.098	.694	NA	.537

[a] Data are presented as a mean ± SD. *P* values are calculated from an independent samples *t* test comparing mean CTP parameter values in the LRC versus LRF groups. CTP parameters were not measured at week 6 in 1 of the 2 patients with LRF; these are indicated by NA.

with LRF (53.4 mL/100 g/min, $P = .004$). Similarly, BF measurements at week 2 (12.72 Gy) of RT were significantly higher in patients who achieved LRC (135.8 mL/100 g/min) compared with LRF (43.9 mL/100 g/min, $P = .0008$).

CP measurements at baseline were significantly higher in patients who achieved LRC (16.6 mL/100 g/min) compared with LRF (7.7 mL/100 g/min, $P = .02$). CP measurements at week 2 (12.72 Gy) of RT were higher in patients who achieved LRC compared with those with LRF, though the difference between the 2 groups trended toward statistical significance ($P = .098$).

When using the mean cutoff for GTV primary (39.46 mL), we found no significant differences between baseline BF ($P = .85$), BV ($P = .64$), MTT ($P = .71$), and CP ($P = .22$) values.

CTP Parameters during RT as a Function of Baseline Values

At week 2 of RT (12.72 Gy), tumor BF parameters showed a 27.5% increase compared with pretreatment BF values in patients who achieved LRC versus an 18.1% decrease from pretreatment BF values ($P = .046$) for those with LRF (Fig 1 and On-line Table 1). Percentage changes in BF parameters at weeks 4 and 6 and after RT were not significantly different between the 2 groups. Paradoxically, the percentage change in BF in the LRC group decreased from baseline at week 4 and then increased at week 6 of RT. In the LRF group, our findings at week 4 were unclear due to a single outlier resulting in very high BF parameters in the LRF group (On-line Table 2). This was attributed to motion artifacts in a patient with laryngeal cancer. For patients with both LRC and LRF, BF appeared decreased 6 weeks after completion of RT compared with their baseline values.

The percentage change in BV increased in patients with LRC compared with those with LRF at week 2 of RT compared with baseline ($P = .053$). MTT parameters were not found to be significantly different between the 2 groups of patients, and no significant patterns were identified. The percentage change at week 2 in CP was noted to be higher in patients with LRC compared with patients with LRF ($P = .106$) (On-line Table 1).

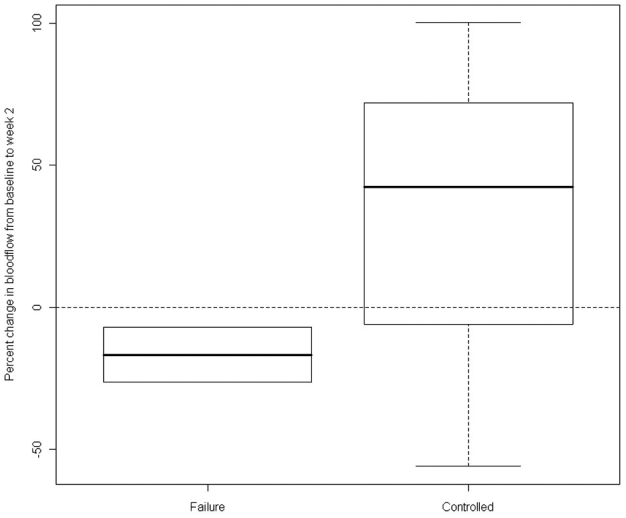

Fig 1. Treatment outcome compared with the percentage change in BF from baseline to week 2 of RT

Discussion

CTP is a functional imaging tool that can supplement conventional CT for mapping the vascularity of the tumor environment. In our study, we found that in patients with HNSCC, blood flow as measured by CTP increased during the 2nd week at 12.72 Gy and then decreased during the 4th week at 33.92 Gy of RT in patients who achieved LRC, whereas patients who had LRF after RT had a decrease in BF relative to their baseline value at 12.72 Gy and then an increase at 33.92 Gy. BF in patients with LRC was noted to rise again at 55.12 Gy and then to subside in the post-RT period compared with that in patients with LRF. These results suggest that a higher BF in tumor tissue at baseline and early during the course of RT resulted in improved tumor control with RT.

Tumors that demonstrated higher baseline BF may represent regions of improved oxygenation and a greater sensitivity to radiation-induced free radical damage. Our study also suggests that in patients with LRC, if BF increases from baseline during the initial course of RT, this change may

result in an increased sensitivity of tumor cells to radiation-induced damage with each fraction of RT. In contrast, in patients with LRF, as the BF decreases during RT, this change may further increase the radioresistance of the tumor as patients go through each fraction of RT.

Our study findings for the baseline perfusion values are consistent with the findings of Hermans et al[8] demonstrating, in a study of 105 patients treated with definitive radiation therapy for HNSCC, that the perfusion rate by using dynamic CT before treatment was a predictor for local outcome with lower pretreatment perfusion rates of ≥83.5 mL/min/100 g correlated with decreased local control. Our study findings for the baseline perfusion values for BF of 118.0 mL/min/100 g in patients who were locally controlled were higher than the 83.5 mL/min/100 g cutoff point, compared with patients who were not locally controlled (53.4 mL/min/100 g). Furthermore, our study demonstrated that BF parameters during the course of RT remained higher than the 83.5 mL/min/100 g cutoff value throughout the duration of RT in patients with LRC. Bisdas et al[9] also showed the long-term predictive value of baseline BF and CP measurements from CTP imaging for local control in 84 patients undergoing chemoradiation. Higher BF and CP values significantly correlated with local control compared with LRF. Patients in our cohort who had LRC also had smaller mean tumor volumes compared with patients with LRF. These findings were similar to those in a series of 19 patients with oropharyngeal cancer undergoing induction chemotherapy, in which there were significant correlations between pretreatment tumor volume and baseline BF and MTT perfusion parameters, which predicted progression-free survival.[10] Smaller tumors may have areas of improved BF and oxygenation compared with larger tumors, which often outstrip their blood supply, resulting in a greater hypoxic fraction and decreased perfusion.

While studies also have shown altered perfusion parameters within malignant tissues of the head and neck before undergoing therapy, few studies examine the variations in perfusion parameters during RT. Surlan-Popovic et al[6] studied 20 patients with locally advanced HNSCC undergoing 2 CTP scans after 40 and 70 Gy of chemoradiotherapy. Patients who were classified as responders showed a significant reduction in BF noted after 40 and 70 Gy. Similar perfusion values can be found in our study at 33.92 Gy and 6 weeks after RT (69.96 Gy), when BF was decreased. Our study, however, measured additional time points that demonstrated an initial increase in BF at 12 Gy and then again at 55 Gy. Our results show that BF fluctuates during the course of RT and may be highly dependent on the cumulative therapeutic radiation dose and relative timing of the CTP. This may explain variations of results in these studies, depending on the design of the study and at which time and dose fraction the CTP measurements were made. The initial rise in BF at week 2 followed by a decrease at week 4 and then a rise again at week 6 shows similarities to animal models of depopulation of oxygenated cells with RT and subsequent tumor reoxygenation due to fractionation of radiation therapy.[11] The fluctuations in perfusion parameters in patients with HNSCC at the different dose points may be similar to those in animal models of tumor response to fractionation, demonstrating that the oxygenation of the tumor is constantly changing as oxygenated cells depopulate and hypoxic areas reoxygenate after each radiation dose.[11]

Surlan-Popovic et al[6] additionally showed that a nonsignificant increase in BF, BV, and CP was seen in patients with LRF at 40 and 70 Gy, which was difficult to ascertain from our study due to the limited number of treatment failures and decreasing number of scans at weeks 4 and 6 of treatment.

In the current study, most patients underwent IMRT by using a simultaneously integrated boost or "dose-painted" technique, while in the study by Surlan-Popvic et al,[6] all patients underwent 3D conformal RT. This method of IMRT results in a more heterogeneously delivered radiation-dose distribution to the tumor compared with 3D conformal radiation therapy, which delivers a uniform dose distribution, and this may be a contributing factor to the variation in our CTP results.

The relationship between perfusion characteristics and regions of oxygenation remain unclear, though the hypothesis is that increase in BF, BV, and CP characteristics are a result of upregulation of angiogenic factors such as VEGF in response to hypoxia to promote angiogenesis and in turn improve the oxygenation of the tumor. This finding is supported by studies that have shown a correlation between pretreatment VEGF levels and CTP characteristics, which show a borderline inverse relationship.[12] Studies in vitro of HNSCC cell lines have also shown that RT increases VEGF levels in tumor and endothelial cell lines and that VEGF levels are dependent on cumulative radiation dose, regardless of the intrinsic radiosensitivity of the tumor and baseline VEGF levels.[13]

Variations in perfusion parameters may also be a function of the point of measurement. The current study used 2 tumor measurements obtained in the center of the tumor while avoiding necrotic areas, to minimize variations of the perfusion parameters at the periphery of the tumor that could be caused by inflammation. Studies have demonstrated spatially heterogeneous vascularity within the tumor, and variations between studies may reflect the point of measurement, though most studies attempt to avoid regions of necrotic tissue, large feeding vessels, and normal tissue. In a study of volumetric CTP in patients with non-small cell lung cancer undergoing palliative RT, perfusion measurements at 9, 18, and 27 Gy obtained in 16 patients at the periphery and center of the tumor showed changes in CP and BV at the periphery of the tumor, which were noted to be higher during the course of RT compared with the center. The hypothesis was that the greater changes noted may be due to increased oxygenation at the periphery compared with the center of the tumor, though perfusion measurements at the periphery of the tumor may be difficult to distinguish from the interface with normal tissue.[14]

MR perfusion by using T1-weighted dynamic contrast-enhanced MR imaging shows results similar to those of CTP in a head and neck cancer study of 14 patients, in which an increase in BV was predictive of local control when performed 2 weeks after initiation of RT (equivalent to 20 Gy), whereas BF was not found to be a significant parameter in predicting local control.[15] In this study, however, pretreatment BV and BF did not predict outcome and BV; moreover, with a small patient series and only 9.7 months median follow-up, it is difficult to

determine whether these findings correlate with longer follow-up. Other MR perfusion techniques include arterial spin-labeling, which potentially has an advantage over CTP in that magnetically labeled blood water acts as an endogenous tracer obviating contrast administration. This method has been tested in small head and neck cancer series without conclusions regarding the ability to predict outcome but may show promise as a perfusion imaging method for patients who cannot undergo contrast administration.[16]

While concurrent chemoradiotherapy remains the standard of care for locally advanced HNSCC, increasing interest in the role of induction chemotherapy regimens has resulted in re-examination of our current standard treatment paradigms.[17,18] Studies of perfusion imaging before and after induction chemotherapy may further assist patient selection for determining which patients will benefit from concurrent chemoradiation. Zima et al[19] studied 17 patients with HNSCC and found elevated pretreatment BF, BV, and CP by using CTP in patients who achieved >50% response to induction chemotherapy. They used the induction chemotherapy response to then select patients for chemoradiation therapy, and the nonresponders were selected to undergo surgery. Nonresponders were found to have a more tightly clustered distribution of low pretreatment BV levels of 3.0–5.4 mL/100 g, which are similar to the pretreatment BV range found in our LRF group. This study suggests that chemotherapy response may be predicted by pretreatment perfusion parameters, and this may have implications for patient selection for subsequent concurrent chemoradiotherapy.

In contrast, Bisdas et al[20] showed that if patients are selected to undergo surgery followed by adjuvant RT, presurgery perfusion parameters including BF, BF maximum, and CP predict local recurrence. This finding suggests that regardless of treatment, whether it is upfront chemoradiation or surgery followed by adjuvant radiation, baseline tumor perfusion characteristics may predict failure regardless of treatment selection because tumors with unfavorable perfusion characteristics represent a more aggressive phenotype. However, these studies only measured the baseline tumor characteristics at a single time point; and as demonstrated from our study examining tumor perfusion during RT, the perfusion characteristics of the tumor are found to be constantly changing.

As PET has become increasingly integrated into the standard work-up and treatment of HNSCC, integrating CTP could play a role in combination with FDG-PET by correlating tumor perfusion parameters to SUV. PET has the advantage of defined regions of FDG uptake (depending on the threshold used) to allow tumor volume delineation and integration into radiation therapy planning. Small series examining CTP and PET have shown correlations among BF, metabolically active tumor volume, and local control, though FDG uptake by using maximum SUV was not well-correlated with local control in HNSCCs.[21] However, SUV and perfusion characteristics do demonstrate characteristics different from those in normal tissues and larger studies are needed to show the relationship between perfusion parameters and SUV and outcome.[22]

The limitation of our study and of similar studies examining CTP in head and neck RT includes the small patient numbers studied, which precluded further multivariate analysis to adjust for other factors such as staging and volumetric considerations. Other limitations of CTP include the requirement of timed contrast and adequate renal function. In our study, we found that renal insufficiency toward the latter half of chemoradiation therapy related to cisplatin-based therapy, and dehydration may preclude CTP in the last 2 weeks of therapy, as patients experience increased radiation- and chemotherapy-related acute toxicities, making it difficult for the patient to undergo CTP. Increasing concern regarding radiation dose to the normal tissues in patients undergoing CTP has led to using lower kilovoltage settings. Although 80 kV has been used for brain perfusion as well as more recent neck perfusion studies,[23] 120 kV with 60 mA has been used for most published CTP studies for head and neck cancers;[5,8,9,24] therefore, we used 120 kV in this study with 50 mA, decreased from 60 mA. Future studies could be performed with lower kilovoltage and milliampere settings to minimize radiation if appropriate perfusion data could be maintained. Furthermore, MR perfusion is an alternative tool for noninvasive tumor perfusion measurement without ionized radiation exposure, though MR images cannot be obtained in the radiation-treatment position with immobilization devices and MR imaging is contraindicated in patients with cardiac pacemakers and other implanted metallic devices as well as metallic foreign bodies in the brain, globe, and spinal canal.

Future studies could investigate the feasibility of integrating CTP into RT planning by combining the study of anatomic changes during RT with CTP parameters, by improving radiation dose coverage to tumor, or by RT dose escalation to improve LRC. Currently, the CTP datasets are too large to be integrated into current RT planning software. Additionally, CTP is limited in the craniocaudal direction for complete image acquisition of the head and neck region. In our study, the CTP scan encompassed only a 4-cm cranial caudal extent of the tumor; newer CT scanners may allow the entire neck coverage, though this would likely also increase the radiation exposure from the diagnostic scan to the patient. If these technical limitations could be overcome, CTP data could identify areas of increased or decreased tumor perfusion during RT and could be integrated into adaptive radiation therapy such that areas of decreased BF in tumor representing hypoxic regions could potentially receive higher doses with dose-painted IMRT.

For patients who do not achieve LRC with concurrent chemoradiotherapy, pretreatment CTP data demonstrating areas of decreased BF in the tumor may be considered for more aggressive therapy, such as induction chemotherapy followed by concurrent chemoradiotherapy or upfront surgery followed by postoperative radiation therapy. Thus CTP data could have potential implications for improving the selection of patients with HNSCC for chemoradiotherapy.

Conclusions

Our study has shown that an increase in BF during the first 2 weeks of RT measured by CTP predicts LRC with RT and supports existing evidence that high pretreatment BF and CP predict improved LRC. CTP performed early during the course of HNSCC treatment could potentially be incorporated into standard CT to help determine appropriate selection of patients for radiotherapeutic treatment.

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