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EARLY PREDICTION OF OUTCOME IN ADVANCED HEAD AND NECK CANCER BASED ON TUMOR BLOOD VOLUME ALTERATIONS DURING THERAPY: A PROSPECTIVE STUDY

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Abstract

Purpose—To assess whether alterations in tumor blood volume (BV) and flow (BF) during the early course of chemo-radiation therapy (RT) for head and neck cancer (HNC) predict treatment outcome.

Methods—Fourteen patients receiving concomitant chemo-RT for non-resectable, locally advanced HNC underwent dynamic-contrast enhanced (DCE) MRI scans pre-therapy and two weeks after initiation of chemo-RT. BV and BF were quantified from DCE MRI. Pre-RT BV and BF as well as their changes during RT were evaluated separately in the primary gross tumor volume (GTV) and nodal GTV for association with outcomes.

Results—At a median follow-up of ten months (range of 5 – 27 months), nine patients had local-regional controlled disease (LRC). One patient had regional failure (RF), three had local failures (LF) and one had local-regional failure (LRF). Reduction in tumor volume after 2 weeks of chemo-RT did not predict for local control. In contrast, the BV in the primary GTV after 2 weeks of chemo-RT was increased significantly in the LC patients compared to the LF patients ($p < 0.03$).

Conclusions—Our data suggest that an increase in available primary tumor blood for oxygen extraction during the early course of RT is associated with local control, thus yielding a predictor with potential to modify treatment. These findings require validation in larger studies.

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INTRODUCTION

Radiation therapy (RT) and concurrent chemotherapy is a leading modality for organ-preserving treatment of head and neck cancer (HNC). However, there is still a substantial rate of local-regional failure (LRF), especially in patients with locally advanced, non-resectable disease.(1) An early prediction of LRF may allow for modification of therapy.

Tumor oxygenation has been associated with local-regional control and survival outcomes in advanced HNC treated by RT.(2–4) Recently, predictive functional and metabolic imaging to assess tumor hypoxia or tumor perfusion prior to therapy in HNC has demonstrated that hypoxia or low perfusion pre-therapy are markers of poor response and prognosis.(5–10) We recently reported a prognostic value for changes in brain tumor perfusion soon after RT initiation compared with pre-therapy.(11) Based upon the pre-therapy functional imaging studies, and our experience with during-therapy perfusion, we hypothesized that alterations in tumor perfusion parameters early after the start of RT for HNC could have better prediction for outcome than pretreatment measurements alone. Thus, we conducted a prospective study of dynamic-contrast enhanced (DCE) MR imaging pre- and during-therapy in patients with advanced HNC.

METHODS

Patients

Following Institutional Review Board approval, fourteen patients were enrolled in this study. Patients and disease characteristics are described in Table 1. All patients received a total of 70 Gy to the gross tumor volume (GTV) by intensity-modulated (12 patients) or 3D conformal (2 patients) RT. In 13 patients RT was delivered once daily at 2 Gy fractions to the GTVs, and in one patient at 1.25 Gy fractions, twice daily. The chemotherapy regimens included carboplatin (1 area under the curve) and paclitaxel 30 mg/sq m (8 patients) given weekly, or cisplatin, 100 mg/sq mm (5 patients) administered once every three weeks. One patient received a loading dose of 400 mg/sq m followed by weekly cetuximab 250 mg/sq m.

DCE MRI

T1-weighted DCE MR imaging that covered the whole tumor and involved nodal GTVs was acquired prior to RT and 2 weeks after the start of RT. Blood volume (BV) images were estimated by using the general Toft model, by which the BV was corrected for vascular permeability.(12) Blood flow (BF) images were estimated using the method described by Mullani (13) and applied to assessment of HN cancer perfusion by Hermans.(14) The BV and BF images were geometrically co-registered with post-Gd T1-weighted MR images and the treatment planning CT.

Gross Tumor Volumes

GTVs were defined on pre-RT post-Gd T1-weighted images as well as during-RT images, cross-referenced with the treatment planning CT and diagnostic PET if available. Considering possible different responses to chemo-RT, the primary and nodal GTVs were drawn separately. Large vessels near and within the nodal GTVs were excluded. The average BV and BF in the primary and nodal GTVs prior to RT and during RT, as well as the alterations between these measures, were calculated.

The pre-RT BV and BF in the primary and nodal GTVs and their changes during the course of RT were stratified based upon local and regional control, respectively. Differences of

perfusion parameters between the two subgroups were tested by Mann-Whitney U test. Two-tailed p value <0.05 was considered significant.

RESULTS

Median follow up for the 10 living patients was 9.7 months (range 5.3–27 months). Nine patients had local-regional controlled disease (LRC). One patient had regional failure (RF), three had local failures (LF) and one had local-regional failure (LRF), see Table 1. Three of the four patients with LF had distant metastases at the time of or after LF. All four patients with LF died.

Tumor volumes and their percentage changes from pre to during-therapy are detailed in Table 2 for the primary tumors and lymph node metastases. The median of the pre-RT primary GTVs for the patients with LC was 15.8 cc (range: 5.3 – 97.5 cc), significantly smaller ($p=0.046$) than the median of 74.3 cc (range: 19.6 – 120.1 cc) for the patients with LF. The early responses of the primary tumor volume to 2 weeks of fractionated RT and chemotherapy did not differ significantly between the patients with LC and LF, with a median reduction of 28% and 21%, respectively (Table 2). The pre-RT nodal GTVs of the two patients with RF were 46 cc and 166 cc, greater than the median (33 cc) of the pre-RT nodal GTVs of the patients with regional control. The nodal GTVs in the patients with RF changed slightly in one and was reduced by 34% in another after 2 weeks of chemo-RT (Table 2), compared with a median reduction of 38% in the lymphatic GTVs of patients with regionally controlled disease.

The pre-therapy BV and BF in the primary GTVs did not differ significantly between the patients with LC and LF (Table 3, Figure 1). However, after 2 weeks of RT, the BV in the primary GTV increased significantly, by a median of 5.1 ml/100g (range: -0.6 to 13.2), in the patients with LC, compared to the patients with LF in whom there was little change (median change of 1.0 mL/100g; $p=0.03$). In comparison, for the BF of the primary GTV, there were no significant differences either in the pre-RT values or in the changes during RT between the patients with LC and LF (Table 3).

In the nodal GTVs, the pre-RT values of BV and BF of the two patients with RF were similar to those of the patients with regional control (Table 3). There was little change in either BV or BF of the nodal GTVs after 2 weeks of fractionated RT for the patients with or without regional control.

DISCUSSION

This study suggests an increase in BV of the primary tumor volume early in the course of RT in patients with LC. This increase is significantly higher than the change in BV of patients with LF. The changes in the primary tumor volume were similar between the two groups, and could not serve as early indication of local control. This finding suggests that a local blood supply increase, potentially a source of increased oxygenation, may be a positive indicator for therapeutic response at the primary tumor site. Thus, it may help individualize treatments, in addition to pre-therapy clinical factors like GTV size (which was a significant factor in our study) or molecular predictive factors.^{1,(15)} It should be noted that the increase in tumor blood volumes occurring early during chemo-RT in our patients with good outcomes is opposite that reported in patients with good responses to induction chemotherapy.⁽⁶⁾ This dichotomy could be due to the different treatment modalities, as well as the different endpoints for local control (tumor volume reduction vs. local tumor control). Also, CT perfusion imaging as reported in the chemotherapy study only allows assessment of a portion of the tumor, while DCE MRI used in our study enables an evaluation of the

whole tumor. Furthermore, the different perfusion characteristics between the primary tumor and affected nodes require separate evaluations in the alterations of perfusion and blood supply of the two entities. The sources of these discrepancies should be investigated further in a larger patient population and a longer follow-up.

In conclusion, this study suggests that early changes in tumor blood volume of the primary tumor site may help predict local control for patients undergoing chemo-RT. Larger scale studies, perhaps coupled with other biomarker investigations, can help better establish our ability to alter a treatment course based on early assessment.

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Figure 1.

Blood volume maps (color) overlaid on post-Gd T1-weighted images in patients with local control (top) and local failure (bottom) prior to RT (left) and after 2 weeks of fractionated RT (right). After 2 weeks of RT there was an increase in the primary tumor blood volume of the patient with local control but little change in the patient with local failure. White contour: primary gross tumor volume.

Table 1

Patients Characteristics

Patients	Age	Sex	Disease Location	Stage	Outcome
1	65	F	soft palate	T2N3	LRF/Dead
2	62	M	Tonsil	T1 N2a	LRC
3	58	M	hypopharynx	T4 N2b	LF/Dead
4	83	M	Larynx	T4N0	LF/Dead
5	61	F	Tonsil	T2N3	RF
6	43	M	BOT + tonsil	T4N2c	LF/Dead
7	49	M	Tonsil	T4N2c	LRC
8	62	M	BOT	T3N0	LRC
9	39	M	UNP	TxN3	LRC
10	57	M	nasopharyngeal	T2N2b	LRC
11	56	M	piriform sinus	T1N2c	LRC
12	42	M	Tonsil	T2N2b	LRC
13	62	M	Tonsil	T2N2b	LRC
14	58	M	Tonsil	T2N2b	LRC

UNP: unknown primary disease. LRC: local-regional control; LRF: local failure; RF: regional failure.

Table 2

Primary and nodal GTVs

	Primary GTV		
	Pre RT (cc)	During RT (cc)	%Changes wk2-pre
LC(9)			
Median	15.8	9.1	-27.9
range	5.3 – 97.5	2.0 – 52.3	-65.4 -- -11.2
LF(4)			
Median	74.3	6.2	-21.4
range	19.6 – 120.1	10.8 – 101.3	-44.6 -- -8.2
p	0.046	n.s.	n.s.
	Nodal GTV		
	Pre RT (cc)	During RT (cc)	%Changes wk2-pre
RC(10)			
Median	33.2	18.5	-38.0
range	10.3 – 65.8	6.6 – 55.6	-62.0 – 15.5
RF(2)			
Median	106.5	97.0	-18.0
range	46.4 – 166.6	30.5 – 163.6	-34.3 -- -1.8
p	NA	NA	NA

LC: patients with local control; LF: patients with local failure; RC: patients with regional (nodal) control; RF: the patient with regional (nodal) failure. Note that one patient had unknown primary and two patients had N0.

Table 3

Blood Volume and Flow in the Primary and Nodal Gross Tumor Volumes

	TBV (mL/100g)		TBF (mL/100g min)	
	Pre RT	Change wk2-pre	Pre RT	Change wk2-pre
Primary Tumor				
LC(9)				
Median	8.5	5.1	45.4	20.1
range	1.3–17.5	–0.6 – 13.2	23.2–104.5	–3.9 – 54.6
LF(4)				
Median	10.2	1.0	64.7	15.0
range	5.0 – 13.0	–1.7 – 1.6	38.1 – 98.4	–22.1 – 41.1
p	n.s.	0.03	n.s.	n.s.
Nodes				
RC(10)				
Median	9.3	0.2	74.9	5.9
range	4.6 – 16.0	–4.6 – 10.0	38.7 – 104.5	–23.6 – 62.8
RF(2)				
Median	10.1	–3.1	53.6	5.2
range	5.9 – 14.3	–4.5 -- –1.8	39.5 – 67.8	–5.2 – 15.6
p	NA	NA	NA	NA

Note that one patient had unknown primary and two patients had N0.