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Post-Radiation Metabolic Tumor Volume Predicts Outcome in Head-and-Neck Cancer

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Abstract

Purpose—To explore the prognostic value of metabolic tumor volume measured on post-radiation ^{18}F-fluorodeoxyglucose positron emission tomography (PET) imaging in head-and-neck cancer patients.

Methods and Materials—Forty-seven head-and-neck cancer patients who received pre- and post-treatment PET/CT imaging along with definitive chemoradiotherapy were included in this study. PET/CT parameters evaluated include the maximum standardized uptake value, metabolic tumor volume ($MTV_{2.0}$-$MTV_{4.0}$; where $MTV_{2.0}$ refers to the volume above an SUV threshold of 2.0), and integrated tumor volume. Kaplan-Meier and Cox-regression models were used to test for association between PET endpoints and disease-free survival (DFS) and overall survival (OS).

Results—Multiple post-radiation PET endpoints correlated significantly with outcome, however the most robust predictor of disease progression and death was $MTV_{2.0}$. An increase in $MTV_{2.0}$ of 21cm^3 (difference between 75th and 25th percentile) was associated with an increased risk of disease progression (hazard ratio [HR]=2.5, p=0.0001) and death (HR=2.0, p=0.003). In patients with non-nasopharyngeal carcinoma (non-NPC) histology (n=34), $MTV_{2.0}$<18cm^3 and $MTV_{2.0}$≥18cm^3 yielded 2-year DFS rates of 100% and 63%, respectively (p=0.006) and 2-year OS rates of 100% and 81%, respectively (p=0.009). There was no correlation between $MTV_{2.0}$ and DFS or OS with NPC histology (n=13). On multivariate analysis only post-radiation $MTV_{2.0}$ was predictive of DFS (HR=2.47, p=0.0001) and OS (HR=1.98, p=0.003).

Conclusions—Post-radiation metabolic tumor volume is an adverse prognostic factor in head-and-neck cancer. Biomarkers such as MTV are important for risk stratification, and will be valuable in the future with risk-adapted therapies.

Keywords

Head-and-neck cancer; Positron emission tomography; metabolic tumor volume

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INTRODUCTION

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging combined with computed tomography (CT) plays an important role in staging and radiation treatment planning in patients with head and neck cancer (HNC) (1-3). Additionally, PET/CT in the pre- and post-radiotherapy setting has emerged as a potential prognostic factor for outcome in HNC (4,5). When analyzing the prognostic capability of PET/CT, the most common PET endpoint analyzed is the maximum tumor FDG uptake measured by the maximum standardized uptake value (SUV_{max}). As an alternative to SUV_{max}, we have previously reported on a more functional PET/CT metric that measures the metabolic tumor burden (6). We found that pre-radiation metabolic tumor volume (MTV) predicted disease progression and survival in HNC, whereas SUV_{max} did not, suggesting that metabolic tumor burden may be a more robust predictor of outcome.

Ideally, SUV_{max} in the post-radiation setting would predict the presence of residual or recurrent disease, however factors such as inflammation and other post-radiation effects tend to obscure the predictive nature of SUV_{max} (7). Indeed, studies that evaluate SUV_{max} as a prognostic factor in the post-treatment setting have been mixed (8-14). A PET/CT endpoint that increases the distinction between residual tumor and treatment effects would enhance the prognostic capability of PET/CT. We hypothesize that an endpoint based on the volume of hypermetabolic tissue above a given SUV threshold would discriminate between tumor and treatment effect, and thus could improve the prognostic utility of post-radiation PET/CT. The purpose of this study was to 1) explore different metabolic volume based threshold techniques, and 2) to test for association between disease progression and overall survival.

METHODS

Patients and treatment

After Institutional Review Board approval, we retrospectively reviewed the medical records of all patients with squamous cell HNC who were treated with definitive chemoradiotherapy at Stanford University between February 2003 and October 2007. At our institution, for non-nasopharyngeal HNC, patient treatment response is typically assessed at six to eight weeks after the completion of chemoradiation with clinical exam, endoscopy and cross-sectional imaging studies (either CT or MRI). After this initial assessment, patients with obvious residual disease or tumor progression are considered for biopsy of the primary tumor site or fine needle aspiration (FNA) of a persistently enlarged node. If there is evidence of viable tumor, patients proceed to immediate salvage surgery. In contrast, patients with equivocal findings or no detectable disease are followed with a PET-CT at 10 weeks to 4 months after completion of chemoradiotherapy. For NPC patients, follow up PET-CT is obtained at one to two months after completion of adjuvant chemotherapy. Patients were included in this study if they had both a pre-treatment PET/CT as part of staging or radiation treatment planning, and had a post-treatment PET/CT for follow up within one year of the last day of radiation. Patients were excluded if they had metastatic disease at presentation, prior definitive surgery, or if the post-treatment PET/CT was done at an outside facility or done after histologic confirmation of disease progression. Patients with salivary gland, paranasal sinus, thyroid and skin primary tumors were also excluded. One-hundred and fifty-two patients with locally advanced HNC received PET/CT scans along with radiation during the above study period. Of these patients, 47 met the above criteria, and these patients formed the cohort of this study. Patient characteristics are provided in Table 1.

FDG-PET CT imaging

The imaging protocol prior to treatment has been reported previously (6), and will only briefly be described here. Prior to simulation, patients were positioned supine with arms by their sides. A custom molded foam cushion (AcuForm, Medtec, Orange City, IA), and a thermoplastic mask (Aquaplast, WFR/Aquaplast Corp., Wyckoff, NJ) were used to support and immobilize the patient's head and neck. Prior to pre- and post-treatment scans, patients fasted for at least 8 hours prior to injection with 10 to 18 mCi of FDG. Image acquisition was done 45-60 minutes after FDG administration. CT imaging was collected in helical acquisition mode. Two-dimensional (2-D) PET imaging was obtained over 3-5 minutes of acquisition time per bed position. The 2-D PET data were reconstructed with an ordered set expectation maximization algorithm, using the CT images for attenuation correction. The complete PET/CT examination required approximately 90 minutes, including patient setup, radiotracer uptake, and CT and PET image acquisition.

Treatment

All patients were treated with definitive chemoradiotherapy, and most (89%) were treated with cisplatin or carboplatin based chemotherapy regimens. The majority of patients (89%) were treated with intensity modulated radiation therapy (IMRT), and the remainders were treated with 3-D conformal radiation therapy. Patients received radiation doses between 66-70 Gy, and 12 of the 13 nasopharyngeal cancer patients were treated with a sequential 7-8 Gy stereotactic radiosurgical boost. Table 2 contains additional treatment characteristics.

PET/CT analysis

At the time of treatment, the primary tumor and nodal gross tumor volumes (GTV) were contoured on the treatment planning CT by the treating physician (Q.L., and B.L.), with the aid of the pre-treatment PET. With the pre- and post-treatment PET/CT scans, the metabolic volumes of interest were retrospectively outlined by an experienced radiation oncologist (J.M., T.L. and K.C.) with the aid of the treatment planning GTV and diagnostic nuclear medicine reports. The pre- and post-treatment metabolic tumor volume (MTV_x) was defined as the volume of hypermetabolic tissue within the region of the GTV (as identified on the pretreatment PET/CT scan) with an SUV greater than a threshold value *x*. We previously defined the pre-treatment MTV threshold as 50% of the maximum SUV ($MTV_{50\%}$) (6). In the post-treatment setting, a relative threshold of 50% of the maximum SUV is often below the surrounding background SUV level, so therefore with post-treatment MTV we utilized an absolute SUV threshold. To identify the optimal absolute SUV threshold with post-treatment MTV, we explored multiple threshold levels with SUVs ranging from 2.0 to 4.0 in intervals of 0.5 ($MTV_{2.0} - MTV_{4.0}$). In determining the MTV, care was taken to exclude normal hypermetabolic tissues such as brown fat, brain or salivary glands. Pre- and post-treatment MTV is demonstrated in Figure 1.

The integrated tumor volume (ITV_x) was defined as the following:

$$ITV_x = \oint_{MTV_x} SUV \times dV$$

ITV_x is also equal to MTV_x multiplied by the average SUV. Analysis of PET/CT imaging for this project was done with the MIM® Software Suite along with the MIMfusion® and MIMcontouring® packages (MIMvista Corporation, Cleveland, OH).

Statistics

Disease free survival (DFS) and overall survival (OS) were calculated from the date of diagnosis. An event for DFS was defined as any disease progression (local, regional or distant) or death from any cause. Survival curves for DFS and OS were generated with the method of Kaplan and Meier (15). Cox proportional hazard models were used for both univariate and multivariate analysis (16). Prognostic factors evaluated included pre- and post-treatment MTV, ITV, SUV_{max}, as well as Karnofsky performance status (KPS) which we previously found to be associated with outcome (6). To enable a rough comparison of hazard ratios, the various SUV thresholds tested with MTV and ITV were individually normalized to their interquartile range (difference between 75^{th} and 25^{th} percentile), prior to analysis with a Cox proportional hazard model. Pearson correlation coefficients were used to test for association between continuous prognostic factors. We used a Bonferroni correction to adjust for multiple comparisons. Statistical analysis was performed with SPSS version 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient outcome

The median follow-up for the entire cohort was 34 months (range 12 – 68 months). Of the 47 patients in this study, three patients ultimately developed isolated distant metastasis. Four additional patients developed concurrent locoregional disease progression and distant metastatic disease. The median time to disease progression was 19 months (range 5.3 – 29 months). Six patients died, and the median time to death was 18 months (range 12 – 42 months). The Kaplan-Meier estimates of 1-, 2-, and 3-year DFS rates for the entire population were 96%, 83%, and 80%, respectively. The Kaplan-Meier estimates of 1-, 2-, and 3-year OS rates were 100%, 91%, and 89%, respectively.

Post-treatment MTV and ITV predict outcome

The median time from completion of radiotherapy to post-treatment PET/CT was 3.4 months (range 0.7-11.5 months; Figure 2). Twelve patients (26%) had their post-treatment PET/CT outside our ideal imaging timeframe (i.e. outside of 10 weeks to 4 months after chemoradiotherapy for non-NPC histology, or outside of 1-2 months after adjuvant chemotherapy for NPC histology). PET/CT imaging was done too early because of scheduling errors (4 patients), and abnormal physical exam findings (1 patient). PET/CT imaging was delayed due to patient preference (2 patients), unrelated medical problems (2 patients), treatment-related complication (2 patients), and delayed wound healing from a post-treatment biopsy (1 patient; biopsy demonstrated radiation-related changes). Forty-three (91%) of the post-treatment PET/CT scans were done for routine surveillance. The four (9%) non-surveillance scans were done to follow up on abnormal MR imaging (2 patients), physical exam findings (1 patient) and suspicious symptoms (1 patient). Of these four non-surveillance scans, only one patient ultimately suffered disease progression.

To explore the relationship between post-treatment PET and outcome, we used a Cox-regression model to analyze post-treatment SUV_{max}, MTV and ITV with multiple SUV threshold levels (Figure 3). Because we tested multiple PET parameters, the Bonferroni adjusted level of significance was p=0.0045. While multiple PET endpoints were associated with outcome, the endpoint that was associated with the greatest hazard of disease progression or death was $MTV_{2.0}$. The median $MTV_{2.0}$ was 15 cm^3 (range 0.5 – 117; interquartile range 21 cm^3). An increase in $MTV_{2.0}$ of 21 cm^3 was associated with an increased hazard of disease progression (DFS) and death (OS), with hazard ratios of 2.5 (95% CI 1.6-3.9; p=0.0001) and 2.0 (95% CI 1.3-3.1; p=0.003), respectively.

Correlation between post-treatment MTV and pre-treatment MTV

We sought to determine the relationship and predictive properties between pre-and post-treatment PET/CT endpoints. We have previously reported that pre-treatment $MTV_{50\%}$ was associated with outcome (6), and this present study demonstrated that several post-treatment PET/CT metrics were associated with outcome. For this analysis, we opted to use pre-treatment $MTV_{50\%}$, and post-treatment $MTV_{2.0}$, as these were the most robust predictors of outcome. First we tested for correlation between these two variables with a Pearson correlation coefficient. There was a positive but weak correlation between pre-treatment $MTV_{50\%}$ and post-treatment $MTV_{2.0}$ (r=0.42, p=0.003). Next we tested pre-treatment $MTV_{50\%}$, post-treatment $MTV_{2.0}$, and KPS (previously shown to predict outcome (6)) in a multivariate Cox-regression model. Post-treatment $MTV_{2.0}$ was the sole predictive variable associated with DFS and OS, with hazard ratios of 2.47 (p=0.0001) and 1.98 (p=0.0033), respectively (Table 3).

Non-nasopharyngeal carcinoma

Given that nasopharyngeal carcinoma (NPC) is associated with a different epidemiology, natural history and response to treatment (18-20) compared with non-nasopharyngeal carcinoma (non-NPC), we explored differences among these two populations with subset analyses. The NPC patients (n=13) had a lower post-treatment $MTV_{2.0}$ compared with non-NPC patients (n=34). The mean $MTV_{2.0}$ for NPC and non-NPC was 14 cm^3, and 26 cm^3, respectively (p=0.043 with two-tailed t-test). Analysis of the non-NPC cohort revealed that higher post-treatment $MTV_{2.0}$ predicted DFS, and OS (Figure 4A and 4C). Because this analysis divided the cohort into two groups, we used a Bonferroni corrected significance level of p=0.025. In non-NPC patients, $MTV_{2.0}$ <18 cm^3 (median value) and $MTV_{2.0}$ ≥18cm^3 yielded 2-yr DFS rates of 100% and 63%, respectively (p=0.0062). Additionally, in non-NPC patients, $MTV_{2.0}$ <18 cm^3 and $MTV_{2.0}$ ≥18cm^3 yielded 2-yr OS rates of 100% and 81%, respectively (p=0.0093). Within the NPC cohort, there was no significant correlation between post-treatment $MTV_{2.0}$ and DFS (p=0.43) or OS (p=0.28) (Figure 4B and 4D).

DISCUSSION

Over the past two decades, strategies combining chemotherapy and radiation have significantly improved outcome in locally advanced HNC (21,22). Despite these improvements, treatment regimens continue to be plagued with heterogeneous rates of locoregional disease progression. There is a need for biomarkers in HNC to categorize patients according to risk of disease progression, especially as we move towards risk-adapted therapy in the future. One potential use of a risk-stratifying biomarker would be to identify high-risk patients who could benefit from closer follow up or earlier intervention with salvage surgery, before the tumor becomes unresectable. The use of a more quantitative PET parameter such as $MTV_{2.0}$ that incorporates volumetric data rather than SUV_{max} alone may help to improve PET's performance in predicting for persistent nodal disease and guide the decision for appropriate neck dissection. PET/CT is emerging as a biomarker for outcome because its functional and anatomical imaging characteristics give it the tools necessary to stratify patients by disease burden.

The prognostic utility of post-radiation SUV_{max} has been extensively studied in HNC. While retrospective studies have demonstrated that SUV_{max} is superior to CT alone in predicting outcome (9,10,12,14), a recently completed prospective trial from M.D. Anderson Cancer Center (MDACC) yielded conflicting results (11). MDACC prospectively evaluated 98 locally advanced HNC patients with PET/CT and contrast-enhanced CT eight weeks after completion of radiotherapy. These investigators found SUV_{max} to outperform CT in patients

with high-risk HNC (human papillomavirus [HPV] -negative tumors, non-oropharyngeal primaries, or history of tobacco use), however found no difference in patients with low-risk disease. These somewhat conflicting results highlight the challenges inherent in using SUV_{max} as a prognostic factor. The primary goal of any SUV based measurement is to discriminate between residual tumor and other sources of FDG uptake. Unfortunately, several factors inherent in an SUV measurement will tend to obscure its predictive power, including post-radiation inflammation, normal tissue FDG uptake and infection (7). In this study we hypothesized that a PET/CT measurement which incorporates the volume of hypermetabolic tissue above an absolute threshold could improve the discrimination between normal tissue and tumor, and therefore could improve the prognostic capability of PET/CT. While we found multiple PET endpoints to predict outcome, the most robust predictor was the metabolic tumor volume ($MTV_{2.0}$).

Another important factor in the discrimination between residual tumor and normal tissue is the timing of post-radiation PET/CT. Imaging done too soon after treatment will be heavily influenced by post-radiation inflammation, whereas imaging done too late may miss the window for potentially beneficial salvage treatment, such as surgery. Andrade *et al*. retrospectively analyzed a cohort of 28 HNC patients, and found that the response to treatment was more accurately assessed when PET/CT was done more that 8 weeks after completion of treatment (23). Greven *et al*. conducted a prospective trial during which 45 HNC patients received post-radiation PET imaging at 1-, 4-, 12- and 24-months (24). Greven found the 4-month PET to be more accurate in predicting recurrent disease than the 1-month PET. In our study, 94% of our imaging occurred more than 2 months after completion of therapy. While the imaging timeframe in this current study is comparable to the above studies, the optimal timing of PET/CT in the post-radiotherapy setting warrants further investigation.

An interesting observation of this present study relates to our multivariate analysis comparing pre- and post-treatment PET measurements. While both pre-radiation $MTV_{50\%}$ (previously demonstrated (6)) and post-radiation $MTV_{2.0}$ (Figure 3) predicted outcome on univariate analysis, only post-radiation $MTV_{2.0}$ remained significant on multivariate analysis (Table 3). This finding suggests that response to treatment (measured by post-treatment MTV) is more predictive of outcome than initial tumor burden (measured by pre-treatment MTV), however this conclusion should be taken with caution because of the small sample sizes in this study.

Although our sample size was too small to determine the prognostic impact of MTV separately for the low- and the high-risk head and neck cancer groups, as defined in the MDACC study (11), we did have a high percentage of NPC patients in our study and therefore evaluated the effect of post-treatment MTV separately for NPC and non-NPC cancers. The association between post-treatment $MTV_{2.0}$ and outcome was only valid in the subset of patients without NPC. In fact, in patients without NPC, no patient with a $MTV_{2.0}$ less than the median value (18 cm^3) suffered disease progression or death (Figure 4). While we found no correlation with MTV in the NPC population, other investigators have found that outcome is associated with post-treatment SUV_{max} (19,25,26). The differing predictive powers of post-radiation MTV and SUV_{max} in the NPC cohort is difficult to explain, however could be related to the increased radiosensitivity inherent in NPC, or could be a spurious finding related to our small sample size.

Limitations of this study include the small sample size, heterogeneous patient population and diversity of treatment regimens. Additionally, the methods involved with determining post-treatment MTV are more labor-intensive and user-dependent than the semi-automated method of determining pre-treatment MTV (6), however we are developing software to help

automate this process. Finally, given the retrospective nature of this study, conclusions put forth here are hypothesis generating, and should be validated prospectively in the future.

In conclusion, this is the first study to demonstrate a relationship between the post-treatment MTV and outcome. While we found multiple PET/CT endpoints to predict outcome, the most robust predictor was the $MTV_{2.0}$. In fact, $MTV_{2.0}$ was the sole independent predictive factor of disease progression and death on multivariate analysis. As we move towards risk-adapted therapy in the future, biomarkers such as MTV will be important to stratify patients into different risk-based categories.

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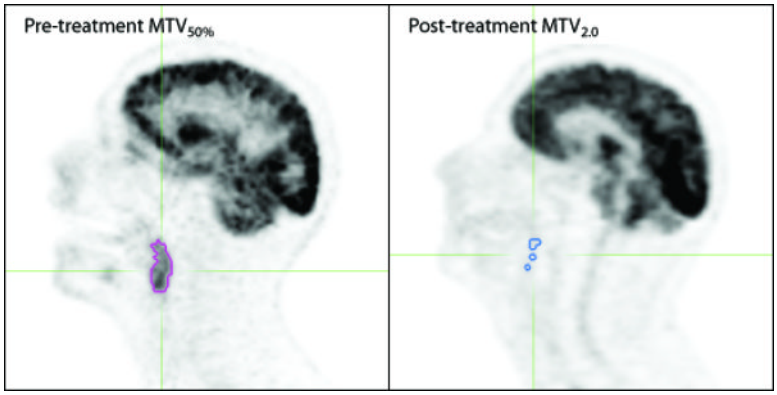

Figure 1.
Metabolic tumor volume on pre- (left) and post-treatment (right) PET images. The purple outline circumscribes the pre-treatment $MTV_{50\%}$ (metabolic tumor volume with relative threshold of 50% maximum SUV), and the blue outline circumscribes the post-treatment $MTV_{2.0}$ (metabolic tumor volume with an absolute SUV threshold of 2.0).

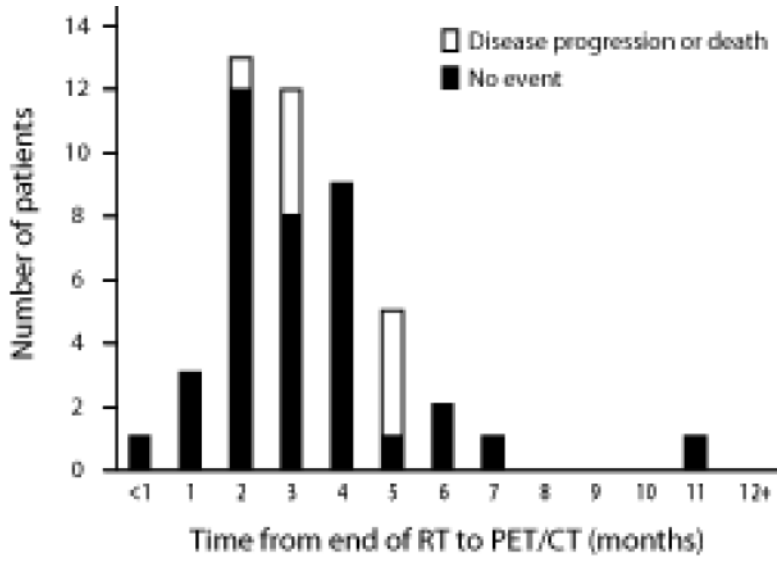

Figure 2.
Time of post-treatment PET/CT. Figure represents the time from end of radiotherapy (RT) to follow up PET/CT. White bars represent the proportion of patients who ultimately developed disease progression or death. Black bars represent patients who did not experience disease progression or death.

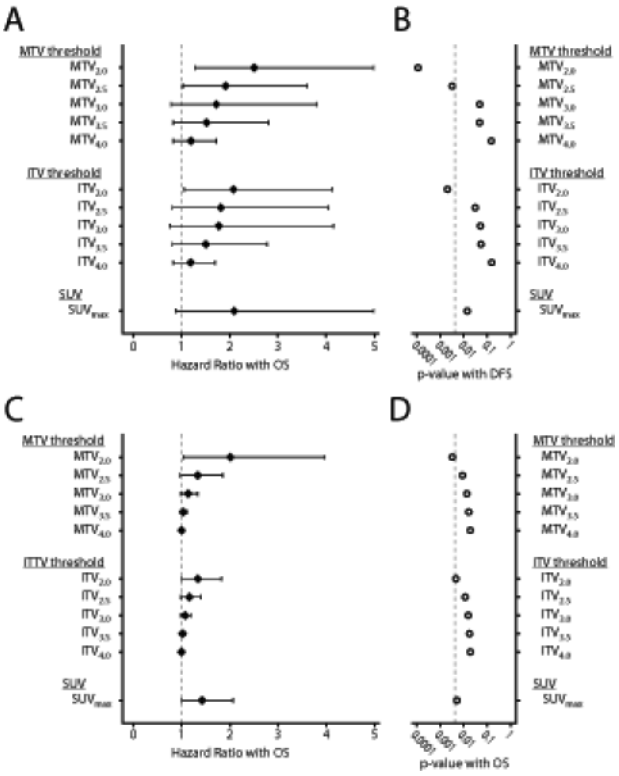

Figure 3.

Multiple post-treatment PET metrics predict outcome.

Plots represent hazard ratios (solid diamonds in A and C) and associated *p*-values (open circles in B and D) from a univariate Cox-regression model for DFS (A and B), and OS (C and D) conducted on the entire study population (n=47). Prior to analysis, each PET parameter was normalized to its interquartile range. The Bonferroni corrected significance level was p=0.0045. Abbreviations: DFS = disease-free survival, OS = overall survival, $MTV_{2.0}$ = metabolic tumor volume with an SUV threshold of 2.0 (described in methods), $ITV_{2.0}$ = integrated threshold tumor volume with an SUV threshold of 2.0 (described in methods), SUV_{max} = maximum SUV.

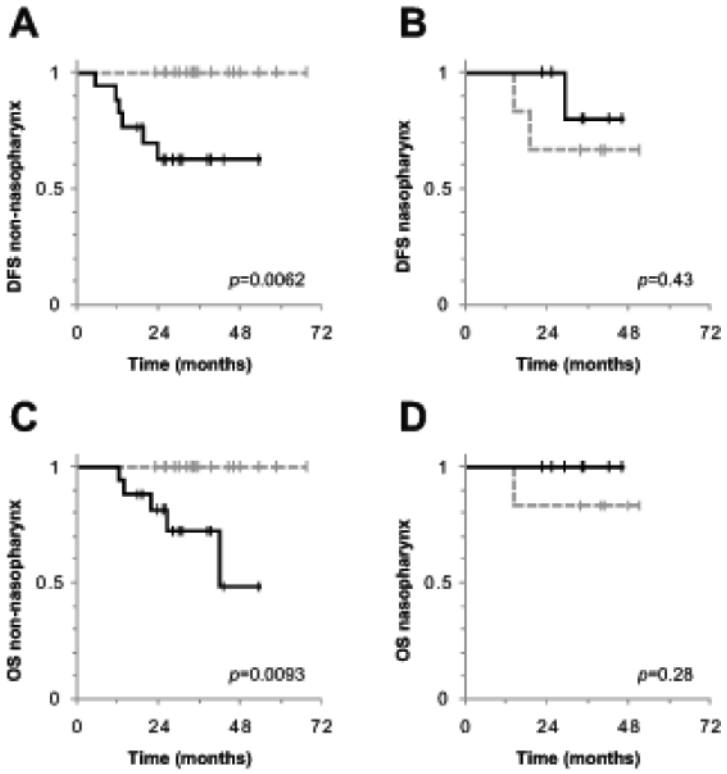

Figure 4.

Post-treatment $MTV_{2.0}$ predicts outcome in non-nasopharyngeal histology.

Plots represent Kaplan-Meier curves of DFS (A and B), and OS (C and D), in patients with non-nasopharyngeal (A and C), and nasopharyngeal histology (B and D). The Bonferroni corrected level of significance was p=0.025. The dotted gray lines represent post-treatment $MTV_{2.0}$ <median, and the solid black lines represent post-treatment $MTV_{2.0}$ ≥median. Abbreviations: DFS = disease free survival, OS = overall survival, $MTV_{2.0}$ = metabolic tumor volume with an SUV threshold of 2.0 (described in methods).

Table 1

Patient characteristics

Parameter	No. of patients (%)
Age	
Median (range)	55.1 (15-86.1)
Gender	
Male	39 (83)
Female	8 (17)
Site	
Nasopharynx	13 (28)
Oropharynx	21 (45)
Oral cavity	2 (4)
Larynx	7 (15)
Hypopharynx	4 (9)
AJCC stage	
II	2 (4)
III	11 (23)
IVA	29 (62)
IVB	5 (11)
Pathology grade	
Well differentiated	2 (4)
Moderately differentiated	15 (32)
Poorly differentiated	24 (51)
Unknown	6 (13)
Karnofsky performance status	
70	2 (4)
80	8 (17)
90	36 (77)
100	1 (2)

Abbreviations: AJCC = American Joint Committee on Cancer

Table 2

Treatment characteristics

Parameter	No. of patients (%)
Radiation dose	
66 Gy in 2.2 Gy fractions	28 (60)
70 Gy in 2 Gy fractions	7 (15)
66 Gy in 2.2 Gy fractions + SRS boost*	12 (26)
Radiation type	
IMRT	42 (89)
3D-CRT	5 (11)
Chemotherapy	
Cisplatin +/− 5-FU/capecitabine	36 (77)
Carboplatin +/− 5-FU/capecitabine	2 (4)
Cis/carbo + cetuximab	1 (2)
Cis/carbo + paclitaxel	3 (6)
Cis/carbo + paclitaxel + cetuximab	1 (2)
Cetuximab only	4 (9)

Abbreviations: CRT = conformal radiation therapy; Gy = Gray; IMRT = intensity-modulated radiation therapy; SRS = stereotactic radiosurgery.

*SRS boost ranged from 7-8 Gy.

Table 3

Multivariate analysis

Variable	*p*-value	HR (95% CI)
Disease free survival		
KPS	0.88	0.99 (0.88-1.12)
Pre-treatment $MTV_{50\%}$	0.11	1.42 (0.93-2.17)
Post-treatment $MTV_{2.0}$	0.0001	2.47 (1.56-3.90)
Overall survival		
KPS	0.95	1.00 (0.87-1.14)
Pre-treatment $MTV_{50\%}$	0.48	1.25 (0.67-2.32)
Post-treatment $MTV_{2.0}$	0.0033	1.98 (1.26-3.12)

Abbreviations: KPS = Karnofsky Performance Status; MTV = metabolic tumor volume