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Original article

The Anatomical Biological Value on Pretreatment ^{18}F-fluorodeoxyglucose Positron Emission Tomography Computed Tomography Predicts Response and Survival in Locally Advanced Head and Neck Cancer

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Abstract

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) has become increasingly relevant in the staging of head and neck cancers, but its prognostic value is controversial. The objective of this study was to evaluate different PET/CT parameters for their ability to predict response to therapy and survival in patients treated for head and neck cancer. A total of 28 consecutive patients with a variety of newly diagnosed head and neck cancers underwent PET/CT scanning at our institution before initiating definitive radiation therapy. All underwent a posttreatment PET/CT to gauge tumor response. Pretreatment PET/CT parameters calculated include the standardized uptake value (SUV) and the anatomical biological value (ABV), which is the product of SUV and greatest tumor diameter. Maximum and mean values were studied for both SUV and ABV, and correlated with response rate and survival. The mean pretreatment tumor ABV_{max} decreased from 35.5 to 7.9 ($P = 0.0001$). Of the parameters tested, only pretreatment ABV_{max} was significantly different among those patients with a complete response (CR) and incomplete response (22.8 vs. 65, respectively, $P = 0.021$). This difference was maximized at a cut-off ABV_{max} of 30 and those patients with $ABV_{max} < 30$ were significantly more likely to have a CR compared to those with ABV_{max} of ≥ 30 (93.8% vs. 50%, respectively, $P = 0.023$). The 5-year overall survival was 80% compared to 36%, respectively, ($P = 0.028$). Multivariate analysis confirmed that ABV_{max} was an independent prognostic factor. Our data supports the use of PET/CT, and specifically ABV_{max}, as a prognostic factor in head and neck cancer. Patients who have an $ABV_{max} \geq 30$ were more likely to have a poor outcome with chemoradiation alone, and a more aggressive trimodality approach may be indicated in these patients.

Keywords: ^{18}F-fluorodeoxyglucose, head and neck cancer, positron emission tomography/computed tomography

Introduction

In recent years, positron emission tomography/computed tomography (PET/CT) has become a commonly used diagnostic test for many types of malignancies. It has been particularly valuable in the majority of head and neck cancers, which tend to have a high level of 18-fluorodeoxyglucose (FDG) uptake, resulting in a sensitivity and specificity in the range of 80-100%.[1,2] Given these properties and the complex anatomy of the region, PET/CT has been shown to play an important role in the staging,[1,2] posttreatment assessment[3,4] and treatment planning,[5] of patients with head and neck cancer.

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Controversy more often exists in the role of a pretreatment PET/CT in predicting response to therapy and survival. Several retrospective studies have attempted to answer this question, with conflicting results. Part of the problem lies in the fact that it is unclear, which PET/CT parameter correlates best with outcome. The most commonly studied parameter in the literature is

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the maximum standardized uptake value (SUV) of a tumor,[6,7] but evidence also exists favoring use of the mean SUV of a tumor.[8] A related term, which we call the anatomical biological value (ABV), takes both SUV and size of a tumor into account, and thus may be a stronger prognostic factor than SUV alone.

In this study, we assessed different pretreatment PET/CT parameters for their ability to predict response to therapy and survival in patients treated for head and neck cancer.

Materials and Methods

The charts of 28 patients with head and neck cancer treated consecutively at our institution were retrospectively reviewed. An Institutional Review Board exemption was granted. All had pre- and post-treatment PET/CT. Patient characteristics are illustrated in Table 1. Staging is reported according to the American Joint Committee on Cancer 7th edition, with workup for all patients including a complete history and physical, biopsy of primary tumor or enlarged lymph nodes (LNs), imaging of the head and neck (including PET/CT for all patients in this study), and chest X-ray or CT.

Treatment consisted of definitive radiation therapy or concurrent chemotherapy and radiation. None of the patients underwent surgery. The median radiation dose was 70 Gy (range: 66.6-70 Gy) in 1.8-2 Gy fractions. CT-based treatment planning and intensity modulated radiation therapy were used for every patient, and PET/CT fusion was utilized to assist in target volume delineation. Normal tissue dose constrains were according to current Radiation Therapy Oncology Group guidelines. Of those patients receiving concurrent chemotherapy, the most commonly used agent was cisplatin alone (30 patients) or in combination with either 5-FU (6 patients) or cetuximab (3 patients). After the completion of therapy, patients were monitored for recurrence in 3-6 month intervals with clinical examination and PET/CT imaging.

Table 1: Patient and tumor characteristics

Characteristic	Number of patients	Percentage
Number of patients	28	
Age (years)		
Median	68	
Range	53-81	
Gender (*n*)		
Male	16	57
Female	12	43
Tumor location (*n*)		
Oropharynx	9	32
Nasopharynx/paranasal sinus	5	18
LNs of unknown primary	2	7
Supraglottis	6	21.5
Hypopharynx	6	21.5
Histology (*n*)		
Squamous	28	100
Stage (*n*)		
I/II	4	14
III/IV	24	86
Treatment protocol (*n*)		
Radiation therapy	4	14
Radiation and chemotherapy	24	86

LN: Lymph node

Integrated positron emission tomography/computed tomography imaging and assessment

We used GE Discovery ST (GE Healthcare) which combines a light-speed CT 16-slice, in-line with PET bismuth germinate oxide detectors. No CT-intravenous contrast was administered. The slice thickness was 3.75 mm; a dedicated neck small field of view acquisition was obtained for all studies. All studies were read by a dedicated nuclear medicine physician specialized in interpreting PET scan images. The primary tumor and metabolically active LNs were individually assessed and assigned a SUV. SUV_{max} is defined as the maximum uptake within a metabolically active mass, and SUV_{mean} is the average uptake within a metabolically active mass. The region of interest used for calculation of the SUV_{mean} comprised the entire volume within the anatomical biological halo, which is the thin region of low SUV uptake surrounding the metabolically active tumor.

Predicting response to treatment

Radiological response by PET/CT criteria was defined as the complete disappearance of FDG activity in the areas of concern. The ABV_{max} or ABV_{mean} is the product of SUV_{max} or ABV_{mean}, respectively, and the maximum tumor diameter (anatomical biological contour [ABC]) in centimeters. The maximum tumor diameter was obtained in axial PET/CT plane and was calculated separately for the tumor as well as the nodes. The ABV_{max} and ABV_{mean} were calculated on pre- and post-treatment PET/CT scans for all 28 patients in the study. Comparisons were made for both the primary tumor and LNs separately. The average number of scans per patient was 2.5 (range: 2-5), while the average interval between scans was 12 months (range: 2-25 months). Complete response (CR) was defined as no evidence of disease on both the PET and CT components of the scan, whereas incomplete response (IR) was defined as any evidence of disease (in the primary tumor or LNs) on either the PET or CT component of the posttreatment scan.

Overall survival was calculated from the time of the pretreatment PET/CT. The median follow up period was 36 months (range: 6-83 moths). Univariate and multivariate analysis were estimated for the following

variables: ABV_{mean}, ABV_{max}, SUV_{mean}, SUV_{max}, LN involvement, stage, and chemotherapy administration.

Statistical considerations

Preliminary analysis was conducted for each of our PET parameters (ABCs, SUVs, and ABVs). Wilcoxon Signed-rank tests were performed to compare between pre- and post-treatment values. The null hypothesis was that ABV_{max} does not predict response or survival. Mann–Whitney test was used to compare between the same variables in CR and IR groups. An ABV_{max} of 30 was found to be a clinically relevant cut-off point and used in subsequent analyses. On the other hand, a cut-off for SUV of 9 was selected after finding that several publications were using the same point for analysis. Fisher's exact tests, univariate and multivariate logistic regression analysis were performed to study factors affecting response. The variables analyzed were ABV_{max}, ABV_{mean}, SUV_{max}, SUV_{mean}, and maximum tumor size. Kaplan–Meier survival curves were generated to estimate overall survival for all patients. Log-rank tests, and Cox proportional hazards regression models were used to correlate end points with various clinical risk factors. Two-sided tests with $P < 0.05$ were considered as significant. STATA software package Manufactured by StataCorp (version 12.1) was used for statistical analysis.

Results

Predicting response using anatomical biological value

The mean of each of the PET/CT parameters analyzed before and after therapy are shown in Table 2.

All the parameters were significantly lower after treatment. Twenty-one out of 28 (75%) patients had CR (CR group) by PET/CT criteria, while 7 (25%) had IR (IR group). Table 3 shows that among all of the PET/CT parameters, only the median pretreatment ABV_{max} was significantly different between complete and incomplete responders, with a value of 22.8 in the CR group compared with 65 in the IR group ($P = 0.021$).

The subjects who had a CR on their first follow-up PET/CT scan within the 1st year after treatment continued to be disease-free for the full duration of the study.

A cut-off ABV_{max} of 30 was found to be of clinical significance. Patients with $ABV_{max} < 30$ had a 93.8% CR rate, compared with 50% in those with $ABV_{max} \geq 30$, ($P = 0.023$). In addition, Fisher exact tests, univariate and multivariate logistic regression analyses showed that $ABV_{max} < 30$ was more predictive of response to treatment than LN involvement, stage of disease, and chemotherapy administration [Table 4].

Positron emission tomography/computed tomography parameters predicting survival

The survival was studied for the whole cohort of 28 patients with an average follow-up period of 36 months (range: 6-83 months).

The median overall survival was 65 months. Patients with CR had a higher median survival (MS) of 65 months compared with 17 months in the IR group. The log-rank test showed that those patients with a CR to therapy had a higher rate of overall survival at 2 years as compared with those patients with IR (90.5% vs. 28.6%, $P = 0.0056$).

In addition, the MS for those patients with a median pretreatment $ABV_{max} < 30$ was 67 months compared with 25 months in those with an $ABV_{max} \geq 30$, ($P = 0.046$), while the 5-year overall survival was 87.5% compared with 58.3%, respectively ($P = 0.028$). In univariate Cox proportional analysis, ABV_{max} was a significant predictive parameter for survival, ($P = 0.05$). Figure 1 shows the Kaplan–Meier survival curve.

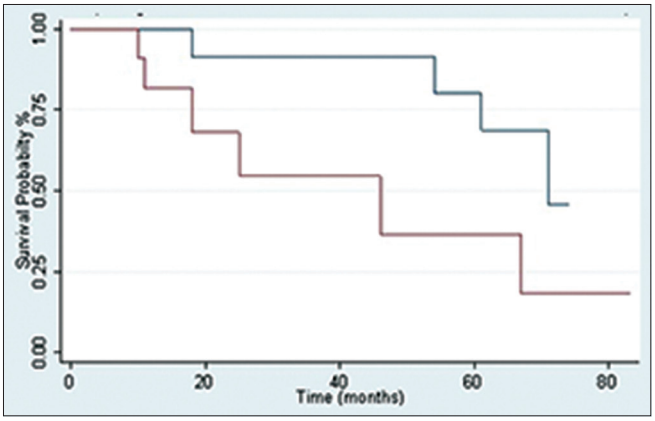

Figure 1: Kaplan–Meier survival estimates based on pretreatment maximum anatomical biological value

Table 2: The means of PET/CT parameters for the metabolically active primary tumor and lymph nodes before and after radiation therapy

	Primary tumor				LNs			
	SUV_{max}	SUV_{mean}	ABV_{max}	ABV_{mean}	SUV_{max}	SUV_{mean}	ABV_{max}	ABV_{mean}
Pre-treatment	11.1	6.7	35.5	21.7	12.4	7.6	35.2	20.4
Post-treatment	1.8	1.2	7.9	4.7	3	1.4	4.4	2.2
P value	<0.0001	<0.0001	0.0001	0.0001	0.003	0.0015	0.0019	0.0019

ABV: Anatomical biological value; SUV: Standardized uptake value; PET: Positron emission tomography; CT: Computed tomography; LNs: Lymph nodes

In multivariate analysis only ABV_{max} had a trend toward significance ($P = 0.055$) [Table 5].

Discussion

The integration of PET and CT scans allows the simultaneous utilization of biological and anatomical imaging data. We have reported previously on the phenomenon of anatomical biological halo to assist in radiation therapy planning in head and neck,[9] lung,[10] and cervix[11] cancers.

In this study, we found that the maximum ABV_{max} of a tumor on a pretreatment PET/CT scan is the most significant prognostic indicator for response to treatment and overall survival in patients with head and neck cancer.

The role of pretreatment PET/CT in predicting response to therapy and survival has been described in previous clinical studies, but remains controversial. An excellent table summarizing these studies was published by Schinagl *et al*.[12] There have been several retrospective series showing that SUV is correlated with survival or local control,[13,14] while there have been other retrospective series showing no correlation.[15,16] Even in those studies that found SUV to be of prognostic value, there is considerable discrepancy regarding the cut-off value that is most suggestive of outcome (ranges from 5 to 10).

The concept of ABV is an extension of SUV that also takes tumor size into account. It is less well-studied, though there have been several reports looking at similar parameters. The metabolic tumor volume defined as the volume of tumor tissue with increased FDG-uptake has been shown to be an independent predictor for disease-free and overall survival in patients with head and neck cancer.[15,16] Higgins *et al*.,[8] studied a term that they called "total lesion glycolysis" (the product of SUV_{mean} and total tumor volume), but did not find it to have any predictive value for outcomes. An important consideration when combining SUV and size into one prognostic factor is to determine if it has any more significance than size alone, which is one of the most important and well-established predictors of outcome in head and neck cancer. In a recent abstract, Chu *et al*.[17] tested the robustness of metabolic tumor volume as an independent variable in a cohort of 176 patients with oropharyngeal cancer, finding that it was predictive of overall survival even after adjusting for T-stage, with a doubling of tumor volume conferring a 1.5-fold increased risk of death. Our study showed similar results, as ABV of the primary tumor improves prediction of response rate and survival beyond TNM stage alone in patients with head and neck cancer.

Our data showed that ABV_{max} was superior to ABV_{mean} in predicting outcomes. We contend that this is because the mean reflects metabolic activity of the entire tumor, some of which may be necrotic or poorly oxygenated, which would have the effect of falsely lowering the FDG uptake to a value that is not truly characteristic of the tumor. Using the maximum uptake value would eliminate this problem. The counterargument is that

Table 3: Comparison between pretreatment PET/CT parameters in CR and IR

Pre treatment	Complete responders	Incomplete responders	*P*
Median ABV_{mean}	13.3 (3.64–93.24)	26.03 (11.93–70.66)	0.1305
Median ABV_{max}	22.86 (4.69–194.47)	65 (17.5–126.73)	0.021
Median SUV_{mean}	6.4 (2–14)	9.1 (2.6–12.1)	0.71
Median SUV_{max}	9.6 (4–29.2)	16.0 (6–24.7)	0.23

ABV: Anatomical biological value, SUV: Standardized uptake value; CR: Complete responders, IR: Incomplete responders; PET: Positron emission tomography; CT: Computed tomography

Table 4: Results of fisher's exact test, univariate and multivariate logistic regression analyses of clinical and therapeutic factors predicting CR

Pre treatment	Subgroup	% CR	*P* value		
			Fisher's exact	Univariate logistic regression	Multivariate logistic regression
Tumor ABV_{max}	<30 (16)	93.8	0.023	0.022	0.021
	≥30 (12)	50.0			
Tumor SUV_{max}	<9 (11)	81.8	0.668	0.506	0.390
	≥9 (17)	70.6			
Stage	I/II	70.0	0.674	0.650	0.415
	III/IV	77.8			
Nodal Involvement	No	73.0	1.000	0.827	0.271
	Yes	77.0			
Chemotherapy	No	50.0	0.144	0.127	0.563
	Yes	81.8			

CR: Complete response; ABV: Anatomical biological value; SUV: Standard unit value

Table 5: Results of log-rank test, univariate and multivariate Cox regression analyses of clinical and therapeutic factors in predicting overall survival

Pre treatment	Subgroup	*P* value		
		Log rank test	Univariate	Multivariate
Tumor ABV_{max}	<30 (16)	0.046	0.061	0.055
	≥30 (12)			
Tumor SUV_{max}	<9 (11)	0.752	0.754	0.473
	≥9 (17)			
Stage	I/II	0.566	0.570	0.767
	III/IV			
Nodal Involvement	No	0.955	0.955	0.660
	Yes			
Chemotherapy	No	0.767	0.093	0.152
	Yes			

ABV: Anatomical biological value; SUV: Standard unit value

SUV_{max} may be an overestimation of tumor metabolism that is less representative of the average cell in the tumor. This concept has led some groups to propose a SUV_{peak}, which would represent the average of the upper 5% SUV's in a tumor.[18] While using the peak may be a compromise between mean and max by eliminating outliers on either end of the spectrum, because it is somewhat time-consuming to calculate and often is not so different than the SUV_{max}, we feel that SUV_{max} is the superior parameter. SUV_{max} is also more reproducible than the mean or peak, given that it is not dependent on accurate delineation of a region of interest to define the volume for calculation. For the same reason, in calculating ABV we chose to use the single largest dimension of the tumor rather than the entire volume of the tumor (as was done in the other series' above) because of the better reproducibility of measuring a single diameter rather than contouring an entire tumor to calculate the volume. Our method is also the simplest technique for a physician to employ, as the size and SUV_{max} are almost invariably written on PET/CT reports. If, however, the tumor volume does prove to have greater predictive potential than the greatest tumor dimension, we would recommend using the halo as a mean of delineating the edge of the tumor volume (in the same way we have done for radiation treatment planning).

The main limitation of our study is the relatively small number of patients. We would point out, though; that because of the long follow-up (range: 6-83 months) we were able to depict outcomes of statistical significance. Furthermore, although our cohort shared many similarities, there were variations in tumor site, number of involved LNs, stage, and chemotherapy administration. Univariate and multivariate analyses showed no significant effect of these variables. There are also several concerns to be raised with any study of this nature. First, we do not have histopathologic confirmation of all of the findings on the posttreatment PET/CT scans. Given the high sensitivity and specificity of PET/CT, and our relatively stringent requirements for defining a CR, we believe that our clinical judgments were generally quite accurate. It is also reassuring to note that our overall survival data is comparable to that reported by SEER for head and neck cancer.[19] Second, SUV is known to vary with respect to time after injection of FDG, the amount of FDG administered to the patient, the plasma glucose level of the patient, the body habitus of the patient, and a number of technical factors related to the hardware and software of the PET scanner.[20] In recent years, there is an increasing degree of homogeneity in the protocol by which various centers acquire PET images, but it should be known that subtle variations remain that may affect the potential of an uptake-based parameter to be used as a universal prognostic factor.

The main clinical implication of our study is that ABV_{max} may serve as a new prognostic factor for guiding therapy decisions in patients with newly diagnosed head and neck cancer, pending further validation in a larger study with a longer follow-up duration. We have also again shown how the simultaneous utilization of biological and anatomical imaging data in a PET/CT can be an invaluable asset in radiation therapy planning. For these reasons, and with the increasing accessibility of PET/CT to the general public, we believe that PET/CT will become a standard part of the diagnostic workup of head and neck cancer.

Conclusion

The ABV is an accurate tool for predicting response to treatment both in the primary tumor and LNs, there is also a direct correlation between higher values and inferior response to treatment and survival.

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