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Fluorodeoxyglucose Positron Emission Tomography as Predictive Factor for the Outcome of Head and Neck Cancer Patients

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ABSTRACT

Objectives: The aim of this study was to determine if fluorodeoxyglucose positron emission tomography (FDG-PET) uptake can be used in pretreatment assessment as an additional prognostic factor for outcome in head and neck cancer patients receiving radiotherapy by helical tomotherapy *(Hi-Art Tomotherapy®)* +/- chemotherapy.

Methods: Between June 2005 and March 2008, 58 patients with a biopsy proven head and neck cancer (HNC) were treated at the Universitair Ziekenhuis Brussel (UZ Brussel). All patients underwent a baseline FDG-PET before treatment. The maximum Standardized Uptake Value (SUV_{max}) was measured within the lesions. Median SUVmax was used as a cutoff to categorize patients into high and low SUVmax groups.

Results: Median SUVmax = 7.92. Median SUVmax for patients who died was significantly higher than living patients (9.16 vs. 7.32, respectively, p= 0.037). 3-years Overall survival (OS) was 80% vs. 54% (p = 0.009) and disease free survival (DFS) was 83% vs. 41% (p = 0.018) for low and high SUVmax groups, respectively. Multivariate analysis also confirmed these observations.

Conclusion: PET-FDG scan before treatment is a good predictor of outcome in HNC patients. It may helps in early identification of patients with poor prognosis for perhaps other therapeutic approaches.

Keywords: FDG-PET, SUV, Helical Tomotherapy, Head and Neck Cancer, Predictive Factor

INTRODUCTION

[18F] Fluorodeoxyglucose (FDG) is a radiolabeled glucose analog that is taken up by cells through the glucose transporter and is subsequently phosphorylated by hexokinase. FDG distribution within the body is a measure of glucose metabolism and may be detected by positron emission tomography (PET). Malignant cells have increased glycolytic activity, in which glucose is preferentially concentrated due to an increase in membrane glucose transporters as well as to an increase in some of principal enzymes, such as hexokinase. [12,23] So, PET imaging with FDG can be used for the detection and localization of a wide variety of malignancies.[17]

Head and neck cancers (HNC) have so far unpredictable response to treatment. Despite careful evaluation of established prognostic factors in these patients, it is currently impossible to reliably predict treatment outcomes; even in patients within the same TNM category [19]. Early recognition of patients with poor outcome is important because these subjects might benefit from intensified or innovative types of treatment.

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This has prompted an intensive search for clinically measurable factors that would assist in selection of optimal treatment and evaluation of prognosis.

The degree of FDG uptake was correlated with outcome in different malignancies as head and neck cancer (HNC)[1,2,11,15,25], lung cancer [9,16] esophageal cancer[18], cervical cancer[26], colorectal cancer[3], breast cancer[20] osteosarcoma [21] and lymphoma [13].

The aim of this study was to determine if FDG-PET uptake can be used as a prognostic factor for assessment of outcome in a group of head and neck cancer patients before treatment with radical radiotherapy +/- chemotherapy.

METHODS

Patients and tumor characteristics

Between June 2005 and March 2008, 58 consecutive patients with a biopsy proven head and neck cancer were treated with helical tomotherapy (Hi-Art TomoTherapy®, Madison, Wisconsin, USA) at the Universitair Ziekenhuis Brussel (UZ Brussel).

Patients were initially evaluated by history, physical examination, complete blood count, hepatic and renal profiles, panendoscopy, biopsy and pathological examination. Radiologic studies as, head and neck computerized tomography (CT) and magnetic resonance imaging (MRI) were done.

Tumors were staged according to the TNM classification (2002) [6]

All patients underwent a baseline (FDG-PET) before treatment. Patient and tumor characteristics are listed in **Table 1**.

About 2/3 of the cases were pharyngeal carcinoma. Different T stages are presented, no N3 patients were included 1/3 of the patients (31%) received chemotherapy concurrently with radiotherapy.

Table -1: Patients and Tumor Characteristics

	(n=58)
Median age in years (range)	56.5 (34-88)
Male/Female	49 /9
Tumor site	
Larynx	9 (16 %)
Hypopharynx	15 (26 %)
Nasopharynx	4 (7 %)
Oropharynx	16 (27 %)
Oral cavity	14 (24 %)
Tumor histology	
Squamous ca	57 (98 %)
Others, Undifferentiated ca	1 (2 %)
T stage	
T1	9 (16 %)
T2	18 (31 %)
T3	21 (36 %)
T4	10 (17 %)
N stage	
N0	24(41 %)
N1	6 (11 %)
N2	28 (48 %)
N3	0 (0%)
AJCC Stage Grouping	
I	2 (3%)
II	11 (19%)
III	16 (28%)
IV	29 (50%)
Concurrent Chemo therapy	
Yes /No	18/40

Treatment technique

Radiotherapy was given with helical Tomotherapy with a simultaneous integrated boost scheme for all patients [4]

A dose of 66-70.5 Gy in 2.2-2.35 Gy/fraction was prescribed to the primary tumor and the pathological lymph nodes (planning target volume 'PTV' 70.5). 66 Gy was given to patients receiving concurrent chemotherapy. The elective node regions were treated with 1.8 Gy/fraction up to 54 Gy.

Delineation of the primary tumor, pathological and elective lymph nodes was performed using co-registration of the CT scan, MRI and PET scan [5, 10]

The electively irradiated nodes were delineated according to primary site and T stage according to recently published guidelines [7]

Chemotherapy (Cisplatinum 100 mg/m², q 21 days, 3 cycles) was added according to the head and neck patient's protocol of the department (age < 65 years, WHO 0-1 performance status, normal renal function)

Follow up was done after completion of radiotherapy, every 2 months during the first year and every 3 months in the second year.

^{18}FDG PET Procedure

Patients were instructed to fast for at least 6 h before the PET scan. The serum glucose level was measured prior to intravenous administration of ^{18}F-FDG; patients with serum glucose levels > 150 mg/dl were excluded.

Acquisition protocol.

Acquisition started 60 min after injection of ^{18}F-FDG using a dedicated PET system (Siemens ECAT ACCEL, Knoxville, TN, USA). Emission data were reconstructed with iterative ordered-subset expectationmaximi-sation algorithm (OSEM), corrected for scatter and a post-reconstruction filter (6 mm Gauss) was applied. For transmission data filtered backprojection was used, the constructed attenuation map was subsequently segmented into regions with similar attenuation factors, and was then forward projected to obtain attenuation correction factors for each line of response.

Interpretation and analysis of 18F-FDG PET data

All pretreatment 18FDG PET images were analyzed by two nuclear medicine physicians. They also have an access to the complete medical record of the patients. Also, all images were analyzed in the presence of radiation oncologist. In case of discrepant interpretations a consensus was reached after discussion.

The standardized uptake value (SUV = (decay-corrected activity per ml tissue) / (injected activity)* (body mass)) was calculated for each pixel of the lesion. The maximum SUV (SUV_{max}) within the lesion was considered as a semi-quantitative measure representing the most metabolic active part of the tumor. Median SUVmax was used as a cutoff to categorize patients into high and low SUVmax groups.

Statistical Analysis

Survival times were calculated from the day of diagnosis. Overall survival (OS), Disease free survival (DFS), Locoregional recurrence free survival (LRRFS) and Metastases free survival (MFS) were calculated at the date of death or relapse or the last date of follow up. Kaplan-Meier method was used for estimation of survival rates. The level of significance was set at $p \leq 0.05$.

RESULTS

Median follow up time was 14.4 months (3.7-38.8). At the last follow up 42 of the 58 patients are living (72%) and 34 patients are living free from disease (59%). 3-years OS and DFS were 67% and 52%, respectively.

The median SUVmax for the patients was 7.92 (2.41-16.38). The relation between SUVmax before treatment and disease stage was studied. For early T stage (T1 and T2) SUVmax was lower than SUVmax for advanced T stage (T3-T4), however the difference was not statistically significant. On the other hand, the medians of SUVmax was significantly lower in node negative patients (6.37) than node positive patients (8.73) (Mann-Whitney test p= 0.015) **(Fig 1)**. With AJCC stage grouping there was no significant difference between groups in SUVmax however, when the patients were categorized into two groups only; early stage disease (I and II) and advanced stage disease (III and IV), The Medians of SUVmax was significantly lower in early stage group (5.45) than advanced stage group (8.42) (Mann-Whitney test p = 0.038). **(Fig 2)**

SUVmax was significantly correlated with outcome. Median SUVmax for patients who died is higher than that for living patients; 9.16 vs. 7.32, respectively (Mann-Whitney test p = 0.037) **(Fig 3)**. The group of patients with high SUVmax showed worse outcome. At time of evaluation 12 patients out of 29 with high SUV max died while only 4 patients of 29 patients with low SUV max died (Fisher exact test p = 0.038).

Overall survival at 3 years were 80% vs. 54% (p=0.009) **(Fig 4)**, DFS were 63% vs. 41% (p= 0.018) **(Fig 5)**, LRFS were 71% vs. 56% (p= 0.04), RRFS were71 vs. 52 (p= 0.03) and MFS were 77% vs. 39% (p=0.004) for low and high

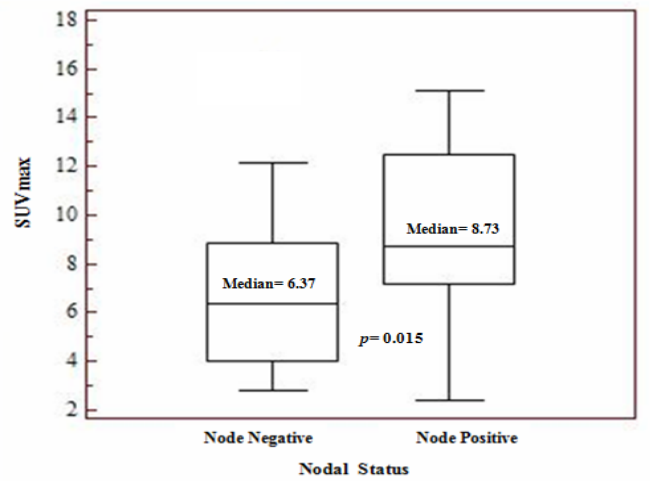

Fig 1: maximum standardized uptake values (SUVmax) according to nodal status

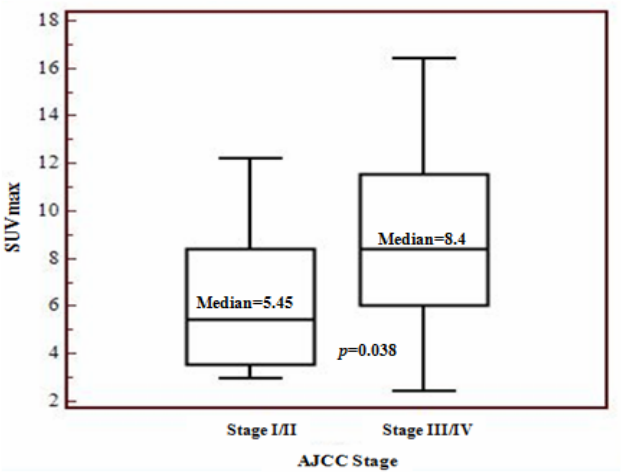

Fig 2: Maximum standardized uptake values (SUVmax) according to AJCC stage.

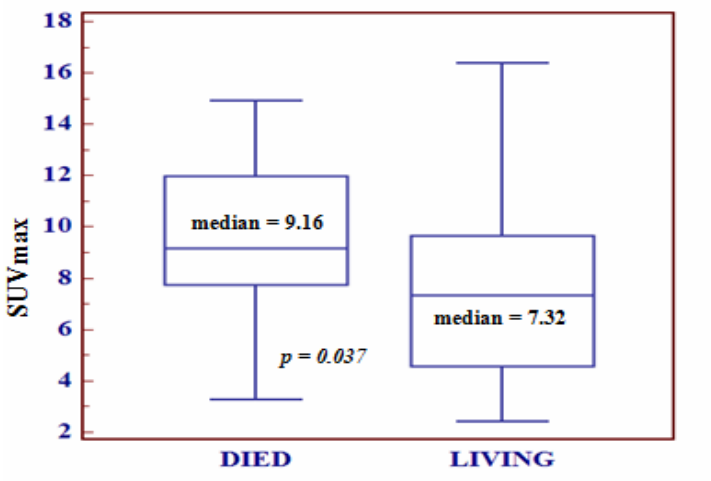

Fig 3: Maximum standardized uptake values (SUVmax) for patients who died and patients who were still living.

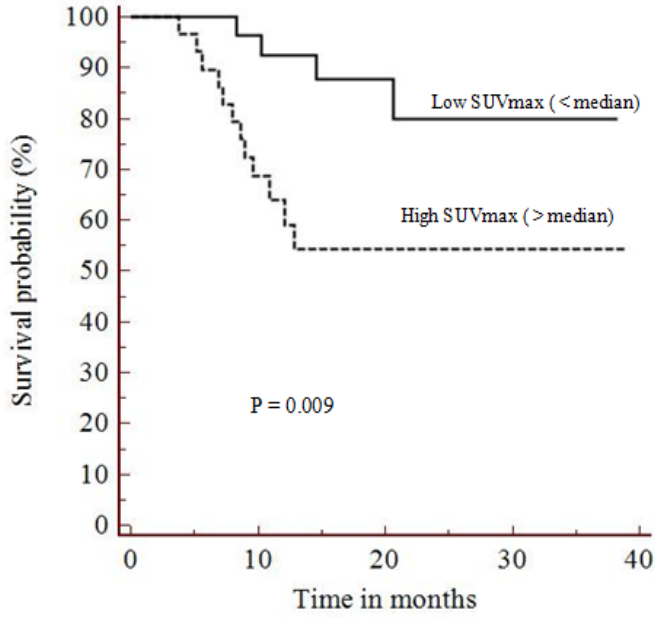

Fig 4: Overall survival (OS) according to maximum standardized uptake values (SUVmax)

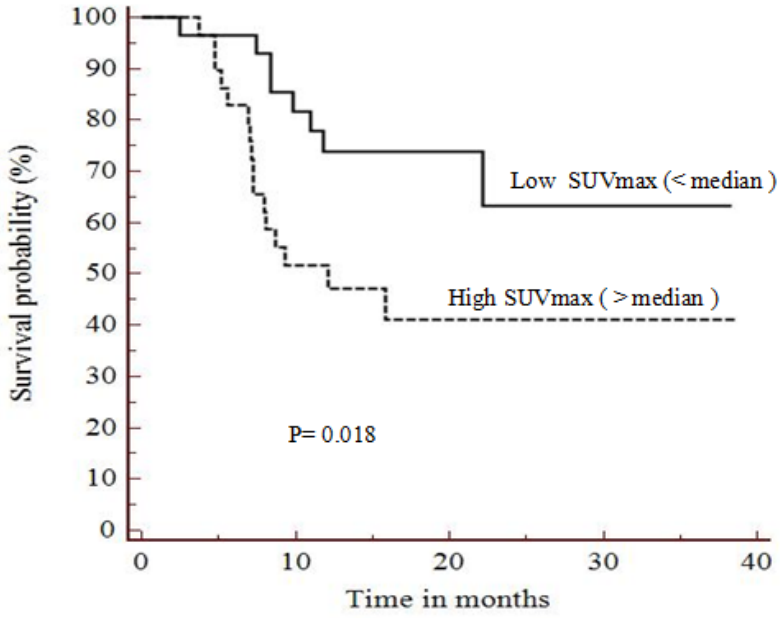

Fig 5: Disease free survival (DFS) according to maximum standarized uptake values (SUVmax)

SUVmax, respectively. LRRFS at 3 y was also in favor of the low SUVmax but was not statistically significant, 63% vs. 54% (p=0.09).
Evaluation of the effect of other prognostic factors on therapy outcome was done **(Table 2)**. As shown, most of the studied factors didn't show significant difference between groups except KPS.
In multivariate analysis, included the SUVmax, KPS, AJCC stage and chemotherapy use, SUVmax was the only factor which showed significant difference in outcome. The 3-y OS (p=0.015), LRFS (p= 0.048), RRFS (p = 0.034), LRRFS (p = 0.1), MFS (p=0.009) and DFS (p=0.027) were in favor of the low SUVmax group. **(Table 3)**

DISCUSSION

Head and neck carcinomas are a distinct group of neoplasms with an unpredictable clinical behavior. Despite, the presence of well established prognostic factors for HNC none of them can reliably predict outcome[19]. The variability in response may be due to a complex interaction of biologic characteristics that are responsible for tumor development, growth, and invasiveness[24].
Several studies showed that pretreatment high FDG uptake was correlated with poor outcome in different malignancies[3,9,13,16,18,20,21,26] including head and neck cancer [1, 2, 11, 15, 25].
In this study we found that the SUVmax at baseline was correlated with outcome and patients with low SUV had a significant better outcome for OS, DFS, LRFS, RRFS and MFS. These results are in accordance with the studies on head and neck cancer which showed better results in patients with low tracer uptake [1,2, 11, 15, 25].

In the present work SUVmax was better than other well known factors in predicting outcome (including TNM, grade, primary site and KPS) **(Table 2)**. Multivariate analysis also confirmed these observations and showed that SUVmax was the only predictor of outcome

An interesting observation is that SUVmax was also significantly correlated with nodal status and AJCC disease stage **(Fig3)** which confirms other observations[1,2,15]. However, the outcome itself was not significantly affected by either disease stage or nodal status **(Table 2)**. The multivariate analysis showed that SUVmax is an independent predictor of survival, and not dependent on stage.
This suggests that FDG uptake may express some intrinsic biologic characteristics of the tumor which are related to tumor aggressiveness such as cell viability[14], proliferative activity[8]. Therefore patients with tumors that are more metabolically active, as demonstrated by FDG-PET imaging, should be considered at high risk for relapse and recurrence, regardless of clinical stage at presentation.
In this study, the use of concurrent chemotherapy didn't improve the results either on the systemic level (MFS) or local level (LRRFS). This may raise the question about the value of chemotherapy when using high dose intensified radiotherapy like tomotherapy. This observation is in accordance with the metaanalysis done by Staar et al,[22] who found that intensified radiotherapy limited the additional benefit of simultaneous chemotherapy.
Currently, no SUVmax cutoff value has been established for defining subgroups of different prognoses. In the absence of a standard cutoff, we choose to use the median SUV (7.9) as the basis for analysis.
Future studies should focus on examining different SUVmax cutoffs to better define prognostic groups before treatment.

CONCLUSION

We conclude that ^{18}FDG-PET before treatment is promising. In the future, it may help in defining response categories, and consequently, will help in choosing more intensive treatment for patients with expected poor outcome.

Table 2- Univariate analysis for the effects of different prognostic factors on outcome.

Factor	GROUPS	3-y OS (%)	3-y LRFS (%)	3-y RRFS (%)	3-y LRRFS (%)	3-y MFS (%)	3-y DFS (%)
Age	**<60**	65.5	60	60	54	54	46
	>60	65.9	66	65	65	65	65
		0.6	*0.33*	*0.77*	*0.96*	*0.66*	*0.57*
Sex	**M**	68	63	64	56	59	51
	F	62	62	61	64	53	55
		0.39	*0.6*	*0.63*	*0.83*	*0.43*	*0.6*
KPS	**≥90**	78	74	78	74	66	66
	<90	53	49	42	37	49	34
		0.15	*0.12*	*0.029*	*0.024*	*0.17*	*0.046*
T Stage	**1/2**	63	63	55	55	55	45
	3/4	69	61	67	59	60	57
		0.73	*0.4*	*0.96*	*0.62*	*0.77*	*0.85*
N Stage	**N0**	64	59	59	54	69	54
	N+	69	66	64	61	49	51
		0.96	*0.99*	*0.75*	*0.79*	*0.14*	*0.34*
AJCC Stage grouping	**I/II**	54	54	42	42	61	42
	III/IV	70	69	67	62	57	55
		0.75	*0.96*	*0.64*	*0.88*	*0.54*	*0.75*
Grade	**1/2**	66	60	64	57.9	58	56
	3/4	56	56	58	58.3	40	42
		0.28	*0.19*	*0.54*	*0.46*	*0.13*	*0.3*
Chemo	**YES**	81	81	76	76	72	72
	NO	63	57	63	58	55	53
		0.38	*0.24*	*0.77*	*0.52*	*0.57*	*0.68*
SUVmax	**LOW**	80	71	71	63	77	63
	HIGH	54	56	52	54	39	41
		0.009	*0.04*	*0.03*	*0.09*	*0.004*	*0.018*

OS=overall survival, LRFS= local recurrence free survival, RRFS= regional recurrence free survival, LRRFS= locoregional recurrence free survival. MFS= metstases free survival, DFS= disease free survival. KPS = Karnofsky Performance Status.

Table 3- Multivariate analysis by Cox Proportional Hazards Models for the effects of different prognostic factors on outcome.

	3y-OS			3y-DFS			3y-MFS		
	RR	**95% CI**	**P**	**RR**	**95% CI**	**P**	**RR**	**95% CI**	**P**
CHEMC	0.58	0.1609 to 2.0902	0.41	0.78	0.3038 to 1.9940	0.6	0.71	0.2565 to 1.9622	0.51
KPS	0.53	0.1989 to 1.4181	0.21	0.66	0.2941 to 1.4707	0.31	0.9	0.3836 to 2.1023	0.81
STAGE	0.69	0.2172 to 2.1928	0.53	1.05	0.3844 to 2.8480	0.93	1.27	0.4205 to 3.8152	0.68
SUVma	4.17	1.3318 to 13.0273	0.015	2.63	1.1195 to 6.1607	0.027	3.54	1.3777 to 9.0751	0.009
	3y- LRFS			**3y-RRSF**			**3y- LRRFS**		
	RR	**95% CI**	**P**	**RR**	**95% CI**	**P**	**RR**	**95% CI**	**P**
CHEMC	0.45	0.1292 to 1.5802	0.22	0.9	0.3175 to 2.5565	0.85	0.7	0.2516 to 1.9250	0.49
KPS	0.47	0.1847 to 1.1816	0.11	0.51	0.2067 to 1.2515	0.14	0.47	0.1988 to 1.1096	0.087
STAGE	0.95	0.3096 to 2.9228	0.93	0.64	0.2240 to 1.8241	0.41	0.84	0.3045 to 2.3336	0.74
SUVma	2.7	1.0138 to 7.2028	0.048	2.9	1.0875 to 7.7248	0.034	2.1	0.8665 to 5.0931	0.1

OS=overall survival, LRFS= local recurrence free survival, RRFS= regional recurrence free survival, LRRFS= locoregional recurrence free survival. MFS= metstases free survival, DFS= disease free survival. Chemo= chemotherapy. KPS = Karnofsky Performance Status. RR= relative risk. CI= confidence interval.

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