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The prognostic value of FDG PET ... head and neck cancer

Correlation with histopathology

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***Aim*. The aim of the present FDG PET study w... l-uate the prognostic value of the standardi... e value (SUVmax) of head and neck cancer (HNSC... ith respect to the chemotherapy response and tumor recurrence.**

***Methods*. The FDG PET findings of 40 p... h HNSCC were compared with the final histopath... g... sults after removal of the primary tumor an... urg... neck dissection. The clinical T staging was bas... on c...nical ex... nations and computed tomogr...hy ... used for a...ss-ment of bone involvement. The p... tment ba...ine SUVmax of the primary tu... were correlated wi... intra-arterial chemothera... re... se prior to ... tum... resection and the frequ... ...or relapse.**

***Results*. The median SUV... f tumors w... h di... ot relapse was 3.4, com... ed to a ...Vmax o...7 ...mors with local tumor ... e =0.36, ... eg...ding chemotherapy res... e tumor SU... was significantly lowe... cas... th comp... rem... ion (CR) (median 2.6, n=1... mpared to thos... h stable disease (5.8, n=10), ... whereas ... with CR after chemothera... elapsed excep... tage IV ...mors, tumor relapse ... s ob... d in bot... ge II and a stage IV tumor wi... chemothera... re... onse.**

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KEY WORDS: Fluc... xyglu... se, F18 - Tomography, emission computed - H... and ...eck neoplasms - Prognosis - Standardized upta... .

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Positron emission tomography (PET) with F-18-2-fluoro-2-deoxy-D-glucose (FDG) is an effective imaging method for the staging and restaging of patients with squamous cell carcinoma of the head and neck (HNSCC).[1] In fact, dedicated PET had been shown to be superior to CT in the diagnosis of the primary or recurrent tumor, and in the assessment of lymph node involvement.[2-5] The status of cervical lymph nodes is a particular important prognostic factor which determines the management approach in patients with HNSCC.[6]

The aim of the study was to evaluate the prognostic implication of FDG PET in patients with HNSCC. PET results were correlated with the histopathological findings and follow-up. Pretreatment baseline tumor SUVmax values were correlated with the clinical intra-arterial chemotherapy response prior to tumor resection and with the patients' postoperative risk for tumor relapse.

Materials and methods

Patients

Forty consecutive patients (17 women, 23 men, mean age±SD, 66±9 y) suffering from previously untreated surgically resectable primary HNSCC were recruited. Pathological stage grouping was done according to the UICC 2002. The FDG PET findings were compared with the final histopathological results that were obtained after removal of the primary tumor in combination with surgical neck dissection.

The patients underwent FDG PET during the period between January 1999 and April 2003. The primary tumor was located in the oral tongue in 14 patients, in the floor of the mouth in 12 cases, in the buccal mucosa in 10 patients and in the retromolar trigone in 4 cases.

After initial staging based on FDG PET, all patients underwent neoadjuvant intra-arterial chemotherapy with cisplatin (150 mg/m^2) which was infused via superselective catheterization into the tumor-feeding vessels at 3-4 weeks before the surgical tumor resection.[7] Patients with an initial negative lymph node status, based on PET, underwent a radical tumor resection and (depending on the laterality of the primary) an ipsilateral or bilateral selective neck dissection including the levels 1 and 2a or (starting in March 2000) lymphoscintigraphy guided sentinel lymph node removal (SLNB). In patients with a positive PET lymph node status a modified radical neck dissection was done in addition to the local tumor resection. The time interval between PET diagnosis and surgical treatment was less than 4 weeks in all patients. The patients were followed up for a period of 18±8 months using clinical examination and computed tomography.

The preoperative T staging of the primary tumor was based on the clinical examination. Bone involvement by the primary tumor was assessed by computed tomography (Somatom Plus 4, Siemens, Erlangen, Germany). Response to chemotherapy was assessed by clinical examination computed tomography included and histopathology. Partial remission (PR) was defined as local tumor volume reduction of 50% or more and complete remission (CR) was defined as no local tumor evidence after intra-arterial chemotherapy as assessed by clinical examination computed tomography included and histopathology. Tumors that showed increase in volume of more than 25% were classified as progressive disease (PD).

Tumor relapse was defined as the occurrence of local tumor recurrence, lymph node metastasis and/or distant metastasis. The occurrence of metachronous second primaries was also evaluated.

PET scanning

The FDG PET studies were done in all patients using a whole body scanner (ECAT EXACT 47, Siemens). After fasting for 12 hours (blood sugar level <150 mg/dl) a mean activity of 281±47 MBq of F-18-FDG, body weight adjusted, was injected in a resting state. Images were reconstructed with an iterative reconstruction algorithm (slice thickness 3.4 mm, pixel size 4.37 mm).

Data analysis

In a retrospective analysis, the transaxial, sagittal and coronal PET images of all patients were reviewed by 2 experienced observers who were blinded to the findings of other anatomic imaging modalities and the clinical data.

In all patients the maximal standardized uptake value (SUVmax) was measured semiquantitatively using lean-body-mass-index correction based on a ROI-analysis.[8] The SUVmax was correlated with the clinical tumor response after intra-arterial chemotherapy as well as with the frequency of tumor relapse.

Statistical analysis

SUVmax values of the primary tumor are presented as median (25th percentile, 75th percentile). Comparisons within the patient groups regarding response to chemotherapy and tumor size (clinical T [cT] stage) were done by the nonparametric Wilcoxon-Whitney U-test.

Statistical significance was assumed at a value of $p<0.05$. Statistical analysis was performed with BIAS (Copyright Epsilon 1989-2002).

Results

The SUVmax values for the HNSCC ranged from 1.3 to 13 (Table I). The tumor size (cT stage) and SUVmax of the primary tumor did not show any correlation (rho: 0.54, $p<0.001$). Significant differences in the FDG uptake values of tumors of a different tumor size (cT stage) were not observed ($p=0.4$, n.s.).

TABLE I.—*Tumor SUVmax (SUV) compared to chemotherapy response and the frequency of tumor relapse.*

N.	Gender	Age (y)	SUV	C stage	Response	Relapse
1	F	67	1.3	II	PR	—
2	F	58	1.7	III	CR	—
3	F	65	1.9	I	PR	—
4	F	70	1.9	II	CR	—
5	F	65	1.9	III	SD	—
6	M	62	2.3	II	PR	—
7	F	72	2.3	II	PR	Local
8	F	69	2.4	II	PR	—
9	M	66	2.4	IVA	PR	—
10	M	64	2.6	II	CR	—
11	F	62	2.6	I	CR	—
12	M	55	2.6	IVA	CR	—
13	F	79	2.6	I	CR	—
14	M	69	3.1	IVA	CR	Local
15	M	65	3.2	I	CR	—
16	M	65	3.2	II	PR	—
17	F	72	3.4	IVA	PR	—
18	M	53	3.6	III	PR	—
19	M	51	3.8	IVA	CR	Cervical
20	M	74	3.8	IVA	PR	Local
21	M	51	4.0	III	PR	—
22	M	54	4.0	III	SD	—
23	F	63	4.2	IVA	SD	—
24	F	69	4.5	II	PR	—
25	F	62	4.9	IVA	PD	St
26	M	54	5.2	III	CR	—
27	M	67	5.2	II	PR	—
28	M	63	5.6	IVA	SD	—
29	M	51	5.7	II	SD	Local
30	M	83	5.8	IVA	PR	—
31	F	92	5.9	IVA	SD	Local
32	M	60	6.1	IVA	SD	—
33	M	74	6.6	III	CR	St
34	F	79	6.8	IVA	PR	—
35	M	62	6.8	IVA	SD	—
36	M	70	7.2	IVA	SD	—
37	F	75	7.3	IVA	SD	—
38	M	63	8.4	IVA	PR	—
39	F	62	8.6	III	PR	—
40	M	74	13.0	IVA	PR	Local

CR: complete remission; PR: partial remission; PD: progressive disease; SD: stable disease; St: metachronous second primaries.

TABLE II.—*Therapy response after intra-arterial chemotherapy in patients with HNSCC compared to the clinical staging (c stage), the chemotherapy response and tumor relapse.*

Response	N=40	C stage	No.	Relapse (n=7)	Time of relapse after tumor resection (months)
CR	11	1	3	—	
		2	2	—	
		3	3	—	
		4A	3	2	6 and 8
PR	18	1	1	—	
		2	7	1	6
		3	3	—	
		4A	7	2	8 and 13
SD	10	1	—	—	
		2	1	1	12
		3	2	—	
		4A	7	1	2
PD	1	4A	1	—	

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease

Thirty-one patients (74%) showed a positive chemotherapy response (defined as clinical CR or PR): CR in 11 cases and PR in 18 cases (Table II). The tumor SUVmax was lower in patients with CR (median, 25th percentile, 75th percentile: 2.6, 1.8, 3.4) compared to patients with SD (5.8, 4.2, 6.9) (p=0.002) and compared to patients with PR (3.7, 2.3, 6.1) (p=0.09, n.s.), (Figure 1). The SUVmax in tumors with PR did not differ significantly from those with SD (p=0.13). Especially the primaries of patients with CR showed significant lower SUVmax values compared to patients with PR, SD or PD.

Stage 0 to III tumors with CR after chemotherapy did not relapse during the follow-up period. Only 2 patients with stage IV tumors who showed CR after chemotherapy developed a tumor relapse. In contrast, 1 stage II tumor and another 2 stage IVA tumors, all with PR after chemotherapy, relapsed. In 25% of the patients (n=10) stable disease (SD) was observed after chemotherapy. Most of these patients (9/10) suffered from a stage III or stage IV disease. Two of these patients with SD developed tumor relapse, 1 stage II and another stage IVA tumor (Table II). Figures 2A, B illustrate the FDG PET of a stage IVA tumor with PR after chemotherapy which relapsed 1 year after tumor resection. Another stage IVA patient showed PD (n=1) after chemotherapy, the SUVmax value of this tumor was 4.9.

Altogether, a total of 7 out of the 40 patients (17.5%) relapsed within 7.9±3.8 months after tumor resection. In 6 out of 7 the tumor relapse was localized locally and in 1 patient cervical lymph node metastases were detected. The median SUVmax (minimum, maximum) of tumors that did not relapse was 3.4 (1.3, 8.6) compared to a SUVmax of 4.7 (2.3, 13) in tumors with local tumor relapse (p=0.36, n.s.). Two patients, 1 IVA tumor and another stage III tumor, developed a

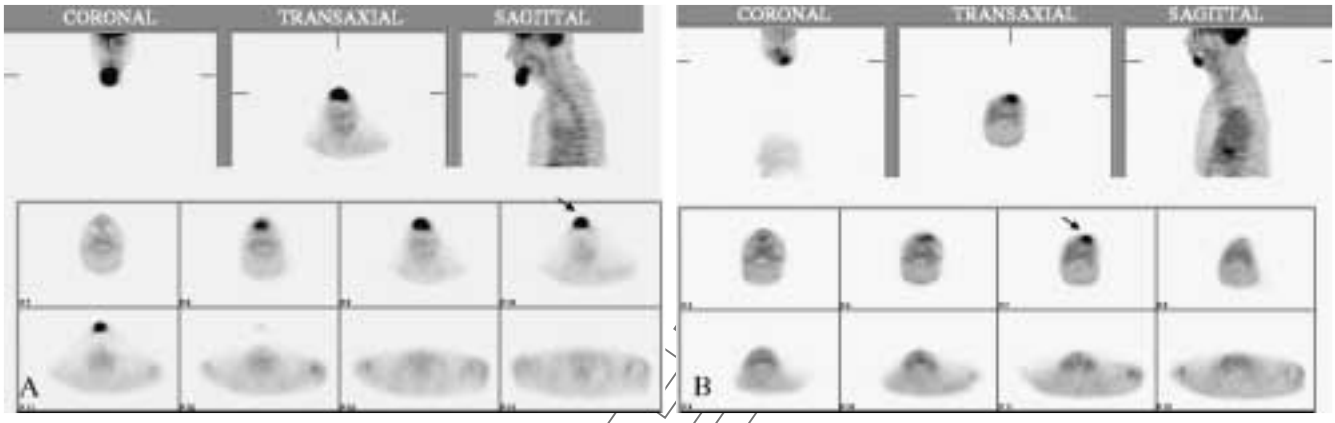

Figure 1.—A) FDG PET of a 74-year-old patient with an extensive stage IVA HNSCC localized in the floor of the mouth, initial SUVmax 13.0, partial remission after intra-arterial chemotherapy. Top: 3D; bottom: axial views. B) FDG PET of the same patient: 1 year after tumor resection he developed tumor relapse Top: 3D; bottom: axial views.

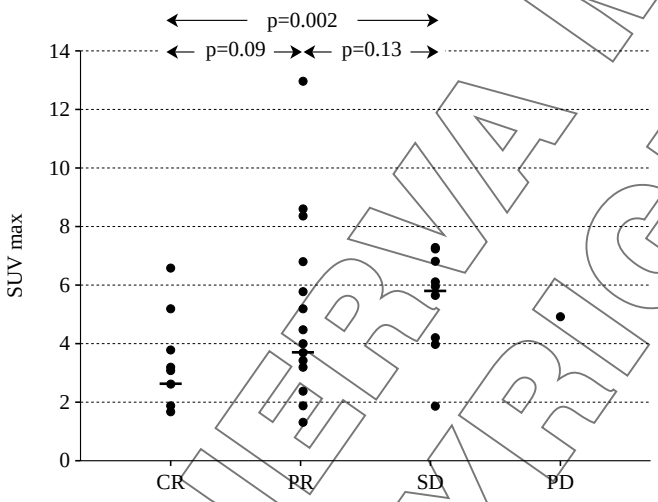

Figure 2.—SUVmax of the primary tumor compared to the chemotherapy response prior to surgical removal of the tumor. CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; no statistical analysis of only 1 patient with PD - median SUVmax.

metachronous second primary. The SUVmax of these tumors were 4.9 and 6.6, respectively.

The SUVmax values of the HNSCC which relapsed did not differ significantly from tumors that did not relapse during follow-up. Low tumor uptake values indicated a good chemotherapy response, whereas only a non significant trend for slightly higher SUVmax values was observed in tumors which relapsed compared to tumors without local recurrence.

Discussion

FDG PET with quantitative SUV measurement has been proposed as a useful technique for monitoring patients with different kinds of tumors receiving chemotherapy. A reduction of the metabolic activity early after chemotherapy correlates closely with the final outcome of therapy in patients suffering from advanced non-small-cell lung cancer,[9] aggressive non-Hodgkin's lymphoma [10] and colorectal carcinoma.[11] Using metabolic response as an indicator of end point may reduce the morbidity and cost of therapy in non-responding patients.[9] Performed early during chemotherapy, FDG PET may be able to predict the clinical outcome and thus distinguish the responders from the non-responders in various tumors.[10, 11] The change in metabolic activity during neoadjuvant systemic radiochemotherapy is associated with tumor response, survival and local control.[12, 13] FDG uptake by HNSCC is proposed as a parameter for assessing tumor aggressiveness that is closely related to proliferative activity and cellularity.[14] Kunkel *et al.* described a high SUV as a predictor for a shorter survival in patients with HNSCC.[15] Pretreatment FDG PET is useful in predicting the response to systemic chemotherapy combined with radiotherapy and in predicting residual viable tumors.[14] The present study demonstrates that the FDG uptake value of the primary tumor itself predicts the patients' intra-arterial chemotherapy response. The SUVmax value of the primary tumor was a reliable predictor for intra-arterial chemotherapy response, especially for patients with CR regardless the tumor size although the initial tumor size did not correlate with the

FDG uptake. Noteworthy, all patients with stage I to III tumors showing CR after chemotherapy did not relapse during follow-up.

Although individual uptake values are heterogenous and the clinical data (*i.e.* tumor stage, histology) underly a high variability [16] quantitative parameters like SUVmax values or average uptake values are helpful to show a trend of therapy response and recurrence in addition to qualitative PET analysis. Low tumor uptake values indicated a good chemotherapy response whereas only a trend for slightly higher SUVmax values was observed in tumors which relapsed compared to tumors without local recurrence during follow-up. In this study, the FDG uptake values of the HNSCC in patients with tumor relapse did not differ significantly from the uptake values of those who did not show a tumor relapse. When treating patients with HNSCC, the prognosis has to be evaluated and an appropriate therapy has to be chosen. Tumors with lower SUVmax values tend to respond better to treatment than those with a high FDG uptake. In the future, alternative chemotherapy regimes have to be discussed for patients with higher tumor SUVmax values.

Conclusions

These preliminary data based on a rather small patient group show that the initial tumor metabolic activity did not correlate significantly with the patients' risk for recurrence but seems to be a prognostic factor for the clinical intra-arterial chemotherapy response in patients with HNSCC. No tumor relapse was observed in tumors showing CR after chemotherapy except stage IV tumors.

These data have to be confirmed in larger patient groups and in a longer follow-up period.

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ORIGINAL ARTICLES

The prognostic value of FDG PET in head and neck cancer. Correlation with histopathology

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Aim. The aim of the present FDG PET study was to evaluate the prognostic value of the standardized uptake value (SUVmax) of head and neck cancer (HNSCC) with respect to the chemotherapy response and tumor recurrence.
Methods. The FDG PET findings of 40 patients with HNSCC were compared with the final histopathology results after removal of the primary tumor and surgical neck dissection. The clinical T staging was based on clinical examinations and computed tomography was used for assessment of bone involvement. The pretreatment baseline SUVmax of the primary tumor were correlated with the intra-arterial chemotherapy response prior to the tumor resection and the frequency of tumor relapse.
Results. The median SUVmax of tumors which did not relapse was 3.4, compared to a SUVmax of 4.7 for tumors with local tumor relapse (p=0.36, n.s.). Regarding chemotherapy response, the tumor SUVmax was significantly lower in cases with complete remission (CR) (median 2.6, n=11) compared to those with stable disease (5.8, n=10), (p=0.002). Whereas no tumor with CR after chemotherapy relapsed except stage IV tumors, tumor relapse was observed in both a stage II and a stage IV tumor without chemotherapy response.
Conclusion. In patients with HNSCC the tumor SUVmax seems to be a useful prognostic indicator for assessing the clinical chemotherapy response, but did not correlate significantly with the recurrence risk. Thus, in tumors with higher SUVmax alternative chemotherapy regimes have to be discussed.

Full-Text (PDF)

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