Fluorodeoxyglucose Imaging of Advanced Head and Neck Cancer After Chemotherapy

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Positron emission tomography (PET) was applied to evaluate therapeutic effects in patients with advanced head and neck cancer for use in monitoring therapy. In 18 patients with histologically proven head and neck cancer, PET studies with 330–440 MBq ^{18}F-fluorodeoxyglucose (FDG) were performed prior to the first chemotherapeutic cycle with cisplatin and 5-FU. A second examination after the first chemotherapeutic cycle was performed in 11 patients. Tumor or lymph node volumes were determined from CT slices and the growth rate was calculated assuming an exponential function. Uptake in a region of interest was used for the quantitative evaluation of the PET images after standardization to injected dose and body weight. FDG data were available for 6 tumors and 10 metastases, volumetric data for 5 tumors and 7 metastases. One lesion showed an increase, seven a decrease in FDG uptake and eight lesions remained unchanged. Multiple lymph nodes in the same patient showed different baseline metabolisms and also different changes following therapy. Tumors were more sensitive to therapy than lymph node metastases. The growth rate and the change in FDG uptake were highly correlated with different regression functions for tumors and lymph node metastases. These data demonstrate that PET with FDG can be used to assess early chemotherapeutic effects. The information gained with PET can be included for treatment planning in patients undergoing systemic chemotherapy.

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Although there are several trials to combine different therapeutic modalities (*1–5*), the treatment of patients with advanced cancer of the head and neck still needs further improvement. Combinations of 5-fluoro-uracil (5-FU) and cisplatin are reported to have remission rates between 50% and 80% (*1,4,5–10*). The synergistic effect of both drugs is explained by the ability of cisplatin to increase the reduced folate pool necessary for the tight binding of fluorodeoxyuridine monophosphate to thymidylate synthetase, which in turn enhances the cytotoxicity of the drug combination (*11*). However there is no consensus about a therapy-induced improvement in prognosis (*12,13*). Therefore, it seems useful to gain information about tumor metabolism and its early changes during chemotherapy for the evaluation and individual planning of chemotherapy. Positron emission tomography [with ^{18}F-deoxyglucose (FDG)] is a specific method that provides information about regional glucose metabolism. In a preliminary study, we found evidence that the PET-FDG method is useful in the evaluation of head and neck tumors treated with systemic chemotherapy (*14*). The aim of our study was to measure early effects of chemotherapy on FDG uptake in head and neck tumors.

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PATIENTS AND METHODS

Eighteen male patients (age 40–80 yr) with histologically proven tumors of the oropharynx or hypopharynx underwent a PET examination prior to the first chemotherapeutic cycle. Histology of biopsied samples from primary tumors revealed squamous cell carcinomas (n = 16), anaplastic carcinoma (n = 1) and hemangiopericytoma (n = 1). The patients were treated with cisplatin and 5-FU using a standardized scheme (cisplatin 100 mg/m^2 BSA on Day 1 and 5-FU 1000 mg/m^2 BSA on Days 1 through 4). A second PET examination was performed 1 wk after the first chemotherapeutic cycle in 11 patients. Seven patients refused either the chemotherapy or the second PET examination. All patients had a tumor or lymph node size exceeding 1.5 cm in diameter.

Computed tomography (CT) was performed using a Siemens Somatom DRH (Siemens, FRG). Eight millimeter thick continuous sections were acquired parallel to the canthomeatal line (window width: 350 HE, center: 35 HE) and skin markings were used for correlative positioning in PET. The tumor and/or lymph node area was measured in each CT cross section using a region of interest (ROI) technique. Thereafter, the volume was calculated from the areas and the section thickness for each lesion. We assumed an exponential function $c = \ln(V0/V1)/t$ with V0 and V1 as the volume before and after therapy and t as the time interval between V0 and V1 for the estimation of the tumor growth rate.

The PET examination was done using a PC2048-7WB scanner (Scanditronix, Uppsala, Sweden) with two detector rings. These are composed of 512 bismuth germanate-gadolinium orthosilicate detectors. Thus, a simultaneous acquisition of two primary and one cross section is possible with a section thickness of 11

mm. The mean sensitivity of the system is 12,500 cps/μCi/cm^3 for the primary sections and 17,500 cps/μCi/cm^3 for the cross section. Prior to the emission scanning, transmission scans with more than 10-million counts per section were acquired. PET images were obtained 1 hr after intravenous administration of 330–440 MBq ^{18}FDG. The emission scanning time was 10 min. The number of counts per slice in all cases exceeded 1 million.

The production of ^{18}FDG was performed as described by Oberdorfer et al. (*15*). Thereafter, the radiochemical purity was measured using high-performance liquid chromatography with values above 98%.

PET images were generated by use of an iterative reconstruction program on a VAX 11/750 (Digital equipment, Maynard, MA) computer system (*16*). The image matrix was 128 × 128 and was interpolated to 256 × 256 for display. The spatial resolution was approximately 5.1 mm. The pixel size in all reconstructed images was 2 × 2 mm. Furthermore, a correction for attenuation and scatter was done.

The quantitative evaluation was performed using a ROI technique. The ROIs were defined for the tumors, lymph nodes and the normal soft tissue (neck muscles) with a region size exceeding 32 pixels. The PET sections were compared with the CT images to identify corresponding anatomical structures. The activity concentration obtained from the PET cross-sections and the FDG uptake was then expressed as the standardized uptake value (SUV): SUV = activity concentration (nCi/g)/(injected dose [nCi] /body weight [g]).

RESULTS

An example of a response to therapy is shown in Figure 1. On the CT scan, a large lymph node metastasis with a central hypodensity is noted. The corresponding PET image shows a hypometabolic central area and a very active periphery. On the other side of the neck, a small lymph node metastasis is demarcated (Fig. 1A–B). After the first chemotherapeutic cycle, a decrease in FDG accumulation was observed.

FDG uptake data prior to therapy were available for 13 tumors, 10 lymph node metastases and one bone metastasis, ranging from 2.0 to 6.98 SUV (normal soft tissue 0.8–1.4 SUV). We observed differences in FDG uptake in different lymph node metastases of the same patient (Table 1, Patient 815). In one patient (Table 1, no. 458), a bone metastasis showed a marked increase when compared to

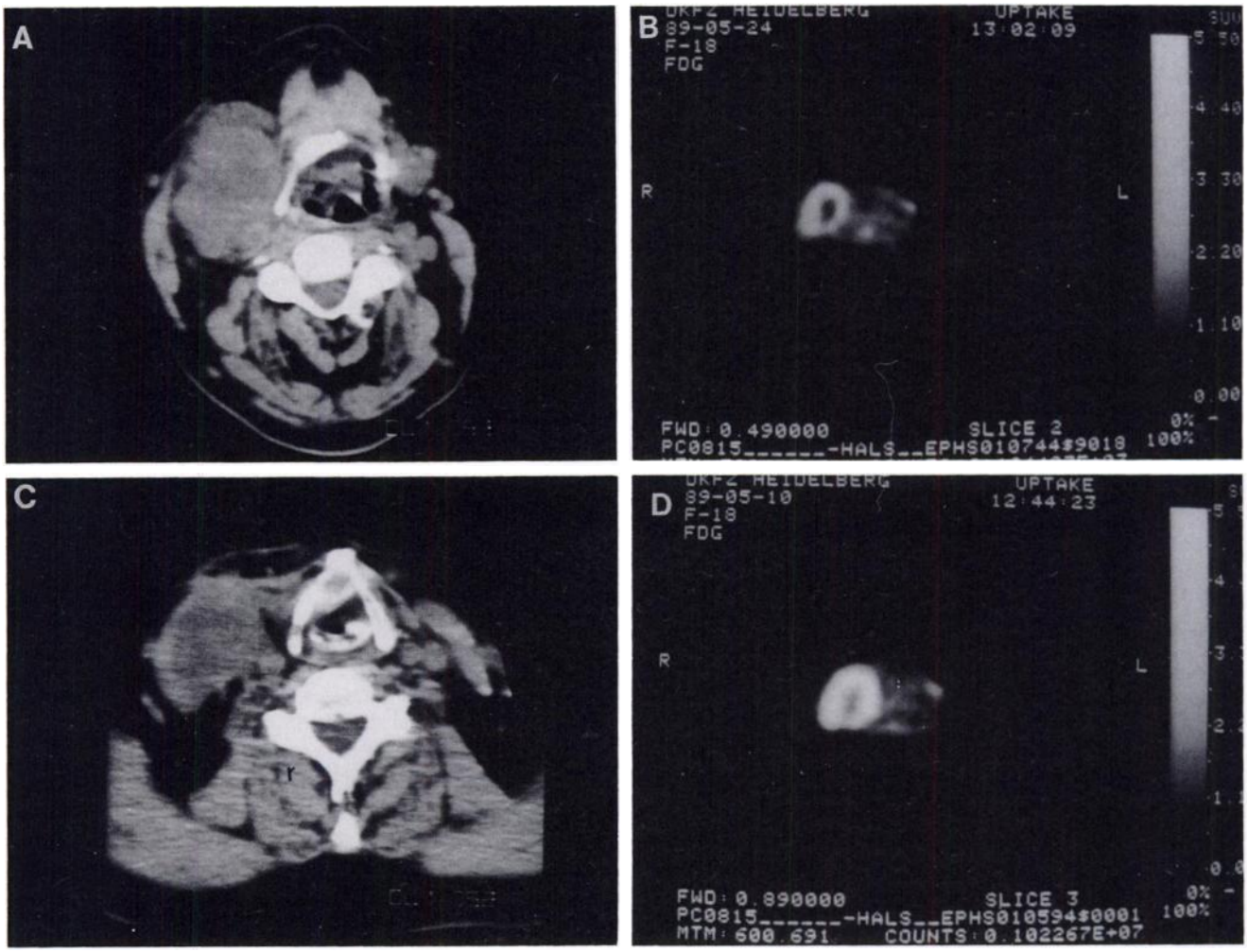

FIGURE 1. CT and PET images of a patient with metastatic squamous cell carcinoma prior to (A and B) and after the first chemotherapeutic cycle (C and D). Quantitative evaluation after therapy revealed a decrease in FDG uptake in the metastasis on the right side and no change in the metastasis on the left side.

the lymph node metastasis. Furthermore, there was a difference between tumor and lymph node metabolism in one patient (Table 1, no. 2423). This is valid for the baseline value as well as for the post-treatment value. After the first chemotherapeutic cycle, FDG values for six tumors, nine lymph node metastases and the bone metastasis were evaluable (Table 1). The SUV values were still elevated in all lesions (1.8–7.56 SUV). The changes in FDG uptake are shown in Figure 2. Only seven lesions had a significant decrease in metabolism. In one lesion (bone metastasis), an increase of tumor metabolism was observed, whereas eight lesions remained unchanged.

Volumetric data were gained for five tumors and seven lymph nodes. Except in three cases, the volumetry exhibited a varying decrease in tumor or lymph node volume. The relationship between tumor or lymph node metabolism during chemotherapy and growth rate is shown in Figure 3. Lesions with a higher FDG uptake prior to therapy were associated with a higher decrease in volume than lesions with a lower FDG uptake (Fig. 3A). Tumors responded to a greater extent in comparison to lymph nodes. The tumor growth rate and the change in FDG uptake were highly correlated in both tumors and lymph nodes, with r = 0.98 and r = 0.94, respectively (significant at the 1% level, Fig. 3B).

TABLE 1
FDG Uptake (SUV) and Growth Rate in Head and Neck Tumors and Lymph Node Metastases

Patient no.	Histology	FDG prior	FDG after	Growth rate	ln/tu
559/90	hap	4.54			tu
614/90	pd, scc	2.23			tu
614/90	pd, scc	2.37			ln
621/90	md, scc	2.4			tu
334/88	md, scc	2.52			tu
1194/88	md, scc	3.84			tu
2547/87	wd, scc	2			tu
357/90	pd, scc	4.1			tu
640/89	wd, scc	2.27	1.76		tu
1724/89	md, scc	2.06	2.45		ln left
1724/89	md, scc	2.5	2.15	−151.44	ln right
2423/88	wd, scc	4.26	4.34		ln
2423/88	wd, scc	5.94	4.51	−1900.6	tu
639/89	md, scc	3.82	2.81	−212.15	ln
707/88	pd, scc	2.46	2.54	−254.4	tu
1980/89	md, scc	3.7	3.46	−569.52	tu
458/89	pd, scc	2.71	2.43	−150.76	ln
458/89	pd, scc	6.98	7.56		bone met
815/89	wd, scc	2.52	2.38	−194.49	ln left
815/89	wd, scc	5.59	2.22	−710.74	ln right
977/90	pd, scc	2.84	2.68	−305.85	tu
235/90	pd, scc	2.49	2.7	22.36	ln
235/90	pd, scc	2.42	2.55	66.64	tu
634/89	ana	2.31	2.06	86.95	ln

hap = hemangiopericytoma; pd = poorly differentiated; md = moderately differentiated; wd = well differentiated; scc = squamous cell carcinoma; ana = anaplastic carcinoma.

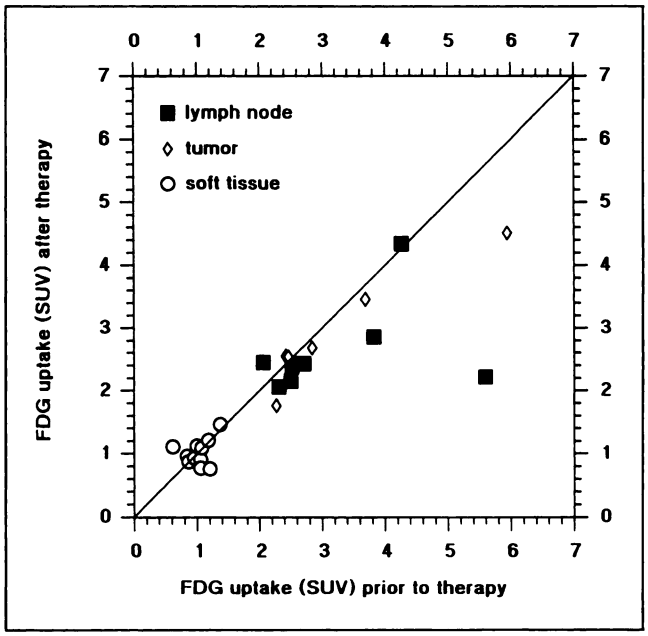

FIGURE 2. FDG uptake (SUV) prior to and after the first chemotherapeutic cycle with cisplatin and 5-FU for soft tissue (n = 11), lymph node metastases (n = 9) and tumors (n = 6). Line = line of identity.

DISCUSSION

The assessment of therapeutic efficacy is of critical value to the clinical oncologist. This is the most prominent task for trials using modalities with severe side effects or in patients with rapidly progressing disease as patients with head and neck tumors. In these tumors, the degree of differentiation is not useful for the prediction of the tumor response to chemotherapy (*17*). To evaluate the effects of therapy, quantitative functional data are needed. In this respect, the use of radiopharmaceuticals delivering information about tumor metabolism is promising. FDG, a widely applied tracer in cancer patients, is transported like glucose into the cell and thereafter trapped in its phosphorylated form (*18*) without further significant metabolism during the examination time. This principle of metabolic trapping has been used for diagnostic procedures in the differential diagnosis of recurrent colorectal cancer (*19*).

The measurement of FDG accumulation has also been applied to estimate metabolic alterations due to different therapeutic modalities. In animal experiments, a reduction of the amount of deoxyglucose uptake after chemotherapy or radiotherapy was associated with less viable tumor tissue (*20*). Abe et al. (*21*) described a decrease of FDG uptake one to two days after irradiation of a mouse mammary carcinoma.

Studies with human brain (*22,23*) or head and neck tumors (*24*) show a fall in regional oxygen utilization (*22*) or in glucose uptake in treated tumors (*23,24*). Minn et al. (*24*) found a significant difference in changes in glucose uptake during therapy between radio-responders and ra-

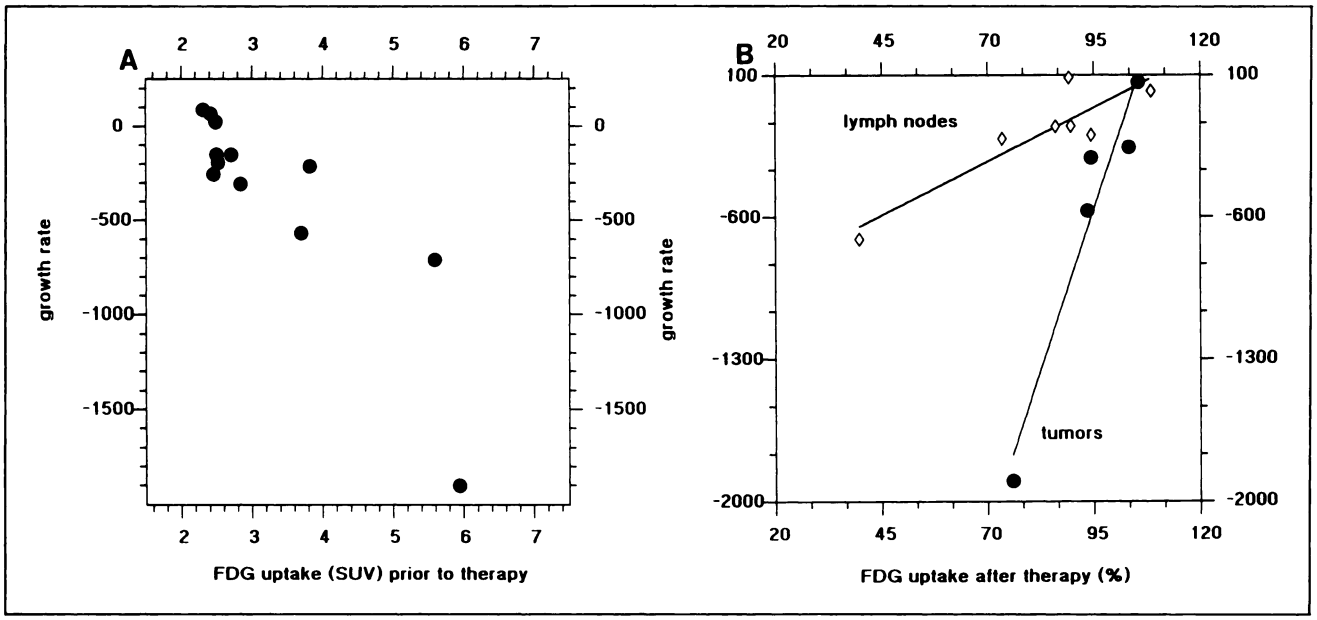

FIGURE 3. (A) Relationship between FDG uptake (SUV) prior to therapy and the growth rate, calculated after the first chemotherapeutic cycle. (B) Relationship between FDG uptake after the first chemotherapeutic cycle, expressed as the percentage of FDG uptake prior to therapy and the tumor growth rate.

dio-nonresponders. A similar finding is reported by Ichija et al. in a mixed tumor population and using a variety of therapeutic schedules (*25*). The responders showed a more prominent decrease in FDG uptake than nonresponders. We were able to show that FDG can be used to assess effects of radiotherapy in patients with colorectal tumors (*26*) and of chemotherapy in rats with chemically induced mammary carcinomas (*27*).

Due to the 3% error in PET radioactivity concentration measurements, it is critical to declare changes in uptake below 10% as significant. Under this assumption, we found a significant decrease in only 43% of the patients. This reflects clinical data about remission rates (*4,5*).

In the study of Ichija et al., the FDG value prior to therapy had no predictive value on the changes in tumor size. However, FDG uptake prior to therapy was higher in the relapse group than in the nonrelapse group (*25*). In our series, we noticed that lesions with higher FDG uptake prior to therapy had a higher decrease in volume. The differences between their data and ours may be explained by the heterogeneity of their tumor population (bronchogenic, esophageal, rectal, pancreatic and thyroid carcinomas, lymphomas and several metastases) as well as their therapeutic approaches (radiation, radiochemotherapy, transarterial and systemic chemotherapy and embolization). The lesions with higher FDG uptake may represent lesions with a higher propensity to divide, which also show a better short-term response to the chemotherapeutic agent. Furthermore, a relationship was found in patients with colorectal carcinoma between the ^{13}N-glutamate uptake and the ^{18}FU accumulation (*28*). This indicates that there is a relationship between tumor metabolism and the uptake of a drug into the tumor cell. However, it is not clear whether the initial FDG uptake can be used as a predictor of prognosis in our study population. The data about survival in our patients are too small and heterogeneous with respect to additional therapeutic measures used later to give reliable results.

Different lymph nodes in the same patient can have a different metabolic activity and also show a different responsiveness to therapy. This can be explained by the concept of cell heterogeneity in human tumors. Different metastatic clones can lead to metastases with a different biologic behavior. Brauneis et al. (*29*) found in a flow cytometric study no significant difference in tumor reaction to therapy in tumors with different proliferation rates. However there was a higher incidence of regional or distant metastases in tumors exhibiting a high proliferation rate. Minn et al. (*30*) observed a strong correlation of FDG uptake and the amount of S-phase-cells. In a study with squamous cell carcinomas of the head and neck, we also noted that FDG uptake was correlated with the proliferation index, but we found that there are two groups, indicating that FDG uptake cannot be explained by tumoral proliferative activity alone (*31*). However, one may speculate that the initial FDG uptake indicates proliferative activity and the incidence of metastatic spread. The comparison of tumors and lymph nodes showed a lower response rate for lymph node metastases. A comparable change in FDG uptake was associated with different growth rates in tumors and lymph node metastases. The difference in response to therapy is also observed in the clinical outcome (*1*).

Possible sources of error in our study are the object size,

which is critical for the quantification of uptake (*32*), and the variability of CT volumetry. Lower FDG values may be the result of partial volume effects. However, the lesion size in this study was above 6 cm^3 in all patients.

Schultz et al. (*33*) found that the errors in CT volumetry depend not only on the choice of the window level, but also on the shape and size of the organ and on the surrounding contrast-forming area. In our study, we used a standardized window width and window center. Therefore, errors due to window differences were avoided. Furthermore, only tumors or lymph nodes that could be clearly delineated were accepted for volumetric measurement.

Heymsfield et al. (*34*) observed an accuracy in CT volumetry of 3%–5% in an excised human liver, kidney or spleen. According to Van Thiel (*35*), the main cause for errors in volume determination of the liver in vivo, is the partial volume effect due to respiratory movement. Staron and coworkers (*36*) found an increase in the coefficient of variation with a decrease in size of the examined area. In a study at our institute, a deviation of 2%–4% was observed when excised livers or spleens were determined (*37*). This deviation increased to 10%–12% when the volumetry was done in vivo, mainly because of respiratory motion. At present, volumetric data of head and neck structures are not available. However, since there is no effect on respiratory motion in the area examined, we presume an error of 3%–5%.

In summary, we observed a comparable response in FDG metabolism to chemotherapy in lymph nodes and tumors. However, a difference in degree was found. Differences in metabolic activity and metabolic changes during therapy in different lymph nodes of the same patient were detected. There was a linear relationship between metabolic change and growth rate during therapy with different regression functions for tumors and lymph node metastases. Our results and those of Minn showed a correlation between glucose metabolism and the proliferation rate. In flow cytometric studies, a high proliferation rate was associated with a higher incidence for metastatic spread. This supports the thesis that FDG uptake may be an in vivo measurement for the aggressiveness of a tumor.

With PET, it is possible to gain absolute and therefore comparable data about tumor metabolism prior to and after chemotherapy. PET is a useful method for the observation and improvement of therapeutic measures in patients undergoing systemic chemotherapy.

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