Positron Emission Tomography in the Early Follow-up of Advanced Head and Neck Cancer

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Objective: To assess the clinical effect of an early follow-up positron emission tomography (PET) examination at the time of the first routine clinical control in patients with advanced-stage head and neck squamous cell carcinoma (HNSCC).

Design: Prospective, nonrandomized, case-control study.

Setting: Single referral center.

Patients and Intervention: A total of 26 patients (mean age, 56 years) with histologically confirmed stage III-IV HNSCC underwent PET before and approximately 6 weeks after the end of a combined treatment with radiation and chemotherapy with curative intent. The PET findings were confirmed by histologic analysis and a 6-month clinical follow-up.

Main Outcome Measures: The presence of distant metastases, secondary synchronous cancers, and residual locoregional tissue was confirmed, and the effect on further clinical management was assessed.

Results: Using PET, we correctly identified residual tumor tissue, distant metastases, or a second primary tumor in 10 patients, 5 of whom had no clinical evidence of such findings. Results were true negative in 14 cases; false positive in 1; and false negative in 1. Sensitivity and specificity for follow-up PET scans were 90.9% and 93.3%, respectively. All patients with positive findings were evaluated for further treatment such as salvage surgery.

Conclusions: Whole-body PET scanning approximately 6 weeks after completion of a combined treatment regimen with radiation and chemotherapy can reliably identify locoregional residual cancer and distant metastases or secondary tumors in patients with advanced-stage HNSCC and has a direct influence on management decisions.


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POSITRON EMISSION TOMOGRAPHY (PET) with fludeoxyglucose F18 (FDG) has widely been used for follow-up examinations of patients with mucosal head and neck squamous cell carcinoma (HNSCC). In most studies, FDG-PET was performed when recurrent disease was clinically suspected. Only a few publications report the use of PET examinations at a fixed time interval after the end of treatment. Previous reports suggest that a follow-up FDG-PET examination performed soon after the end of treatment is less reliable for the identification of residual tissue than a scan acquired after several months because an inflammatory reaction after therapy may cause false-positive results. Additionally, a negative PET scan 1 month after the end of treatment cannot reliably rule out the presence of viable tumor cells. However, early identification of residual vital tumor tissue has the potential to improve local control by facilitating early salvage surgery. In the early posttreatment period after completion of radiation therapy, edema can complicate the clinical examination; during this early period, noninvasive imaging could help to assess treatment success.

Salvage surgery can be of great value, but it can only improve life expectancy in those patients without distant metastases or a secondary synchronous cancer. Therefore, the use of an imaging method that could also provide information on the whole body should be favored.

In our hospital, patients undergo a routine clinical follow-up every 6 weeks after the end of treatment for the first year. Because clinical examination can be difficult at the time of the first control and because recent reports suggest that a follow-up FDG-PET scan after 4 weeks is too
early to reliably assess sterilization of tumor tissue, FDG-PET scanning was done in the present study as an adjunct to the first clinical follow-up examination. The aim of this prospective study was to evaluate the clinical effect of routine short-term follow-up FDG-PET scanning for the assessment of local residual disease in patients with advanced-stage disease and to evaluate if whole-body PET imaging provides additional information in this patient group.

**METHODS**

**PATIENTS**

We focus on 26 patients of an earlier study group of 48 patients\(^{13}\) with histologically confirmed stage III-IV HNSCC (any T, N=2 or T=3, any N) to assess the clinical effect of staging and follow-up PET examinations. Our study was performed in accordance with the ethical standards of the committee on human experimentation of our institution. A previous study\(^{13}\) described 48 patients (42 men, 6 women; mean age, 61 years; age range, 33-85 years) who underwent FDG-PET for staging of the whole body (ie, from the head to the pelvic floor) before beginning treatment. They also underwent a routine workup consisting of physical examination, panendoscopy, chest radiography, and contrast-enhanced helical computed tomography (CECT) scanning of the head and neck before beginning treatment.

The staging PET showed discordant findings compared with CECT in 7 (15%) of 48 patients for the assessment of lymph node involvement. In 3 patients the N category was up-staged, and in 4 patients PET underestimated lymph node involvement. Findings from PET suggested distant metastatic lesions in 6 (13%) of 48 patients. Cytologic workup confirmed distant metastases in 2 patients (4%) and second primary tumors in another 2 (4%). False-positive PET results occurred in 2 cases (4%) owing to inflammatory changes. Treatment was affected by all true-positive PET findings.\(^{15}\)

The present report describes 26 patients who underwent a 6-week early follow-up FDG-PET examination. Only patients without previous evidence of distant metastases or second primary tumors remained for this follow-up study. Twenty-two patients were not included for the following reasons: distant metastases or secondary tumors at the time of initial staging (n=4); death, which was not directly related to the HNSCC (n=3); patient refusal to continue the study (n=8); too long a delay (>2 weeks) between the first clinical follow-up control and the follow-up PET scan (n=4); treatment started after the clinical follow-up control but before the PET scan (n=2); and chemotherapy administered alone, without radiation treatment (n=1).

Twenty-five patients underwent a combined treatment with radiation therapy (median dose, 70 Gy in 6 weeks) and chemotherapy with cisplatin.\(^{11,15}\) One patient underwent only radiation therapy because of a preexisting neuropathy. All 26 patients (25 men and 1 woman; mean ±SD age, 56 ±9.2 years; age range, 35-76 years) underwent FDG-PET 6 to 8 weeks after the end of treatment (mean, 45 days; range, 40-59 days). At the time of this FDG-PET scan, no additional imaging using CECT was performed, but all patients underwent the first posttherapeutic clinical control by routine examination, including flexible laryngoscopy and sonography of the neck. Clinical examination of a patient was always performed by the same otolaryngologist, and routine clinical follow-up examinations of all patients were performed after treatment every 6 weeks during the first year. The early follow-up PET scan was done between 2 days before and 11 days after the first clinical evaluation of the patient. All PET findings suggestive of residual locoregional disease were confirmed by histologic analysis and clinical follow-up examinations. Findings that suggested distant metastases or a secondary cancer were confirmed by histologic analysis and CECT imaging. Negative cases were further controlled with regular follow-up examinations, and 6-month follow-up was used as the standard of reference.

**DATA ACQUISITION**

The patients fasted for 4 to 6 hours prior to the intravenous injection of a standard dose of 300 to 400 MBq of FDG, which was performed approximately 45 minutes prior to scanning. The FDG was produced in house using a 16.8-MeV Cyclotron (PET Tracer 2000; GE Medical Systems, Uppsala, Sweden) and an automated FDG synthesis module (PET Tracer Synthesizer; Nuclear Interface GmbH, Muenster, Germany). The patients were instructed not to chew or talk during the FDG uptake time to minimize muscular uptake. All removable metallic foreign bodies or artificial devices were removed before the beginning of PET scanning or replaced by plastic tracheal cannula to allow for PET scanning without generating artifacts on the attenuation-corrected PET images.\(^{15,16}\)

The patients were scanned on either an Advance full-ring PET camera (n=3) or a combined Discovery LS PET/CT scanner (n=21) (both GE Medical Systems, Waukeisha, Wis). The in-line PET/CT camera is a combination of a full-ring PET camera with a multislice computed tomography (CT) scanner (GE Medical Systems, Waukeisha, Wis). Both PET cameras have an axial field-of-view (FOV) of 14.6 cm and an in-plane resolution of 4.8 mm full-width at half-maximum at the center of the FOV (for the PET camera). The PET emission scanning was performed for 4 minutes per FOV using 6 cradle positions to scan the body from the head to the pelvic floor. All scans were corrected for attenuation either by means of a transmission scan acquired by the built-in germanium 68 (\(^{68}\)Ge) sources or by using the data of low-dose CT (80 mA, 0.5 s/rotation, 120 kV) on the combined scanner, which was also acquired from the pelvic floor to the head.\(^{11}\) Conventional transmission scans using the built-in \(^{68}\)Ge sources was done with 2-minute acquisition time per FOV. Attenuation data was either segmented when using the conventional transmission scan or measured when using CT data. To obtain an adequate quality of the attenuation map and of the coregistration, the patient performed a breathing protocol during CT acquisition, which has previously been described.\(^{18}\) In addition, patients received oral contrast for CT scanning, but no intravenous contrast was given.\(^{19}\) All images were reconstructed using an iterative “ordered subset expectation maximization” algorithm (28 subsets, 2 iterative steps).

**DATA ANALYSIS**

The PET images were visually evaluated by 2 experienced nuclear medicine physicians. Image analysis of PET studies acquired on the Advance scanner was done by using static images in the 3 different planes as well as a movie mode on a digital viewing system (GE View; Innomed GmbH, Dormstadt, Germany). The coregistered PET/CT images in those patients who underwent imaging on the Discovery scanner were viewed with the software provided by the manufacturer (eNtega; GE Medical Systems, Haifa, Israel) and images of PET, CT, and coregistered PET/CT were visualized in 3 orthogonal planes. However, for this study only the results of PET images (ie, regions with visually increased FDG uptake) were used to assess the presence of residual tumor tissue or distant disease. Information visible only on the non–contrast-enhanced CT images was not used for this evaluation.
FDG-PET revealed the presence of distant disease. One edema, which complicated the clinical examination. not reveal the residual cancer. Two of these 5 had neck patients (1, 11, 12, 17, and 26), clinical examination did only 4 (15%; patients 2, 8, 9, and 19). In 5 patients (19%; patients 1, 2, 8, 9, 11, 12, 17, 19, and 26), while the clinical examination indicated locoregional residual tissue in (patients 1, 2, 8, 9, 11, 12, 17, 19, and 26), but FDG-PET identified a lung lesion suggestive of mediastinal and lung metastases (see Figure) residual cancer, found at clinical examination. Follow-up* Residual cancer, found at clinical examination. Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up Follow-up* Follow-up and additional spiral contrast-enhanced computed tomography. Follow-up and additional histologic analysis Residual cancer, found at clinical examination, lung metastases and secondary rectal carcinoma. Follow-up Follow-up Residual cancer, found at clinical examination. Follow-up Follow-up No residual cancer, secondary bronchogenic cancer Follow-up Follow-up Residual cancer, not found at clinical examination. 

Visual interpretation of images is the preferred method in our institution, and standard uptake values are not routinely measured.13,20 Images were read in a sensitive way, meaning that FDG uptake more than normal background activity was considered possible residual cancer tissue. Previous work has shown that there is a wide overlap of standard uptake values between benign and malignant disease and that positive or equivocal scans indicate a high likelihood of disease recurrence.13,10,20

All results of FDG-PET were discussed after verification with the head and neck surgeon who sent the patient for follow-up examination and the radiooncologist who performed the combined treatment with radiation and chemotherapy. A consensus was reached on the effect of the PET findings on the further treatment strategy of each patient.

The results are summarized in the Table. In 10 (38%) of 26 patients, whole-body FDG-PET findings were true positive (ie, residual tumor tissue, distant metastases, or a second primary tumor was correctly identified). The PET revealed locoregional residual cancer in 9 patients (patients 1, 2, 8, 9, 11, 12, 17, 19, and 26), while the clinical examination indicated locoregional residual tissue in only 4 (15%; patients 2, 8, 9, and 19). In 5 patients (19%; patients 1, 11, 12, 17, and 26), clinical examination did not reveal the residual cancer. Two of these 5 had neck edema, which complicated the clinical examination.

In 3 patients (patients 1, 17, and 23), whole-body FDG-PET revealed the presence of distant disease. One of these patients had locoregional residual cancer and mediastinal metastasis, as found with PET (patient 1; Figure). This was confirmed by histologic analysis and helical CECT. In the second patient (patient 17), residual cancer, lung metastases, and an additional rectal carcinoma, which was endoscopically verified, were found. The third patient (patient 23) had no local residual cancer, but FDG-PET identified a lung lesion suggestive of secondary bronchogenic cancer, which was cytologically confirmed. In these 3 patients, the clinical examination did not allow identification of the distant metastases and/or secondary cancers.

In 14 patients, FDG-PET scan findings were true negative as confirmed by routine clinical examinations with additional sonography every 6 weeks during the 6-month follow-up. There was 1 false-negative PET scan in a patient with residual vital tumor cells within an otherwise necrotic lymph node (patient 10). This lymph node was easily identified by clinical inspection but showed no increased FDG uptake on PET images. Furthermore, there was 1 false-positive FDG-PET scan (patient 18) corresponding to an inflammatory reaction in a lymph node as confirmed by histologic analysis. The clinical follow-up confirmed the benign nature of this lesion in that the patient remained without evidence of locoregional recurrence during the 6-month follow-up period. Based on these findings, the sensitivity was found to be 90.9%; specificity, 93.3%; accuracy, 92.3%; positive predictive value, 90.9%; and negative predictive value, 93.3%.

### Results of Positron Emission Tomography Scans and Clinical Findings

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>True Positive</th>
<th>True Negative</th>
<th>False Positive</th>
<th>False Negative</th>
<th>Clinical Findings/Confirmation</th>
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<tbody>
<tr>
<td>1/M/56</td>
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<tr>
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<td>Follow-up*</td>
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</tr>
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<td>Follow-up</td>
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<td>6/M/55</td>
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<tr>
<td>16/M/57</td>
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<td></td>
<td></td>
<td>Follow-up and additional spiral contrast-enhanced computed tomography</td>
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<tr>
<td>17/M/58</td>
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<td>Residual cancer, not found at clinical examination, lung metastases and secondary rectal carcinoma</td>
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<td>Follow-up</td>
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<tr>
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<td></td>
<td>Follow-up</td>
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<tr>
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<td>Follow-up</td>
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<td>Follow-up</td>
</tr>
<tr>
<td>26/M/56</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td>Residual cancer, not found at clinical examination</td>
</tr>
</tbody>
</table>

*Follow-up consisting of clinical examination and ultrasound of the neck was done every 6 weeks. A 6-month negative follow-up was considered the reference standard to rule out the presence of residual cancer.
The consensus regarding the clinical impact of FDG-PET scanning in these patients was that all patients with positive PET findings underwent an evaluation for further treatment with salvage surgery of the residual primary tissue and neck dissection. The patient with secondary bronchogenic cancer was scheduled for a thoracic surgery with a curative intent. In the 2 patients with distant metastases, a treatment strategy with additional chemotherapy was evaluated.

The results of this study show that FDG-PET performed 6 to 8 weeks after completion of a combined radiation and chemotherapy regimen in patients with advanced-stage HNSCC can be used to assess the presence of residual tumor tissue and that this information has a direct effect on further patient management. Previous reports have shown that PET with FDG is highly sensitive for the identification of locoregional recurrence in HNSCC. However, other authors found that the specificity was rather low because of false-positive findings due to inflammation reaction and that the time interval between the end of therapy and PET scanning was the reason for this low specificity.

In the present study, the specificity was rather high with only 1 false-negative and 1 false-positive finding. The data of this study also indicate that nonspecific inflammation reactions as seen on PET images are not a common finding 6 to 8 weeks after the combined radiation and chemotherapy approach. Therefore, an early FDG-PET scan at the time of first clinical follow-up examination can provide reliable and relevant additional information. However, we believe that the extent of the primary lesion (ie, the T and N stage) and the type of therapy are likely to influence the rate of false-positive findings on follow-up PET images. Therefore, the results of this study can be applied only to patients with advanced-stage disease who undergo a combined radiation and chemotherapy regimen with curative intent.

Six to 8 weeks after treatment is probably the best time to identify patients with residual HNSCC. These patients can immediately be evaluated for salvage surgery, and in patients where clinical inspection is difficult, an additional 6-week interval to the next routine control can be avoided. This is suggested by the fact that in our patients, clinical examination did not reveal distant metastases or secondary tumors, and in 5 patients, local residual disease was not identified. Patients and physicians want a reliable assessment of treatment effect as early as possible, and FDG-PET can provide this information in a noninvasive manner and can improve the management of patients with equivocal results at their first clinical examination.

Most studies have evaluated patients with clinical signs of recurrence. To obtain optimum local control of a cancer, it is best to identify residual disease as soon as possible after completion of therapy so that patients may undergo salvage surgery when the extent of the residual cancer tissue is limited and there is a better chance for a cure. The present study shows that FDG-PET has the potential to identify patients who could benefit from salvage surgery very soon after completion of therapy.
A rather astonishing result of this study is that 2 patients were found to have secondary cancers even though the time interval between the staging PET examination before treatment was begun and the first follow-up examination was only about 4 months. It is possible that these 2 patients already had their primary cancers at the time of initial evaluation, but that the synchronous cancers were still too small to be identified with PET. The patient with a bronchogenic carcinoma was scheduled for a surgical intervention because the synchronous cancer was staged to be operable by the follow-up examination. In contrast, it is very possible that the patient with distant HNSCC metastases in the lung developed the metastases during his treatment.

Using PET for an early follow-up examination, we found the sensitivity, specificity, and negative and positive predictive values to be very high. In 10 patients (38%), PET had an effect on further clinical management. Therefore, we believe that FDG-PET could become an effective adjunct to the first routine clinical examination in patients with advanced-stage HNSCC who undergo combined radiation treatment and chemotherapy. However, it remains unclear if further therapy controls with FDG-PET at later time intervals would improve patient management. Future studies will be needed to evaluate if such an early follow-up PET examination could improve patient survival and if this approach would be cost-effective.

In conclusion, the results of this study suggest that FDG-PET performed in patients with advanced-stage HNSCC between 6 and 8 weeks after the end of a combined radiation and chemotherapy regimen may have an important impact on patient management. Whole-body FDG-PET can identify residual local and regional cancer tissue, distant metastases, and secondary tumors with a high sensitivity and specificity and can help to identify patients who should receive additional treatment.

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