Diagnosis and Staging of Head and Neck Cancer

A Comparison of Modern Imaging Modalities (Positron Emission Tomography, Computed Tomography, Color-Coded Duplex Sonography) With Panendoscopic and Histopathologic Findings

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Objective: To compare the clinical value of positron emission tomography (PET) using fludeoxyglucose F 18, computed tomography (CT), color-coded duplex sonography (CCDS), and panendoscopy in the detection and staging of head and neck cancer.

Design: Prospective nonrandomized controlled study.

Setting: Medical school.

Patients: Convenience sample of 50 patients with suspected primary or recurrent head and neck cancer.

Intervention: Biopsy, tumor surgery.

Main Outcome Measures: Information of diagnostic procedures compared with histopathologic features.

Results: Both PET and panendoscopy had a sensitivity of 95% and 100% for detection of primary tumor or recurrent carcinomas, respectively. Specificity for PET and panendoscopy was 92% and 85% in primary tumors and 100% and 80% in recurrent carcinomas, respectively. Sensitivity of CCDS and CT was 74% and 68% in primary tumors and 67% and 63% in recurrent carcinomas, respectively. Specificity was 75% and 69% in primary tumors and 100% and 80% in recurrent neoplasms. When assessing neck nodes, all imaging procedures exhibited identical sensitivity (84%). Specificity was 90%, 96%, and 88% in PET, CT, and CCDS, respectively. In recurrent lymph node metastases, sensitivity was 100%, 67%, and 67% and specificity was 87%, 91%, and 87% for PET, CT, and CCDS, respectively.

Conclusions: Positron emission tomography was the most reliable imaging procedure in the detection of primary tumor and recurrent carcinomas localized in the head and neck region. Owing to its limited anatomical depiction, it cannot as yet replace other diagnostic procedures in preoperative planning but does contribute valuable complementary diagnostic information. Computed tomography may have difficulties in identifying recurrent carcinomas. For routine diagnosis of nodal spread in the neck, CCDS is recommended. Panendoscopy is a valuable diagnostic procedure that can provide key information in cases of superficial mucosal tumor involvement.

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ACCURATE pretherapeutic localization of a suspected malignant neoplasm and early detection of lymph node metastases plays a crucial role in the prognosis as well as in the choice and extent of the therapeutic procedure required by patients with head and neck cancer. In primary tumor localization with a statistical metastasizing rate of 20% or less, a neck dissection is optional in N0-stage patients. It is a well-known fact that in 40% of the clinically nonapparent lymph nodes, a metastatic involvement can be demonstrated. The 5-year survival rate is as low as 30% in patients with pretherapeutic locoregional spread. Staging procedures usually comprise modern imaging techniques such as sonography, computed tomography (CT), or magnetic resonance imaging.

Because of their ability to demonstrate all regions of interest with high resolution, CT and magnetic resonance imaging are often regarded as methods of choice, with a reliable T staging in 80% to 90% of the cases. Conventional B-mode sonography shows good results too, but fails to depict all regions of the upper aerodigestive tract. The fact that not all tumors and metastases can be detected by these techniques demonstrates the need for alternatives.

Positron emission tomography (PET) with the glucose analogue fludeoxyglucose F 18 (18FDG) allows a functional imaging of suspected regions by visualization of the local glucose metabolism.
PATIENTS AND METHODS

In a prospective, nonrandomized controlled study, 50 patients with a suspected primary (n=37) or recurrent (n=13) head and neck tumor were admitted to the hospital between October 1, 1997, and November 30, 1998. Exclusion criteria were diabetes mellitus and a history of acute or chronic inflammatory disease. The cohort consisted of 36 men and 14 women with an average age of 60.5 years.

All 50 patients underwent diagnostic and therapeutic procedures in the Departments of Ear, Nose, and Throat, Radiology, and Nuclear Medicine, the University of Aachen, Aachen, Germany. Imaging procedures were performed 1 to 20 days preoperatively. Panendoscopy, including biopsy specimens from the suspected primary or recurrent carcinoma localization, was performed on each patient after diagnostic imaging. Thirty-three patients underwent bilateral neck dissection. In all other cases a lymph node biopsy was performed. A total of 940 lymph nodes have been investigated. The mean patient follow-up was 12.5 months.

Sonographic evaluation included a high-resolution gray scan and a CCDS scan for each patient. Color-coded duplex sonographic scans were performed with a variable transducer (Sonoline Elegra; Siemens Corp, Erlangen, Germany) with a 7.5-MHz linear array. Criteria for the diagnosis of a malignant neoplasm were as follows: a rare or atypical vascularization, the finding of a central anechoic zone in suspected tissue, size and shape of a lymph node, signs of invasion of neighboring tissue or blood vessels, and irregular margins. In particular, irregularities in the vascularization pattern were highly indicative of malignancy. As not all primary tumors localized in the upper aerodigestive tract are accessible to sonographic examination, the comparison of sonographic findings with histopathologic findings were limited to suspected alterations in depictable areas only (n=27). Therefore, 9 patients admitted with the diagnosis of a carcinoma of unknown primary tumor were excluded from the statistical evaluation of the sonographic findings.

Computed tomography was performed using an ionized contrast medium (Ultrastat 370; Schering Corp, Berlin, Germany), injected using a power injector with a flow of 2 mL/s. The total volume injected was 100 mL. Computed tomographic scans were acquired in the spiral mode (Somatom Plus; Siemens Corp), with a collimation of 3 mm, table feed of 5 mm, and a reconstruction thickness of 3 mm. The scans were assessed by applying routine criteria.

Positron emission tomography was performed with a scanner (ECAT Exact 922/47; Siemens-CTI Corp, Knoxville, Tenn). After a minimum 12-hour fast (mean±SD 212±59 MBq $^{18}$FDG was administered intravenously. The scan acquisition started 45 to 60 minutes later and was performed in static 2-dimensional mode from the skull base to mediastinum with a duration of 12 to 15 minutes per bed position. For attenuation correction this was followed up by a transmission scan using 3 rotating germanium Ge 68/gadolinium Ga 68/rod sources. For the 3-dimensional scan reconstruction an iterative algorithm was used. Regions with an increased glucose metabolism were susceptible for malignancy. Standard uptake value (SUV) for $^{18}$FDG was represented by the following ratio:

$$SUV = \frac{[\text{Tissue Activity} \times \text{cps}] - \text{Decay-Corrected \text{Injected Activity}/\text{Body Weight}] \times \text{Calibration Factor}}{[\text{Body Weight}]^{-1}}$$

The gold standard for the comparative evaluation of diagnostic information obtained by the various procedures was the histopathologic result of the biopsy specimen. Statistical analysis of the data was performed with the Fisher exact test using SAS software (SAS for Windows; SAS Corp, Cary, NC). $P<.05$ was selected as the level of statistical significance.

In the head and neck region, PET showed effectiveness in the detection of unknown primary tumors. Color-coded duplex sonography (CCDS) is a further refinement of sonographic imaging. By depicting small vessels in tissues, it allows a qualitative assessment of suspected regions. The objective of this study was to evaluate the imaging modalities of PET, CT, and CCDS in comparison with panendoscopy and histopathologic findings in the diagnosis and staging of primary and recurrent head and neck malignomas.

RESULTS

In 44 (88%) of 50 patients, the suspected malignant neoplasm could be verified by the diagnostic procedures used in this study. Nine patients (18%) were admitted to our clinic with the diagnosis of a carcinoma of unknown primary tumor. In 2 (22.2%) of the 9 patients the primary tumor was detected in the nasopharynx and hypopharynx.

Eleven carcinomas (25%) were found in the mouth and 9 (20.5%) of the malignant neoplasms were detected in the oropharynx. A malignant tumor was found in 7 (15.9%) in the larynx, in 6 (13.6%) in the hypopharynx, and in 3 (6.8%) in the nasopharynx. In one patient (2.2%) the primary tumor was located in the parotid gland. In 15.9% the primary tumor localization remained unknown despite intensive diagnostic investigation. T-stage assessment prior to therapy was 22% TX, 12% T1, 24% T2, 18% T3, and 24% T4. Posttherapy T stage remained 14% TX. Six percent of our patients presented a T1 stage, 26% T2, 16% T3, and 26% T4. In 12% no malignancy could be found. In 88.6% histopathologic findings confirmed squamous cell carcinoma.

Of the imaging procedures applied, PET had the highest overall sensitivity and specificity for the detection of primary tumor and recurrent carcinomas. Sensitivity was 95% and 100%, specificity was 92% and 100%, respectively.

Sensitivity for the CT scan was 68% for primary tumor detection and 63% for recurrent carcinoma. Specificity was 69% and 80%, respectively.

Color-coded duplex sonography showed an overall sensitivity of 74% and 67% and specificity of 75% and 100% in the accessible regions. While sensitivity of panendoscopy for primary tumor and recurrent carcinomas was equal to that of PET (95% and 100%), its specificity was 85% for primary tumor and 80% for recurrent carcinoma.
Diagnostic accuracy was 0.94, 0.68, 0.74, and 0.92 for PET, CT, CCDS, and panendoscopy, respectively, for the detection of the primary tumor localization. In recurrent carcinoma, diagnostic accuracy was 1.00, 0.69, 0.75, and 0.92 for PET, CT, CCDS, and panendoscopy, respectively.

Positive predictive value was 0.97, 0.86, 0.94, and 0.95 for PET, CT, CCDS, and panendoscopy, respectively, in primary tumor diagnosis and 1.00, 0.83, 1.00, and 0.89 for PET, CT, CCDS, and panendoscopy, respectively, in recurrent carcinoma diagnosis. Negative predictive value was 0.86, 0.43, 0.33, and 0.85 for PET, CT, CCDS, and panendoscopy, respectively, in primary tumor diagnosis and 1.00, 0.57, 0.50, and 1.00 for PET, CT, CCDS, and panendoscopy, respectively, in recurrent carcinoma diagnosis. Color-coded duplex sonography was limited to 27 depictable areas (Table 1).

The comparison of the diagnostic procedures applied in this study showed a statistical significant correlation between the assumed diagnosis and histopathologic features for PET, CT, or panendoscopy for primary tumor diagnosis in the Fisher exact test ($P<.05$). Because of the smaller sample size, CCDS failed to show statistical significance despite comparable good results.

A total of 940 lymph nodes were resected. Of those, 120 (12.7%) had a metastatic involvement. We could prove nodal metastases in 32 (32%) of the 100 sides of the neck examined.

At admission we located suspected lymph nodes in 13 ipsilateral sides of the neck, bilateral in 7 patients, and contralateral to the tumor side in 2 patients. N stage was assumed to be in 56% N0, 2% N1, 34% N2, and 8% N3. Postoperatively we demonstrated ipsilateral lymph node metastases in 12 patients and bilateral involvement in 10 patient. The determined N stage was 56% N0, 4% N1, 30% N2, and 10% N3.

Overall sensitivity for nodal neck metastases was uniformly 84% for all imaging procedures applied, but only 63% for palpation. Sensitivity of recurrent nodal metastases was 100% for PET, 67% for CT, 67% for CCDS, and 33% for palpation. Specificity of diagnosis in lymph nodes in primary tumor ranged between 88% and 96% or between 87% and 100% in recurrent metastases (Table 2). There was a statistically significant correlation between the results of imaging procedures for lymph node metastases in primary tumor and histopathologic features using the Fisher exact test ($P<.05$).

Mean SUV for $^{18}$FDG was 8.08 for G2 tumors and 8.03 for G3 tumors in all tumor lesions. There was no G1 tumor in this study. We could not demonstrate a significant statistical correlation between G2 and G3 histological grading and $^{18}$FDG uptake.

**Table 1. Primary (and Recurrent) Tumor Diagnoses in 50 Patients**

<table>
<thead>
<tr>
<th>Type of Imaging</th>
<th>Type of Result</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Accuracy Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>True Positive</td>
<td>95 (1.00)</td>
<td>92 (1.00)</td>
<td>94 (1.00)</td>
</tr>
<tr>
<td></td>
<td>False Negative</td>
<td>68 (0.63)</td>
<td>69 (0.80)</td>
<td>68 (0.69)</td>
</tr>
<tr>
<td>CT</td>
<td>True Positive</td>
<td>74 (0.67)</td>
<td>70 (1.00)</td>
<td>74 (0.75)</td>
</tr>
<tr>
<td></td>
<td>False Negative</td>
<td>64 (0.63)</td>
<td>65 (0.80)</td>
<td>64 (0.69)</td>
</tr>
<tr>
<td>CCDS</td>
<td>True Positive</td>
<td>95 (1.00)</td>
<td>85 (0.80)</td>
<td>92 (0.92)</td>
</tr>
<tr>
<td></td>
<td>False Negative</td>
<td>63 (0.67)</td>
<td>63 (0.78)</td>
<td>63 (0.69)</td>
</tr>
<tr>
<td>Panendoscopy</td>
<td>True Positive</td>
<td>74 (0.67)</td>
<td>75 (1.00)</td>
<td>74 (0.75)</td>
</tr>
<tr>
<td></td>
<td>False Negative</td>
<td>62 (0.59)</td>
<td>63 (0.79)</td>
<td>62 (0.60)</td>
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**Table 2. Results of Evaluation of 100 Sides of the Neck**

<table>
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<tr>
<td>PET</td>
<td>True Positive</td>
<td>84 (1.00)</td>
<td>88 (0.88)</td>
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<tr>
<td></td>
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<td>70 (0.68)</td>
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<td>84 (0.67)</td>
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unknown primary tumor localization were found by PET. These tumors were located in the hypopharynx and the nasopharynx. The tumor located in the nasopharynx was not detected by any other method.

A major drawback of the PET scan is its limited anatomical depiction. False-negative results were found in cases of small metastatic lymph nodes situated close to the primary tumor. They occurred also in malignant neoplasms with only a few metastatic cells. The most important source of false-positive results in PET was inflammatory tissue reaction. In all false-positive cases of our study, inflammatory changes ranged from tonsillitis in a patient with a long history of excessive alcohol abuse and nicotine consumption to tuberculosis in other cases.

Positron emission tomography proved to be the most reliable procedure for detecting recurrent carcinoma. The smallest tumor detected had a diameter of only 5 mm. Since inflammation may cause false-positive results, our routine assessment of PET scans relies more on the finding of a negative result. A negative PET scan can exclude recurrent carcinoma with high diagnostic security.

As to the prognostic value of the SUVs, we found conflicting results in the literature. It is assumed that high grading of a tumor is associated with a worse prognosis. In a semiquantitative evaluation of the SUVs of our patients we did not find significantly higher values in G3 than in G2 tumors.

The advantage of CT is the better spatial resolution of the areas investigated by this method, but in the diagnosis of recurrent carcinomas results were comparatively poor. In our study, it was impossible to distinguish scarification from recurrent disease in some cases. False-negative results occurred in CT in primary glottic carcinoma and in mucosal carcinoma with superficial spread. In these cases the morphologic alterations are very limited and, therefore, difficult to detect by CT. Also after therapies that inevitably cause alteration of the local morphology such as irradiation and/or surgery, the assessment by a procedure that focuses mainly on morphologic aspects can be difficult, sometimes impossible. Nevertheless, the CT scan is an indispensable diagnostic procedure for planning head and neck surgery in most of our patients because of the overview of the anatomical situation provided.

Color-coded duplex sonography showed nearly equal results to CT scan in primary tumor detection but was better in recurrent carcinoma. The demonstration of the local vascularization pattern by this method helped to identify lesions not found by CT. A major disadvantage is the fact that not all regions of interest are accessible. Infratemporal and pterygopalatine fossa, skull base, parts of the parapharyngeal space, nasopharynx, hypopharynx, and the larynx cannot be sonographically investigated, in part or whole. This is a serious limitation for a more general use of the procedure. Some authors reported good results of CCDS. Hence, the application of CCDS was of limited value only for the detection of a primary tumor site. Although we do not consider CCDS the procedure of choice for the identification of all primary tumor sites in the head and neck, we routinely apply it for this purpose while we search for suspected lymph nodes. From our experience, CCDS occasionally can provide useful supplementary information about a suspected tumor site.

Despite the progress and refinement of various imaging procedures, panendoscopy is still a valuable diagnostic procedure for the detection of tumors in the upper aerodigestive tract and cannot be replaced by any imaging procedure tested in this study. Early mucosal lesions, often undetected or overlooked by all imaging procedures applied here could be successfully demonstrated by panendoscopy. The higher figures for false-positive results in panendoscopy in recurrent disease depend in part on the experience of the clinician. After therapeutic treatment, it can be difficult in some instances with panendoscopy, too, to distinguish scarring from a recurrent carcinoma.

The results in the detection of nodal neck metastases differ from those obtained in the comparison of primary tumor lesions. In neck imaging all procedures showed exactly the same sensitivity. As expected, the palpation was significantly less sensitive.

There was no significant difference in specificity between PET and CCDS, but both procedures had a higher number of false-positive results than CT. Various studies demonstrated that leukocytes have a high glucose utilization and, therefore, store high amounts of [18F]FDG. We found histopathologic verification of inflammatory changes in all cases of false-positive PET scans. In CCDS, lymph nodes larger than 10 mm or problems in the demonstration of the vascularization pattern yielded false-positive results. False-negative results occurred in patients with lymph nodes smaller than 10 mm and unsuspicious shape and in patients in whom depiction of vascularization was uncertain.

The results of the our study show that panendoscopy is still a first-choice procedure for the detection of primary tumor and recurrent carcinomas in the head and neck region. Particularly for the detection of recurrent carcinoma after irradiation and surgery, PET was the most reliable imaging procedure in this study. Owing to its limited anatomical depiction, functional imaging cannot replace morphologic-based imaging procedures such as CT or magnetic resonance imaging in the planning of the therapeutic procedure at the moment. Advanced technology that provides better resolution of the PET scans might help to solve this problem in the future.

At present, the most promising strategy is to combine the advantages of both procedures by coregistration of PET imaging with CT (or magnetic resonance imaging). This approach can efficiently support a more reliable localization of a malignancy suspected in PET.

Computed tomography and, to a more limited extent, CCDS have their place in the detection and evaluation of the local spread in suspected tumor localization. Our study demonstrated that for routine evaluation of lymph nodes in the neck, CCDS is a first-choice procedure. Tracer uptake values failed to prove significant correlation to the tumor grading in this study. Because of the high costs, PET is not a part of the standard diagnostic program and is limited to specialized medical centers at the moment.
REFERENCES


