Purpose: To assess the value of 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in patients with nasopharyngeal carcinoma as compared with PET and conventional imaging (CI) alone, and to assess the impact of PET/CT on further clinical management.

Methods and Materials: Thirty-three patients with nasopharyngeal carcinoma had 45 PET/CT examinations. The study was a retrospective analysis. Changes in patient care resulting from the PET/CT studies were recorded.

Results: Positron emission tomography/computed tomography had sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92%, 90%, 90%, 90%, and 91%, respectively, as compared with 92%, 65%, 76%, 86%, and 80% for PET and 92%, 15%, 60%, 60%, and 60% for CI. Imaging with PET/CT altered further management of 19 patients (57%). Imaging with PET/CT eliminated the need for previously planned diagnostic procedures in 11 patients, induced a change in the planned therapeutic approach in 5 patients, and guided biopsy to a specific metabolically active area inside an edematous region in 3 patients, thus decreasing the chances for tissue sampling errors and avoiding damage to nonmalignant tissue.

Conclusions: In cancer of the nasopharynx, the diagnostic performance of PET/CT is better than that of stand-alone PET or CI. Positron emission tomography/computed tomography had a major impact on further clinical management in 57% of patients. © 2007 Elsevier Inc.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor distributed mainly among well-defined ethnic populations. Nasopharyngeal carcinoma is very common in southern China, with an incidence of 10–30/100,000 population per year, has intermediate rates among Arabs in North Africa and parts of the Middle East (1), and represents 0.2% of malignant diseases in the white population (1). Nasopharyngeal carcinoma is characterized by local aggressiveness and very high regional spread to cervical lymph nodes. The status of cervical lymph nodes has a major impact on overall survival and distant failure (2). Approximately 30% of patients will eventually develop distant metastases, which represent the most important prognostic factor (3, 4). Thus, early detection of distant metastases and proper staging are of clinical significance and can influence treatment options and prognosis.

Computed tomography (CT) and magnetic resonance imaging (MRI) are standard diagnostic modalities for the evaluation of patients with NPC. These tests are, however, based on morphologic diagnostic criteria, such as nodal size and contrast-enhancement patterns, which do not always accurately reflect the true staging. After treatment, imaging is widely used to assess response and for early diagnosis of recurrence. However, because of head-and-neck anatomy distortion by surgery and/or radiation, the distinction between posttreatment changes and recurrence or residual tumor is difficult to make with imaging modalities that rely on morphologic criteria, and CT or MRI have a known limited accuracy in these cases (5).

Fluorine-18 fluorodeoxyglucose (FDG) positron emission
Positron emission tomography (PET) plays an increasing role in primary staging (6) and posttherapy management of head-and-neck cancer (7). Positron emission tomography, a functional imaging modality, assesses the metabolic status of tumors and has been proved superior to CT and MRI in differentiating recurrence from postradiation effects or scar in patients with NPC (8, 9), as well as for diagnosis of distant metastases (10). However, PET is limited by the lack of anatomic boundaries, and the precise localization of suspicious findings is therefore difficult. Variable physiologic and inflammatory uptake of FDG in the head-and-neck region, mainly after treatment, can also confound interpretation of suspicious foci.

The combined imaging modality of PET/CT allows sequential acquisition of PET and CT in a single imaging session, with fusion of anatomic and metabolic data. Preliminary studies have shown that PET/CT improves the anatomic localization of FDG-avid abnormalities and reduces the number of equivocal PET interpretations in tumors of the head and neck (11).

The purpose of the present study was to assess the role of PET/CT compared with PET and conventional imaging (CI) as stand-alone modalities in a homogenous group of patients with NPC. The impact of the PET/CT results on patient care was also evaluated.

METHODS AND MATERIALS

Thirty-three patients with NPC had 45 PET/CT examinations at the Department of Nuclear Medicine at our institution between July 2001 and December 2004. The study group included all patients with nasopharyngeal carcinoma that had PET/CT at our center. The clinical characteristics and referral patterns of the patient population are presented in Table 1.

High-resolution contrast-enhanced CT and/or MRI (represented in transaxial, coronal, and sagittal views) of the region of the head and neck, and in relevant cases also of the chest and the abdomen, were obtained in all patients at a mean of 1.3 months (range, 1–2 months) before the PET/CT study.

Patients were injected intravenously with 370–555 MBq (10–15 mCi) of FDG after a 4–6-h fasting period. Whole-body PET and non–contrast-enhanced CT with 1.25-mm slice thickness were acquired in all patients consecutively 60–90 min after the tracer injection, using the PET/CT system (Discovery LS; General Electric Medical Systems, Milwaukee, WI), combining a third-generation multislice spiral CT scanner with a dedicated full-ring PET scanner with bismuth germanate crystals. The PET and CT devices are mechanically aligned back to back and share a common table. Proper registration of the PET and the CT images is ensured by shared positional information of the table and the patient. The PET, CT, and fused PET/CT images are displayed for review in axial, coronal, and sagittal planes.

All studies were interpreted and reviewed with knowledge of the patient’s clinical history and results of previous imaging studies. Two experienced nuclear medicine physicians interpreted the stand-alone FDG PET images. Every focus of increased FDG uptake was recorded and classified as malignant, equivocal, or benign, on the basis of its shape, size, intensity, and localization. A site of increased FDG uptake was defined as benign and unrelated to cancer when it was located in an area of the physiologic biodistribution of the tracer or in a known nonmalignant process.

A focus of increased FDG uptake, with intensity higher than that of surrounding tissues, in areas unrelated to physiologic or benign processes, was defined as malignant. Any other area of increased FDG uptake that could not be clearly characterized was defined as equivocal.

A PET study showing at least one site of abnormal FDG uptake characterized as malignant or equivocal was defined as positive. Positron emission tomography studies with all lesions defined as benign, or showing no areas of increased FDG uptake, were interpreted as negative.

A head-and-neck radiologist reviewed the separately performed high-resolution contrast-enhanced CI study and the CT component of the PET/CT studies, independent of the interpretation of the PET scan. Findings were classified as negative, malignant, or equivocal according to accepted criteria for suspicion of malignancy on CI.

A combined team of nuclear medicine physicians and a head-and-neck radiologist interpreted the fused PET/CT images after completion of the PET and CI review. Changes in lesion definition and localization provided by PET/CT were recorded.

The PET, CI, and PET/CT findings were classified as true positive (positive lesion or imaging study confirmed as presence of cancer), true negative (negative lesion or study with no further
evidence of cancer), false positive (positive lesion or imaging study with no evidence of cancer), or false negative (negative lesion or imaging study with missed imaging diagnosis of further proven cancer). The criteria representing the standard of reference for presence or absence of cancer included histopathologic sampling obtained from biopsy, fine-needle aspiration (FNA), or surgery in 18 patients. In 12 patients clinical and radiologic follow-up were used as the reference standard. The mean follow-up period was 22.5 months (range, 12–36 months) and for patients with no further evidence of active malignancy it was 26 months (range, 18–36 months). Three patients with diffuse metastatic disease on PET/CT were treated with palliative therapy without any additional diagnostic procedures. A senior staff oncologist made the final diagnostic and therapeutic decision.

The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy for CI, PET, and PET/CT were calculated for the entire patient population for a lesion- and study-based analysis using standard definitions. The differences in performance indices between different imaging modalities were compared using the McNemar and the chi-square tests as appropriate, with \( p < 0.05 \) considered statistically significant.

Changes in clinical decision making induced by PET/CT were reviewed and recorded for impact on patient management for each study. This included changes in further diagnostic assessment, such as the need for or exclusion of further invasive diagnostic procedures. Intra- and intermodality changes in the therapeutic strategy included the initiation of previously unplanned treatment, referral of the patient from a treatment modality to a different one, or changes in the previously planned approach, such as a modified surgical technique, a change in number and doses of chemotherapy, or a change in location and size of radiation fields and duration of radiotherapy.

**RESULTS**

**Active malignancy was the final diagnosis in 28 of the 45 PET/CT studies (62%)**

On CI, 40 studies (89%) were diagnosed as positive (including 23 malignant and 17 equivocal studies) and 5 as negative for malignancy. There were 23 true-positive, 17 false-positive, 3 true-negative, and 2 false-negative studies.

On PET, 30 studies (67%) were diagnosed as positive (including 21 malignant and 9 equivocal studies) and 15 as negative for malignancy. There were 23 true-positive, 7 false-positive, 13 true-negative, and 2 false-negative studies.

On PET/CT, 25 studies (56%) were diagnosed as positive (including 24 malignant and 1 equivocal study) and 20 as negative for malignancy. There were 23 true-positive, 2 false-positive, 18 true-negative, and 2 false-negative studies.

The two false-positive studies on PET/CT occurred in patients evaluated for suspicion of recurrent NPC and showed abnormally increased FDG uptake in the nasopharynx. The clinical follow-up was negative, as were repeat PET studies performed after 3 and 4 months, respectively. The two false-negative PET/CT studies occurred in patients with very aggressive tumors who were evaluated for suspicion of recurrent NPC. The PET study results were normal, without any pathologic uptake (even on retrospective reassessment). Local recurrence in the nasopharynx was diagnosed 4 and 6 months later.

There was a statistically significant difference between CI and PET/CT regarding specificity \( (p < 0.01) \), PPV \( (p < 0.01) \), and accuracy \( (p < 0.01) \) (Table 2). There was a borderline difference between PET and PET/CT in specificity \( (p = 0.06) \) and accuracy \( (p = 0.06) \) (Table 2).

For the site-based analysis, 98 suspicious lesions were evaluated in the 45 studies. Positron emission tomography/computed tomography improved the diagnostic accuracy of PET for 46 of the total 98 foci (47%). Positron emission tomography/computed tomography changed the characterization of 15 sites on PET from equivocal to benign. Five foci in the nasopharynx were diagnosed as postradiation changes. Three foci in the anterior neck were defined as physiologic asymmetric thyroid uptake, and four sites in the lateral neck were defined as physiologic uptake in tense muscles. Three foci were localized by PET/CT to inflammatory pulmonary infiltrates or calcified lymph nodes and were therefore defined as unrelated to malignancy. Positron emission tomography/computed tomography changed the characterization of seven additional sites on PET from equivocal to malignant, in the nasopharynx \( (n = 3) \), neck \( (n = 2) \), lung \( (n = 1) \), and iliac bone \( (n = 1) \). In 24 sites, PET/CT improved the localization of abnormal FDG uptake to anatomic structures of the nasopharynx and the neck and thus provided a better definition of the extent of disease.

There was a statistically significant difference between CI and PET/CT regarding specificity \( (p < 0.01) \), PPV \( (p < 0.01) \), NPV \( (p < 0.01) \), and accuracy \( (p < 0.01) \) and a statistically significant difference between PET and PET/CT in specificity \( (p = 0.02) \), PPV \( (p < 0.05) \), and accuracy \( (p = 0.02) \) (Table 3).

**Table 2. Diagnostic accuracy of CT, PET, and PET/CT:**

<table>
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<tr>
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<th>CT/MRI</th>
<th>PET</th>
<th>PET/CT</th>
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<tr>
<td>Sensitivity (%)</td>
<td>92</td>
<td>92</td>
<td>92</td>
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<tr>
<td>Specificity (%)</td>
<td>15</td>
<td>65</td>
<td>90</td>
<td>0.02, PET vs. CT ( &lt; 0.01 ), CT vs. PET/CT ( &lt; 0.01 ), PET vs. PET/CT ( &lt; 0.01 )</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>60</td>
<td>76</td>
<td>90</td>
<td>0.06, PET vs. PET/CT ( &lt; 0.01 ), CT vs. PET/CT ( &lt; 0.01 ), PET vs. CT ( &lt; 0.01 )</td>
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<tr>
<td>NPV (%)</td>
<td>60</td>
<td>86</td>
<td>90</td>
<td>0.03, PET vs. CT ( &lt; 0.01 ), CT vs. PET/CT ( &lt; 0.01 ), PET vs. CT ( &lt; 0.01 )</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>60</td>
<td>80</td>
<td>91</td>
<td>0.02, PET vs. CT ( &lt; 0.01 ), CT vs. PET/CT ( &lt; 0.01 ), PET vs. PET/CT ( &lt; 0.06 )</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; ns = nonsignificant; PPV = positive predictive value; NPV = negative predictive value.

* Total of 45 studies.
Impact on patient care

By precisely matching the metabolic and anatomic abnormalities, PET/CT altered the further clinical management of 19 patients (57%). Positron emission tomography/computed tomography eliminated the need for previously planned diagnostic procedures in 11 patients, including biopsy of the nasopharynx ($n = 9$) and FNA of enlarged cervical nodes ($n = 2$). These procedures had been initially planned on the basis of suspicious clinical examination and/or radiologic data and were cancelled because of the absence of hypermetabolic lesions on the PET component of the PET/CT images.

Positron emission tomography/computed tomography induced a change in the planned therapeutic approach in 5 patients. Positron emission tomography/computed tomography diagnosed distant metastases in 3 patients, changing the treatment protocol from curative to palliative (Fig. 1). One patient was referred to surgery after the diagnosis of a positive neck lymph node by PET/CT. Fine-needle aspiration from this node was negative. Despite that, neck dissection was performed, and the final pathologic results showed an 8-mm metastatic lymph node (Fig. 2). A negative PET/CT study eliminated the need for neck surgery in 1 patient with clinically suspected cervical lymph node metastases who refused to undergo FNA. The patient has no evidence of disease for a follow-up of 26 months.

![Fig. 1. The role of positron emission tomography (PET)/computed tomography (CT) in finding distant metastases. This study was done for staging purposes in a patient with T1N3MO (according to CT and physical examination). (a) CT scan of the thigh area was diagnosed as normal. (b) PET scan demonstrated pathologic uptake in the right thigh (arrowhead). (c) PET/CT localized the uptake to the right ischium (white arrow).](image-url)

Table 3. Diagnostic accuracy of CT, PET, PET/CT: Lesion-based analysis*

<table>
<thead>
<tr>
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<th>CT/MRI</th>
<th>PET</th>
<th>PET/CT</th>
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<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>83</td>
<td>97</td>
<td>97</td>
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</tr>
<tr>
<td>Specificity (%)</td>
<td>38</td>
<td>67</td>
<td>92</td>
<td>&lt;0.01, CT vs. PET/CT</td>
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<tr>
<td>PPV (%)</td>
<td>0.08, CT vs. PET/CT</td>
<td>0.01, PET vs. CT</td>
<td>&lt;0.01, CT vs. PET/CT</td>
<td>&lt;0.01, CT vs. PET/CT</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>60</td>
<td>92</td>
<td>95</td>
<td>0.005, PET vs. PET/CT</td>
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<tr>
<td>Accuracy (%)</td>
<td>65</td>
<td>84</td>
<td>95</td>
<td>&lt;0.01, CT vs. PET/CT</td>
</tr>
</tbody>
</table>

Abbreviations: CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; PPV = positive predictive value; NPV = negative predictive value.

* Total of 98 lesions.
Positron emission tomography/computed tomography guided biopsy to a specific metabolically active area inside an edematous region in the nasopharynx in 3 patients. Biopsy was positive for squamous cell carcinoma in all 3 patients.

**DISCUSSION**

Nasopharyngeal carcinoma is an aggressive type of squamous cell carcinoma with a high incidence of locoregional spread and of distant metastases at presentation (3). Accurate and early diagnosis is important for proper treatment with high cure rates. Radiotherapy is the main treatment modality, combined with chemotherapy in high tumor stages. Although recurrent NPC has, as a rule, poor prognosis, early detection of recurrence can significantly improve the outcome (10).

Assessment of NPC includes CI methods, such as CT and MRI. These modalities rely on morphologic diagnostic criteria, such as nodal size and contrast-enhancement patterns, which do not always accurately reflect the true staging. The reported sensitivity, specificity, and accuracy of CT for cervical nodal metastases were 88%, 86%, and 87%, respectively (12), with specificity dropping to 39% for CT and 48% for MRI when a 10-mm size criterion is used (13).

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**Fig. 2.** The role of positron emission tomography (PET)/computed tomography (CT) in diagnosing malignancy in normal-size lymph nodes. Posttreatment images of a patient with advanced nasopharyngeal tumor who was evaluated for suspicion of local recurrence 2 years after chemoradiotherapy. (a) Computed tomography scan demonstrated a normal-size (8-mm) cervical lymph node (white arrow). (b) Positron emission tomography scan of the same region showed increased uptake in the right neck (black arrow). (c) Positron emission tomography/computed tomography localized the uptake to a jugulodigastric lymph node (arrowhead). Fine-needle aspiration from the node was negative. Despite that, neck dissection was performed, and the final pathologic results showed an 8-mm metastatic lymph node.
Radiation therapy alters the normal nasopharyngeal anatomy. Treatment-related edema, fibrosis, inflammation, and scarring are limiting factors that hamper the role of physical examination and imaging with CT or MRI in the diagnosis of recurrent nasopharyngeal carcinoma. The differential diagnosis between radiation-related anatomic asymmetry and early recurrence poses a diagnostic challenge with the use of MRI or CT.

The present study shows a significantly lower specificity for CI as compared with both PET and PET/CT. As expected, 82% of the 17 false-positive CI studies in the present study belonged to the locoregional recurrence group. In addition to the known inability of CI to distinguish between posttreatment edema and local recurrence, the significant difference in performance in the present study may also be related to biased selection criteria in our study population. Most patients were referred for PET/CT after abnormal or uncertain findings on CI and not as the primary imaging modality.

Fluorodeoxyglucose PET plays an increasing role in the assessment of a population with various types of head-and-neck cancer, being more accurate than CT or MRI at detecting both primary (15) and metastatic disease (6). Fluorodeoxyglucose PET was more sensitive and accurate than MRI in primary staging of NPC (16), as well as for detection of distant metastases (10), and was superior to CT and MRI in detecting recurrent or residual NPC (8, 9, 17).

A major drawback of FDG-PET is the lack of anatomic details. This, in addition to the FDG-avidity of benign and physiologic processes, can explain the relatively high false-positive rate and low specificity of this modality. In our study, FDG-PET had a specificity of 65% and PPV of 76%. Lack of anatomic landmarks on PET hinders localization and characterization of increased FDG uptake. Most false-positive PET studies were found in postirradiated patients because FDG accumulates in metabolically active tissue, including inflammation and infection, which are known postirradiation sequels.

Of the seven false-positive PET studies in the present series, five were accurately diagnosed as foci of physiologic uptake by PET/CT. The sequential acquisition of CT and PET defines the anatomic boundaries of tracer uptake more accurately and increases the confidence of distinguishing physiologic or benign foci from malignant FDG-avid lesions. Positron emission tomography/computed tomography decreased the number of equivocal PET reports, which might have lead to further noninvasive, imaging, and invasive biopsy procedures, with associated morbidity, additional costs, and emotional stress. The added CT component of the hybrid imaging study defined 15% of suspicious PET sites as physiologic or benign, localized mainly in the region of the head and neck. Computed tomography landmarks are essential in the presence of the delicate and complex nasopharyngeal and neck anatomy, as well as the known potential pitfalls of increased FDG activity unrelated to cancer in this region.

Nasopharyngeal carcinoma is a very aggressive tumor with 5% incidence of distant metastases at presentation (18) and up to 30% after primary radiotherapy (3). Early detection of distant metastases is important for improving appropriate treatment planning and patient outcome. Conventional imaging modalities have relative low sensitivity for detection of distant metastases (3). Whole-body MRI survey is generally impractical for tumor staging. Fluorodeoxyglucose PET scans the whole body and therefore has the advantage of disclosing unexpected tumor foci outside the head-and-neck region with a high sensitivity. In the present study, previously unsuspected distant metastases were identified in 24% of patients and were correctly defined as such by PET/CT in 89% of lesions.

Yen et al. (19) found that early restaging by FDG-PET after the first or second course of induction chemotherapy is useful for predicting therapeutic response and outcome in patients with locoregionally advanced NPC. Those patients who are unresponsive to induction chemotherapy according to FDG-PET may be switched to alternative treatment options and thus avoid unnecessary chemotherapy. A recent publication in 33 patients with NPC assessed the role of PET/CT with respect to the specific need for additional salvage radiation treatment (20). The present study is, to the best of our knowledge, the first to demonstrate the incremental value of hybrid imaging on patient care and further clinical management of NPC. Our data indicate that the diagnostic or treatment strategy planned before performing PET/CT was modified in 57% of patients on the basis of results from this test. This is a retrospective analysis with patients that were followed for 22 months only. We record a change in clinical management in 19 patients. However, to assess the impact of PET/CT on survival and quality of life of patients with NPC, long-term follow-up and large, randomized, multicenter studies need to be performed.

**CONCLUSIONS**

Positron emission tomography/computed tomography is an effective noninvasive diagnostic tool for the assessment of nasopharyngeal squamous cell carcinoma, with an overall diagnostic accuracy of 92%. It is of value mainly in the postirradiated nasopharynx. In assessment of locoregional disease, PET/CT provides better anatomic localization of foci with abnormal FDG uptake and significantly reduces the number of false-positive or equivocal PET and CI results. When a PET/CT study is negative, additional clinical and radiologic follow-up can be postponed, at least temporarily. Positron emission tomography/computed tomography is also of particular value to define the presence and extent of disseminated disease in view of the high rate of distant metastases in patients with NPC.
REFERENCES