Significance of radiologically determined prognostic factors for head and neck cancer
Lodder, W.L.

Citation for published version (APA):
Lodder, W. L. (2013). Significance of radiologically determined prognostic factors for head and neck cancer

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 5

Detection of extranodal spread in head and neck cancer with [18F]FDG PET and MRI: Improved accuracy?

Wouter L. Lodder
Wouter V. Vogel
Charlotte A.H. Lange
Olga Hamming-Vrieze
Marie-Louise F. van Velthuysen
Frank A. Pameijer
Michiel W. M. van den Brekel
Alfons J.M. Balm

Quarterly Journal of Nuclear Medicine and Molecular Imaging 2013, in press.
ABSTRACT

Aim
Preoperative detection of extranodal spread (ENS) in head and neck cancer can have important consequences for patient management. The aim of this study was to determine whether 18-fluorodeoxyglucose positron emission tomography ([18F]FDG PET) or a combination with Magnetic Resonance Imaging (MRI) could more accurately predict ENS, especially with the near availability of fully integrated [18F]FDG PET/MRI scanners.

Methods
In retrospective cohort design a total of twelve patients, with 18 lymph node metastases were studied with [18F]FDG PET and MRI. Presence of ENS was scored on MRI, and [18F]FDG PET images using a SUV max cut-off point of 12. Histopathology results were used as reference standard. Sensitivity, specificity and accuracy were calculated.

Results
The sensitivity, specificity and accuracy of [18F]FDG PET for ENS reached 70%, 100% and 83%, respectively. The mean SUVmax of ENS positive lymph nodes was 13.6 versus 8.7 for lymph node metastases without ENS (p=0.03). The sensitivity, specificity and accuracy of MRI for ENS were 70%, 100% and 83%, respectively. When the [18F]FDG PET and MRI findings were combined sensitivity, specificity and accuracy were 80%, 100% and 89%, respectively. Thus, accuracy increased from 80% to 89%.

Conclusion
When there is no ENS or doubt of ENS on MRI, [18F]FDG PET seems to have additional value since it improves sensitivity and resolves uncertainty in case of high FDG uptake. This benefit needs to be confirmed prospectively in a larger cohort.
INTRODUCTION

Extranodal spread (ENS) is one of the most important prognostic factors for overall survival in regionally metastatic head and neck cancer. Moreover, it has an impact on treatment as patients with ENS can benefit from adjuvant chemotherapy next to postoperative radiation treatment. In these patients, primary concomitant chemoradiation can be advocated, leaving surgery as a salvage modality. This change in treatment is not yet implemented as a standard treatment protocol in all head and neck cancer centres.

Several authors studied CT- and MR-images to evaluate their role in the assessment of ENS on preoperative imaging. Different characteristics were studied including growth into adjacent planes and nodal border irregularity leading to suboptimal sensitivity and specificity ranging from 65% - 95% and 72% - 100%, respectively. Therefore, cross-sectional imaging is not yet accurate enough to direct preoperative decision-making. Possibly, the wide range in sensitivity and specificity is caused by use of different characteristics by radiologists as well as observer variation among pathologists.

At present, 18-fluorodeoxyglucose positron emission tomography ([18F]FDG PET) is one of the imaging tools proven to be useful for non-invasive identification and staging of lymph node involvement in head and neck cancer, although microscopic tumor is generally not detected with this technique. ENS can be regarded as a pure anatomical feature, i.e. tumor has grown beyond the lymph node capsule. However, it is probably also a sign of an aggressive growth pattern related to biological processes in tumor tissues. In theory, with a more aggressive tumor, a higher glucose consumption rate should be found, possibly indicating that aggressive growth is associated with ENS. Proliferation and growth in a tumor are positively correlated with standardised uptake values (SUV) determined on positron emission tomography imaging (PET) with 18F-fluorodeoxyglucose (FDG). Recently, two publications reported on the role of [18F]FDG PET in the assessment of extranodal spread. In these reports, lymph nodes with ENS, in head and neck cancer, demonstrated a significantly higher mean SUVmax value than lymph nodes without ENS.

Recent studies also show the future prospective for the use of combined [18F]FDG PET/MRI scanners. Next to [18F]FDG PET, MRI provides a superior visualisation of soft tissue structures, which makes a combination of these
modalities first choice for cases with suspected tumor in the head and neck area.\textsuperscript{21}

Therefore, the aim of this study was to determine whether \([18F]FDG\) PET, or a combination with MRI, is a better predictor of ENS.

**MATERIAL AND METHODS**

*Ethical considerations*

Institutional approval was received and patient consent was not required for this retrospective review of records and images because patient anonymity was preserved.

*Definitions*

Normal looking nodes were studied if the minimal axial diameter was more than 1 cm. Lymph nodes were divided in six levels according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) 2002 classification. On MRI, all abnormal looking nodes (i.e. irregular contour, inhomogeneous enhancement, central nodal necrosis) were studied regardless of size. For the final MRI scoring set, consensus was reached in all cases. The observers were blinded to results of clinical examinations, histologic findings or clinical outcome. Suspicion of nodal involvement by squamous cell carcinoma and the presence or absence of ENS was recorded. By recording the combination of the largest diameter, short axial diameter and neck level of each lymph node, it was possible to perform a topographical correlation for each lymph node per neck level.

*Patient data*

This study was conducted retrospectively. The combination of \([18F]FDG\) PET and MRI was purely dependent on the location of the primary tumor. In our institution patients with a tumor located above the hyoid bone receive a MRI, patients with tumors below the level of the hyoid bone are evaluated with CT images. From our histopathology database we selected 60 patients with a primary neck dissection for head and neck squamous cell carcinoma during the period of 2007-2010. Thirty-nine patients had undergone preoperative MRI. Within this group we selected 12 patients who also had undergone \([18F]FDG\) PET for neck node
metastasis from unknown primary origin, presence of multiple lymph nodes or bilateral lymph nodes according to current institutional guidelines.

Patient characteristics are shown in table 1.

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>N = 12 (total 96 nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Women</td>
<td>2 (17%)</td>
</tr>
<tr>
<td><strong>Age</strong> (range; median)</td>
<td>50-75 year (61)</td>
</tr>
<tr>
<td><strong>Primary tumor characteristics</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Larynx</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unknown primary tumor</td>
<td>7 (58%)</td>
</tr>
<tr>
<td><strong>Pathological N-classification</strong></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>N2a</td>
<td>3 (26%)</td>
</tr>
<tr>
<td>N2b</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>N2c</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>N3</td>
<td>4 (33%)</td>
</tr>
</tbody>
</table>

Table 1. Patient and tumor characteristics.

**Imaging data**

**[18F]FDG PET**

A combined [18F]FDG PET/CT machine (Gemini II, Philips, Eindhoven, The Netherlands) was used and [18F]FDG was administrated in a dosage of 173–200 MBq. Patients fasted for at least 6 h before intravenous injection of FDG. Diabetes mellitus was regulated in advance, with plasma glucose < 10 mmol/l. At 60 +/- 10 minutes after injection, [18F]FDG PET/CT images were acquired with the patient in supine position. A high-resolution image was generated of the head and neck, with an image acquisition of 4 minutes per bed position, reconstructed to 2 mm voxels. In addition, a standard body acquisition was performed of the neck to the thighs, with 1:30 minutes per bed position and a voxel size of 4 mm. Low-dose CT images (40 mAs, 3 mm slices in the neck and 5 mm slices in the body) were acquired without oral or intravenous contrast, for attenuation correction and anatomical correlation. Generated images ([18F]
FDG PET, low-dose CT, and [18F]FDG PET/CT) were evaluated using an Osirix Dicom viewer in a UNIX-based operating system (MAC OS X, Mac Pro, Apple, Cupertino, CA) and were evaluated on the basis of 2-dimensional orthogonal slicing. By recording the exact location of each lymph node, it was possible to perform a topographical correlation for each lymph node per neck level.

[18F]FDG PET assessment
An experienced nuclear medicine physician (W.V.) assessed all [18F]FDG PET images. [18F]FDG uptake in lymph nodes was quantified on the high-resolution head and neck images using the maximum SUV value, which was defined as SUVmax—maximum activity concentration (MBq/ml)/[injected dose (MBq)/body weight (g)]. An automatic 3D-growing contour was generated around the metabolically active part of the lymph node using an iso-contour based on 50% of the maximum lesion uptake, and SUVmax was automatically defined as the most active voxel in this volume. In nodes that were very small, nodes that had very low FDG uptake, or nodes that were otherwise hard to delineate automatically, SUVmax was determined manually in the slice with the highest visual activity. Different cut-off values of SUVmax were studied to determine the most optimal value for the detection of ENS on [18F]FDG PET. Also the SUVmean values were studied.

MRI-technique
MRI examinations were performed at 3.0 T. (Philips Achieva release 3.2.1, Philips Medical Systems, Best, The Netherlands) using a dedicated 16-channel SENSE neurovascular coil. The following series were acquired: STIR TSE COR, TR (repetition time), IR (inversion time), TE (echo time) 3,880/180/20 ms, ETL: 12, FOV 300/228/40 mm, matrix: 320/320, 2 nex, slice thickness 4 mm; STIR TSE TRA, TR/IR/TE 4,228/180/20, ETL: 12, FOV: 180/200/80 mm, matrix 300/312, 2 nex, SW 3.5 mm, T1 TSE TRA, TR/TE: 780/10, ETL: 5, FOV 180/180/80, matrix 384/384, 2 nex, slice thickness: 3.5 mm; T1 3D Thrive [performed after intravenous injection of 15 cc gadoterate meglumine (Dotarem)], TR/TE: 5/2,22, ETL:90, TA: 10, FOV 230/272/220, matrix 288/288, 2 nex, slice thickness: 0.8 mm; T1 TSE COR (post contrast): TR/TE: 812/10, ETL: 6, FOV: 180/150/96 mm, matrix: 320/320, 3 nex, slice thickness 3.5 mm.
Radiological assessment
For every lymph node that was scored, the following features were recorded by two experienced head and neck radiologists (C.L. and F.P.): Short axis in axial plane, longest axis, capsular contour (smooth/lobulated or indistinct), infiltration of adjacent tissue planes (fat, vessels or muscles) and central nodal necrosis inside lymph nodes. Whenever a lymph node was located in two levels, the level that contained most of the nodal cross-sectional volume was recorded. Different pre-defined lymph node characteristics suggestive for ENS were studied. In a previous performed study we showed that the MRI-finding “infiltration of adjacent tissue planes” represents a 100% specific indicator. Therefore in this study we used this as a criterion for the presence of ENS.

Histopathological assessment
All neck dissection specimens were labelled for the neck levels postoperatively in the operation room by the surgeon for pathological orientation. The pathologist manually identified and localized the lymph nodes per neck level in the neck dissection specimen. The maximal diameter of all lymph nodes was recorded. Subsequently, lymph nodes were fixed, sectioned, and hematoxyline-eosine (HE) stained, and the presence of tumor in each lymph node was examined microscopically. One experienced pathologist recorded the presence/absence of ENS in all neck dissection specimens. The histological results were used as the reference standard.

The following criteria were scored: Total number of lymph nodes, number and level of tumor positive lymph nodes and largest diameter of tumor positive lymph node. The following lymph node characteristics of capsule extension were listed: a) Uncertain extension (in some cases the histopathologist could not distinguish between growth into the surround capsule and growth beyond); b) Growth into the surround capsule but not through or beyond; c) Tumor growth into the hilum area; d) Growth into surrounding fat, growth into surrounding structures other than fat (e.g. muscles); e) Extent of growth beyond the capsule in mm.

In accordance to the guidelines of the American Academy of Pathology, ENS was reported when there was “growth into surrounding fat, growth into surrounding structures other than fat” and in “uncertain extension”, thus a, d and e. In case of “growth into the hilum area” or “growth into the lymph node capsule but not beyond” no ENS was reported.
Statistical analysis
Student’s t-test was used to determine the significance of SUVmax for the detection of ENS. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of using [18F]FDG PET for the detection of nodal involvement and presence or absence of extranodal spread were calculated and compared to MRI. Also for the combination of MRI and [18F]FDG PET sensitivity and specificity were calculated. When “infiltration of adjacent planes”, “central nodal necrosis” or “indistinct contour” was present on MRI, ENS was scored positive. When the specific characteristic was absent, cut-off value SUV> 12 was used as criterion for ENS. The data set was analyzed by version 18.0 of SPSS for Mac OS X.

RESULTS

Histopathological assessment
In total 452 nodes were resected and studied in 12 patients. Of these nodes, 96 were positive for metastases (96/452 = 21% positive nodes). Eighteen out of these 96 nodal metastases were identified as pathological at both [18F]FDG PET and MRI. No lymph nodes were positive on [18F]FDG PET only or MRI. Ten out of these 18 nodes (divided over eight patients) were positive for extranodal spread (10/96 = 10%) on histopathology.

In total 78 nodal metastases were not identified by imaging because of their size (<5mm). None of them showed signs of ENS.

[18F]FDG PET assessment
All lymph nodes with FDG uptake were studied. The mean time between [18F] FDG PET and neck dissection was 21 days (range 10-54; SD 10). SUVmax of the 18 identified nodal metastases, ranged from 5.1-19.6 (mean 11.4, SD 4.5), SUVmean ranged from 3.4 – 13.6 (mean 7.5, SD 3.0). The mean SUVmax of the 10 ENS positive lymph nodes was 13.6 versus 8.7 (Fig. 1) for the 8 lymph nodes without ENS, which was significantly different (student’s t-test; p = 0.03).

None of the 78, not identified, nodal metastases, had a SUV of > 8.
Figure 1. Box-plot with the mean SUVmax of ENS positive lymph nodes (left) of 13.6 (95% CI 10.2 – 17.1; median 14.4) versus 8.7 (95% CI 7.1 – 10.3; median 8.5) for lymph nodes without ENS (right), which was significantly different (p = 0.03).

**MRI assessment**

Mean time between MRI and neck dissection was 23 days (range 0-60; SD 8.0). Of the 18 lymph nodes studied, one node (6%) had a smooth contour, six (33%) had a lobulated surface and 11 (61%) had an indistinct contour. Seven (39%) showed infiltration of adjacent planes and 11 (61%) showed no infiltration. Fifteen nodes (83%) had central nodal necrosis. Based upon the criterion “infiltration of adjacent planes” seven nodes (39%) were staged ENS positive. Figure 2 shows [18F]FDG PET and MRI of a lymph node with ENS. Table 2 shows the value of the different radiologically determined characteristics for the detection of extranodal tumor spread compared to histopathology.
CHAPTER 5

<table>
<thead>
<tr>
<th>Radiologically determined criteria</th>
<th>Pathologically determined ENS</th>
<th>No</th>
<th>Yes</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest diameter &gt; 2 cm</td>
<td></td>
<td>3</td>
<td>0</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>5</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>5</td>
<td>1</td>
<td>90%</td>
<td>63%</td>
</tr>
<tr>
<td>Largest diameter &gt; 3 cm</td>
<td></td>
<td>3</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>7</td>
<td>0</td>
<td>100%</td>
<td>88%</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indistinct capsular contour</td>
<td></td>
<td>8</td>
<td>3</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>0</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>2</td>
<td>1</td>
<td>90%</td>
<td>25%</td>
</tr>
<tr>
<td>Infiltration of adjacent planes</td>
<td></td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nodal necrosis</td>
<td></td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Sensitivity and specificity of radiologically determined criteria for the detection of extranodal tumor spread on MR imaging.

Figure 2. Patient with a T1N2b squamous cell carcinoma of the oral cavity. An enlarged lymph node with proven extranodal spread (ENS) on histopathology is present in Level III on the left side. A: Fused PET/CT image; SUVmax was 19.6; B,C: Axial and coronal T1 contrast-enhanced images with fat suppression at the level of the same level III lymph node (white arrow) on the left shows infiltration of adjacent planes (also note: central nodal necrosis /indistinct capsular contour laterally and posteriorly).

Sensitivity and specificity
Table 3 shows the sensitivity and specificity for both MRI and [18F]FDG PET images for ENS detection/prediction. For MRI the sensitivity was 70% and the specificity was 100%. With a cut-off point of SUVmax = 12, the sensitivity for [18F]FDG PET in our study was 70% and the specificity 100%. In search for radiological findings of ENS that could select patients who invariably have ENS, SUVmax of 12 was selected with specificity of 100%. When the results of
the [18F]FDG PET and MRI were combined with the characteristic “growth into adjacent planes” sensitivity was 80% and specificity 100%, accuracy reached 89%, “central nodal necrosis” sensitivity was 90% and specificity 25%, accuracy reached 61%, “indistinct capsular contour” sensitivity was 100% and specificity 88%, accuracy 94%.

<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>70%</td>
<td>100%</td>
<td>100%</td>
<td>73%</td>
<td>83%</td>
</tr>
<tr>
<td>PET/CT SUVmax &lt;8 vs &gt;8</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>80%</td>
<td>25%</td>
<td>57%</td>
<td>50%</td>
<td>56%</td>
</tr>
<tr>
<td>PET/CT SUVmax &lt;9 vs &gt;9</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>80%</td>
<td>63%</td>
<td>73%</td>
<td>71%</td>
<td>72%</td>
</tr>
<tr>
<td>PET/CT SUVmax &lt;10 vs &gt;10</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>80%</td>
<td>75%</td>
<td>80%</td>
<td>75%</td>
<td>72%</td>
</tr>
<tr>
<td>PET/CT SUVmax &lt;11 vs &gt;11</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>70%</td>
<td>88%</td>
<td>88%</td>
<td>70%</td>
<td>78%</td>
</tr>
<tr>
<td>PET/CT SUVmax &lt;12 vs &gt;12</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>70%</td>
<td>100%</td>
<td>100%</td>
<td>73%</td>
<td>83%</td>
</tr>
<tr>
<td>MRI infiltration + PET/CT SUVmax &lt;12 vs &gt;12</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
<td>80%</td>
<td>89%</td>
</tr>
<tr>
<td>MRI necrosis + PET/CT SUVmax &lt;12 vs &gt;12</td>
<td>9</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>90%</td>
<td>25%</td>
<td>60%</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>MRI contour + PET/CT SUVmax &lt;12 vs &gt;12</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>100%</td>
<td>88%</td>
<td>91%</td>
<td>100%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Table 3. TP: true positive, TN: true negative, FP: false positive, FN: false negative, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, AC: accuracy, MRI infiltration: infiltration of adjacent planes on MRI, MRI necrosis: central nodal necrosis on MRI, MRI contour: indistinct contour on MRI. When “Infiltration of adjacent planes”, “central nodal necrosis” or “indistinct contour” was present ENS was scored positive, when the specific characteristic was absent, cut-off value SUV> 12 was used as criterion for ENS.

**Discordance between imaging and histopathological assessment of Extranodal Spread**

Table 4 shows the lymph node characteristics of MRI and [18F]FDG PET. Evaluation with [18F]FDG PET alone, with a cut-off value for SUVmax of 12 to predict ENS, resulted in a specificity of 100%. However using these criteria three cases were found to be false negative for ENS (on histopathological assessment these nodes showed growth into adjacent planes): The first node had a SUVmax of 6.9 (at MRI this node was scored true positive with an indistinct capsular contour, central nodal necrosis and infiltration of adjacent planes). The second node had a SUV of 5.1 and the third node had a SUVmax of 10.6, both nodes were also false negative on MRI (one showed central nodal necrosis).
Table 4. MRI, PET/CT and histopathological characteristics

Lymph node 4, 5 and 7 were false negative using cut-off value SUV>12 for detection of ENS on PET/CT. The combined conclusion is based upon the combination of the MR-findings and PET/CT results. When “Infiltration of adjacent planes” was present ENS was scored positive, when “Infiltration of adjacent planes” was absent, cut-off value SUV > 12 was used as criterion for ENS. The line is colored gray when the conclusion was false compared to the histopathological conclusion.

Looking at MRI evaluation alone, another three cases were found to be false negative for ENS (two of which are already described above, being accordingly false negative by [18F]FDG PET): The first case showed at MRI a lymph node of 2.2 cm (maximal diameter) with an indistinct capsular contour, without central nodal necrosis (at [18F]FDG PET the SUVmax was 5.1, this was scored also false negative). The second case showed at MRI a lymph node of 4.8 cm (maximal diameter) with an indistinct contour and central nodal necrosis (at [18F]FDG PET the SUVmax was 10.6, this was also scored false negative). The third case showed a lymph node of 4.0 cm (maximal diameter) at MR with an indistinct contour and central nodal necrosis (at [18F]FDG PET the SUVmax was 12.8, this was scored true positive).
DISCUSSION

In this study the value of [18F]FDG PET and MRI for the detection of ENS was studied. In this relatively small series, accuracy for the detection of ENS increased from 80% to 89% when the results of MRI were combined with [18F]FDG PET findings. When there is doubt based upon MRI (sensitivity 70%, specificity 100%), [18F]FDG PET could be of additional value since it resolves uncertainty in case of high FDG uptake. These findings are especially of interest since fully integrated [18F]FDG PET/MRI scanning will become available in the near future. To our knowledge this is the first study with the results of a combination of characteristics studied on both [18F]FDG PET and MRI.

SUVmax is measured by calculating SUV in a region of interest. Most authors use the area in which the largest diameter can be found or the volume. Measurements from different studies are therefore not directly suitable for comparison. Furthermore, presence of central necrosis may influence SUVmax measurements. Grabenbauer et al. reported that lymph node metastases with central necrosis more often exhibit ENS. Since SUVmax is dependent on metabolically active tumor, a large amount of central necrosis in a node may lower FDG uptake. A possible explanation for the 3 false negative cases could be that the central necrosis (in 2/3=67% of the cases present) resulted in a lower FDG uptake in these nodes and subsequently in a low SUV. We were not able to study the influence of central nodal necrosis as a separate parameter, looking at the total of 18 nodes; 9/10 nodes with ENS and 6/8 nodes without ENS showed central nodal necrosis.

Two recent studies have reported their results with respect to ENS on [18F]FDG PET imaging. In the search for novel prognostic factors that predict surgical outcome in nasopharyngeal carcinoma (NPC), Chan et al. studied 69 patients with recurrent NPC. In total 22 of the 69 patients had cervical metastasis, ENS was found in 42% of the metastatic lymph nodes (26/62). Lymph nodes with ENS demonstrated a significantly higher mean SUVmax value than lymph nodes without ENS (7.1 vs 2.6, p=0.012). They concluded that SUVmax value could be of importance for the detection of ENS in the preoperative assessment.

In 2010, Kubicek et al. studied 212 patients, of whom 22 had ENS on histopathological assessment. Fifteen of these 22 patients had reported
SUVmax values. The median SUVmax of lymph node metastases with ENS was 11.9 vs 5.0 (p<0.0007) for lymph node metastases without ENS. They concluded SUVmax is predictive of ENS and it may be beneficial to treat higher SUV lymph nodes to a higher radiotherapy dose. In these 2 studies only the correlation between the SUV and ENS is described; no cut-off values were calculated. Our results, with a mean SUV max for ENS positive nodes of 13.6 versus 8.7 for lymph node metastases without ENS show a similar correlation.

However, retrospective image fusion is technically demanding in the head-and-neck area, mainly because of the varied patient positions used for the various scanners and the anatomic complexity of this region. It can be expected that fully integrated scanning will allow for superior evaluation of [18F]FDG PET/MRI images. With the availability in the near future, of fully integrated [18F]FDG PET/MRI scanners, ENS characteristics can then be studied on a more routine basis.

Combined [18F]FDG PET/MRI offers, next to the determination of ENS, a unique possibility to examine multiple pathophysiological tumor parameters simultaneously. Apart from the assessment of ENS, the integration of [18F]FDG PET/MRI data may improve radiotherapy treatment planning in terms of more precise target volume delineation.

Some limitations should be discussed here. In this study patient selection was performed on a retrospectively collected clinician’s database. This introduces a possible selection bias. A total of only 18 nodes could be used for the current study, as in these cases both MRI and [18F]FDG PET images were available. As this is a retrospective database correlation between the nodes on [18F]FDG PET, MRI and histopathology was based upon level classification combined with the largest diameter. Although peroperative marking of the removed node would have been preferred, in all cases correlation could be achieved with the available information by the multidisciplinary expert data analysis. For the calculation of sensitivity and specificity statistics were not accounting for clustered data (18 nodes were studied of 12 patients). No outcomes to response to treatment were determined.

No correlations were made with HPV status of the patients. However, a recent review showed that cystic changes in lymph nodes did not allow accurate predictions of HPV status.
Secondly, the limitations of [18F]FDG PET assessment are discussed. A FDG uptake threshold was determined retrospectively. However, for clinical use it is important to validate this threshold in a prospective matter. Further, for [18F] FDG PET reconstruction a high-resolution image was generated of the head and neck area. In this study the value of SUV of lymph nodes in the neck was studied, therefore we did not use the whole body series. Based upon the results of our data we selected the SUV of 12, however these measurements were performed with the use of a standardized threshold for high-resolution head and neck series. Our results could be compared to the results in literature, but only when standardized high-resolution head and neck series are used.

Also the measurement of SUV introduces a possible bias; patient’s body weight, time-differences between the time of injection and acquisition, use of ROI dimensions and PVE correction could cause differences in results.

Finally, this study focuses on the added value of [18F]FDG PET next to MRI. In our series, only low dose CT images were gathered. Therefore, we did not study the CT images for the value of detection of ENS.

In literature not only CT, MRI and [18F]FDG PET/CT were used for the determination of ENS. Steinkamp et al. demonstrated the value of ultrasound in the diagnosis of extracapsular spread reaching a specificity of 81.8 % and a sensitivity of 78.6 % in 110 patients with squamous cell carcinoma of the head and neck area26 and could be used for comparing various imaging modalities.

As mentioned in the introduction, the presence of ENS is of prognostic importance, but also dictates treatment. Two large randomized clinical trials6,7 showed improvement of survival in case of extranodal spread when postoperative concurrent chemoradiation (CCRT) is applied compared to radiotherapy alone. In a combined analysis of the 2 trials, Bernier et al. showed patients with positive margins and ENS benefitted most from chemoradiation.8 Other reports mention benefit in a subgroup of patients with ENS.5,27 Possibly the findings in this study could be used for the treatment planning as ENS is detected more reliable preoperatively. With the combination of MRI and [18F]FDG PET findings accuracy increased with 6% (83% vs 89%). However, large prospective trials are needed to confirm the results of this study and to determine the outcome of patients with ENS treated primarily with CCRT. In the cases where ENS remains unclear, histopathological assessment remains the gold standard.
CONCLUSION

This study shows that a combination of [18F]FDG PET findings (SUVmax cut off value 12) and MRI-findings ("infiltration of adjacent planes") for the detection of extranodal spread in pathological lymph nodes of head and neck cancer reaches a sensitivity of 80% and specificity 100%. When there is no ENS or doubt of ENS on MRI, [18F]FDG PET seems to have additional value since it improves sensitivity and resolves uncertainty in case of high FDG uptake. This benefit needs to be confirmed prospectively in a larger cohort. It can be expected that with future availability of [18F]FDG PET/MRI these combined measurements can be done on a more routine basis.
References