Iron Oxide Particle-enhanced Magnetic Resonance Imaging for Detection of Benign Lymph Nodes in the Head and Neck: How Reliable are the Results?

MEHRAN BAGHI1, MARTIN G. MACK2, JENS WAGENBLAST1, MARKUS HAMBEK1, JÖRG RIEGER3, SOTIRIOS BISDAS2, WOLFGANG GSTOETTNER1, KNUT ENGELS4, THOMAS VOGL2 and RAINALD KNECHT1

Departments of 1ENT-Surgery, 2Diagnostic and Interventional Radiology, 3Maxillofacial Surgery and 4Pathology, J.W. Goethe University, School of Medicine, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany

Abstract. Aim: To evaluate the accuracy of ultrasmall paramagnetic iron oxide (USPIO: Sinerem®)-enhanced MRI in patients with head and neck cancer and enlarged lymph nodes compared with current staging examinations using histology as a gold standard. Patients and Methods: Seventeen patients with a histologically proven squamous cell cancer of the head and neck (SCCHN) and different N-stages underwent a non-enhanced and a USPIO-enhanced MRI examination. Signal intensity (SI) was measured in a region of interest evaluation. Pathohistological examination was used as a reference. Results: On a patient basis, USPIO-enhanced MRI showed a higher specificity and diagnostic accuracy (94%) compared with non-enhanced MRI (53%). One patient showed a lymph node of 6 mm in the short axial diameter which was suggested as being metastatic in Sinerem®-enhanced MRI according to the enhancement pattern of Sinerem®. This patient was staged as N1 with Sinerem®-enhanced MRI. The histopathological examination did not confirm the Sinerem®-enhanced MRI result. Conclusion: The high values for the specificity and diagnostic accuracy of Sinerem®-enhanced MRI justifies further investigations with this contrast agent. USPIO-enhanced MRI could be advantageous in avoiding surgical overtreatment.

The N-staging of patients with head and neck cancer presenting with borderline-sized lymph nodes remains problematic and is mainly carried out by clinical examination and imaging studies. The current imaging techniques such as magnetic resonance imaging (MRI), computer tomography (CT) and ultrasonography (US) contribute to visualization of lymph nodes which may not be palpable on physical examination (1). These cross-sectional techniques use the node size and the presence of central necrosis as criteria for malignancy (2, 3). The diagnosis and the decision for operative treatment such as neck dissection depend mostly on measurement of nodal dimensions, such as maximum or minimum axial diameter, or ratios of maximum longitudinal to maximum transverse diameter. Thus the sensitivity of the current node size criterion in the detection of metastasis is very limited, as reported by Anzai et al. (4). To reduce the rate of inaccurate diagnoses, a smaller size criterion has been applied at the expense of specificity (4). Furthermore, studies have shown that the size criterion may differ depending on the level of the neck that was established by the American Joint Committee on Cancer (5) (AJCC). For instance, van den Brekel and co-workers have shown that a minimum transverse diameter of 7 mm for level II and 6 mm for the remainder of the neck revealed the optimal compromise between sensitivity and specificity in necks without palpable metastases (6). Using only the size criterion for the judgment of the lymph node is not enough. Van den Brekel indicated that in 25% of clinical N0-necks, micrometastases could be found (7).

In addition, the enhancement pattern, shape and grouping of the lymph nodes are further criteria for the judgment of the lymph node status but are usually of less importance. All of these criteria are controversial; none of them allow a reliable differentiation between benign and malignant lymph nodes. Consequently, morphological criteria such as the depiction of small tumor areas inside a lymph node will become more important as the contrast and spatial resolution of imaging techniques increases (8).

The current imaging techniques differentiate only between enlarged benign lymph nodes and large metastatic...
lymph nodes with central necrosis. Lymph node metastases in the head and neck will often be less than 10 mm, occasionally equal to or less than 6 mm in diameter, as reported in earlier studies (3, 9). There is also a need to know more about the functionality of the lymph nodes. New contrast agents such as intravenously injected small iron oxide particles (USPIO) such as Sinerem® pass through the vascular endothelium into the interstitium independently of their size and are taken up by normally functioning lymph nodes and inflamed lymph nodes, and phagocytosed by components of the reticuloendothelial system, such as macrophages or histiocytes. These normal lymph nodes show a signal intensity (SI) reduction on T2*- and T2-weighted MR images due to the effects of magnetic susceptibility and T2 shortening of the iron deposits. Metastatic lymph nodes, however, lose their mechanism for phagocytosis and, therefore, do not show the reduced SI, which potentially allows them to be differentiated from benign lymph nodes (Figure 1).

The purpose of our study was to determine the specificity and the diagnostic accuracy of USPIO-enhanced imaging in the evaluation of borderline-sized cervical lymph nodes by using pathological evaluation as the gold standard.

Table I. Clinical T and N staging with unenhanced-MRI.

<table>
<thead>
<tr>
<th>T-stage</th>
<th>N-stage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Patients and Methods

Patients. In this prospective study, 17 patients with a squamous cell carcinoma of the head and neck (SCCHN) were included. The staging examination consisted of clinical and ultrasound (US) examination, as well as precontrast MRI. All patients showed a minimum of 3 enlarged cervical lymph nodes between 6-13 mm in the short axial diameter independent of the location of the nodes. According to the results of the clinical examination, US evaluation and precontrast MRI, 9/17 patients were staged as N0 whereas in 8/17 patients, the clinician and radiologist reported suspicious single lymph nodes. These patients were staged as N+ (Table I). A total of 110 levels according to AJCC consisting of 550 lymph nodes equal in size or larger than 6 mm were removed. All the removed lymph nodes were identified with USPIO-MRI in the correct level. This study was approved by the ethics committee; informed consent was obtained from the patients.

Inclusion and exclusion criteria. Patient inclusion criteria were age older than 18 years and a confirmed primary SCCHN which was intended for neck dissection. Pregnant or lactating women were excluded. Patients who had previous radiation of this area were also excluded.

Contrast agent. The iron contrast agent Sinerem® (Guerbet, Paris, France) was provided as a lyophilized powder consisting of ultrasmall superparamagnetic particles covered with low-molecular-weight dextran, with a total particle diameter in solution between 170 and 210 Å (17-21 nm). Sinerem® (2.6 mg of iron per kg of body weight) was diluted in 100 mL of 0.9% saline solution and administered intravenously after precontrast MRI was performed in a single dose by drip infusion through an infusion filter (0.22 µm pore size) at a rate of 4 mL/min. Twenty-four to 36 hours after the application of Sinerem®, postcontrast MRI was performed.

Evaluation. Enlarged lymph nodes were evaluated by examining individual nodes with US and precontrast MRI. The suspicious nodes were grouped according to the guidelines of the American Joint Committee on Cancer (5) (AJCC) and the established level.
classification (10). The size and the signal intensity (SI) of the lymph nodes were measured on non-enhanced and Sinerem®-enhanced MRI using the T2-weighted TSE sequences using a region of interest (ROI) evaluation in relation to the background noise.

For each patient, SI measurements were taken of all suspicious lymph nodes and a further 10-15 benign lymph nodes for comparison, if available. Specificity was calculated in borderline-sized lymph nodes on a single node basis which were separately removed from the neck block by the surgeon. Patients with lymph nodes ≥6 mm in the short axial diameter were staged as N+ on precontrast images. Visual analysis for postcontrast MRI was based on the criteria reported by Anzai et al. (4). The following criteria were considered for classifying metastatic lymph nodes: No or almost no reduction of the signal of the lymph node; a central strong signal with darkening along the peripheral rim, and heterogeneous architecture; partial darkening whereby more than 50% of the node has an area of strong signal intensity with a heterogeneous architecture. The following criteria were considered for classifying the possibly metastatic lymph nodes: Less than 50% of node has a strong signal intensity with heterogeneous architecture. The following criteria were considered for classifying lymph nodes as non-metastatic: overall dark signal with speckles of subtle granularities with homogenous structure; overall dark signal intensity and a homogenous architecture.

The image evaluation was performed by two experienced head and neck radiologists by consensus. All images were discussed with an experienced head and neck surgeon who subsequently performed the neck dissection. The surgical plan, the indication for neck dissection as well as the extension of neck dissection were based on clinical and radiological evaluation, with the use of the information on size and shape obtained after US evaluation and precontrast MRI. The primary tumor was removed and selective neck dissection was performed within 10-14 days of USPIO-enhanced MRI. The specimen was resected and prepared separately by the same surgeon. Resected lymph nodes were cut into 1 mm serial sections by the pathologist prior to paraffin embedding. Paraffin blocks were cut into 2 µm sections. The sections were analyzed histopathologically by the same pathologist and were compared with those of unenhanced and Sinerem®-enhanced MRI by the radiologist and the surgeon. However, comparison of all lymph nodes was not possible, particularly in patients who underwent a unilateral neck dissection.

Statistical analysis. Statistical analysis was performed using the SPSS software (SPSS Inc., Chicago, IL, USA, 2004). Descriptive statistics were performed comparing the precontrast and postcontrast MRI results with the histological results of the lymph nodes. Specificity was stated on a single patient basis, determined as the number of true negative divided by the sum of true negative and false positive nodal status. The diagnostic accuracy was determined by the sum of true negative and true positive nodal status divided by the sum of all patients.

Results

Seventeen patients (14 male, 3 female) with a median age of 59 years (range, 42-69 years) were included in this prospective study. All patients tolerated the injection of Sinerem® well without any side-effects during or after application of this contrast agent. According to the diagnostic work-up without Sinerem® MRI, 9/17 patients were clinically staged as N0 and 8/17 patients were staged as N+. Eight patients underwent a bilateral selective (suprahoid) neck dissection (level 1-3); in 5 patients a bilateral neck dissection in level 1-4 was performed. Four patients underwent an unilateral selective (lateral) neck dissection (level 2-4). Sinerem® MRI showed N0-status in 16 patients. In one patient with a T1 supraglottic laryngeal cancer, a single lymph node was staged as metastatic, according to the criteria reported by Anzai et al. (4). This lymph node was 6 mm in the short axial diameter localized in level II. Histopathological examination of this lymph node in serial sections as described above showed no metastatic infiltration. This was the only false-positive lymph node in this study. The specificity and the diagnostic accuracy of USPIO-MRI was, on a patient basis 94% versus 53% for conventional staging consisting of palpation, US examination and precontrast MRI. Furthermore there were 80 lymph nodes in 12 patients which were ≥6 mm but ≤13 mm in short axial diameter in level I-IV; all 80 lymph nodes were detected as non-metastatic in USPIO MRI according to their signal intensity and the pattern of Sinerem®-enhancement (Figure 2a and b). In these selected patients, all 12 patients showed an N0-neck with USPIO-MRI (specificity and diagnostic accuracy 100%) whereas 7/12 patients showed an N0-neck on non-enhanced MRI (specificity 58%), using histology as reference (Table II).

Discussion

The nodal staging of head and neck cancer has a major influence on the treatment and prognosis of the patients. In the case of positive nodal status, a treatment with neck dissection or radiation is performed. In patients with a negative nodal status (N0), depending on the primary tumor site, a “wait and see strategy” or sentinel lymph node biopsy can be justified. However, the safe diagnosis of a nodal negative neck (N0) presenting with questionable and borderline-sized lymph nodes remains problematic and their treatment is a continuing source of controversy.

The size of the nodes and the presence of necrosis are most important criteria for the radiological evaluation of malignant lymph nodes. However, size alone as a criterion shows great variability; 6-30 mm is commonly used (6, 9). The optimal size criterion should be both sensitive and specific. In several studies to re-evaluate the size criterion for head and neck cancer, 39% of patients with N0 disease at ultrasonography had metastatic nodes at surgery (6, 11). Thus it is important to use a preoperative imaging method that does not use the size criterion alone but can also demonstrate functional changes inside the lymph nodes in case of nodal invasion.
Several reports have shown the efficacy of ultrasmall paramagnetic oxide particles for MR imaging of the head and neck (2, 3). Similar studies with ferumoxtran 10, another iron oxide agent, yielded a high sensitivity and specificity of this diagnostic modality for the detection of nodal metastases in the abdomen, chest and pelvis (12-18).

In terms of detection of nodal metastasis, the results of conventional MRI indicate that, in clinical practice, a more sensitive test or other criteria are needed in patients with a high risk of occult metastases. Neck dissection used only as a diagnostic tool is a highly invasive procedure that can cause a high morbidity (2, 19, 20). On the other hand, an undertreatment of the neck having probable occult metastatic lymph nodes is not acceptable and the presence of the untreated metastatic lymph nodes worsens the prognosis of these patients.

Our results indicate that USPIO-enhanced MRI is a highly specific imaging technique (specificity on a patient basis of 94%) for nodal staging in head and neck cancer patients, especially those with borderline enlarged lymph nodes, considering not only the size but also the pattern of enhancement of this contrast agent. Nevertheless, the detection of micrometastases remains further problematic due to the limited resolution of MR imaging sequences as reported by Mack et al. (2).

Table II. Nodal staging with and without Sinerem®-MRI in lymph nodes ≥6 mm ≤13 mm compared with staging based on histology.

<table>
<thead>
<tr>
<th>No. patients</th>
<th>T-stage</th>
<th>N-stage on MRI precontrast</th>
<th>N-stage on MRI postcontrast</th>
<th>N-stage on histology</th>
<th>No. LN ≥6 mm ≤13 mm</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T1</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>7</td>
<td>III,IV</td>
</tr>
<tr>
<td>1</td>
<td>T1</td>
<td>N2b</td>
<td>N0</td>
<td>N0</td>
<td>5</td>
<td>I,II,III</td>
</tr>
<tr>
<td>6</td>
<td>T2</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>36</td>
<td>II,III,IV</td>
</tr>
<tr>
<td>2</td>
<td>T2</td>
<td>N1</td>
<td>N0</td>
<td>N0</td>
<td>16</td>
<td>II,III,IV</td>
</tr>
<tr>
<td>1</td>
<td>T2</td>
<td>N2a</td>
<td>N0</td>
<td>N0</td>
<td>9</td>
<td>II,III,IV</td>
</tr>
<tr>
<td>1</td>
<td>T3</td>
<td>N1</td>
<td>N0</td>
<td>N0</td>
<td>7</td>
<td>I,II,III</td>
</tr>
</tbody>
</table>

LN: lymph nodes, N-precontrast: N-staging without Sinerem®-enhanced MRI (plain), N-postcontrast: N-staging with Sinerem®-enhanced MRI, N-histology: N-staging according to the histology (pN). Level: level of the lymph nodes according to the American Joint Committee on Cancer (5). Values represent the number of patients and number of lymph nodes ≥6 mm ≤13 mm in the short axial diameter seen in the plain MRI.
A limitation of our study was that only lymph nodes from the resected side were evaluated and included in the statistical analysis. Furthermore, our results do not confirm the rate of occult metastases reported in patients with SCCHN which vary from 20-40% depending on the primary tumor site (7-9, 11, 21). We suggest that this difference results from our selected group of patients who had small tumors (16/17 T1 or T2). Furthermore our staging examination was not only based on US evaluation, as currently performed, but also on USPIO-MRI evaluation. This could be another reason for the lack of patients with occult metastases in our study.

Nevertheless, this study shows that USPIO-enhanced MRI improves the specificity and the diagnostic accuracy (94% on a patient basis) of nodal staging in SCCHN patients, avoiding overtreatment and reducing postoperative morbidity. Comparing the logistic burden (2 MRI examinations within 36 hours) and the "high" costs of this diagnostic modality with the high operative risk and hospitalization for some patients, and the costs of a neck dissection for the health services, this diagnostic modality can be justified in a selected group of patients. Further investigations should verify the efficacy of USPIO-enhanced MRI, especially in patients with SCCHN and a questionable nodal status.

References