Preoperative Axillary Lymph Node Diagnosis Using Ultrasmall Particles of Iron Oxide Combined with MRT


In basic comparative studies (Mohr and Weißleder 1996), lymphotropic iron oxide compounds with storage in sinus histiocytes of lymph nodes and gadolinium (iD) DTPA-PGM were tested; the results indicated that both categories of compounds improved the differential diagnosis between tumor-free and cancer-infiltrated lymph nodes, irrespective of size.

While iron oxides are already in uses in clinical studies, GDDTPA-PGM is still being evaluated in preclinical study programs.

After various experimental studies on different sites of primaries, a first stringently statistically controlled study has been now performed to evaluate USPIO in the diagnosis in breast cancer patients (Stets et al. 2000, 2002). Qualitative and quantitative parameters were evaluated in axillary lymph nodes by USPIO contrast agent and MR. The studies were planned on the basis of experience in different lymph node basins, referred to other tumor categories.

Data from two scientific centers taking part in a multicenter trial were obtained (Heywang-Köbrunner et al. 2002). Each of the diagnostic centers used the same techniques. This made it possible to pool the cases.

It was shown that cancer-infiltrated node areas with destruction of the pre-existent node architecture were characterized by markedly less iron oxide storage than elsewhere, caused by the loss of the so-called sinus histiocytes that are active in phagocytosis. According to experiences already available, the presence of USPIO in preserved lymph node structures can be detected with optimal accuracy by MRI. Iron oxide acts as a paramagnetic agent and causes signal drop out, particularly in T2-weighted and T2-sequences.

In the two radiodiagnostic institutes taking part in the study, 21 patients were collected for the planned investigations. The inclusion criteria were breast cancer and scheduled axillary dissection after informed consent.

Standardized MR without contrast agent (plain MRI) was followed by intravenous administration of 2.6 mg USPIO/kg bodyweight (30-min infusion with filtration). Postcontrast MRI (using the same pulse sequences as for the precontrast studies) was performed 24–36 h after USPIO administration.

The en bloc axillary specimens were precisely marked for comparative studies with the imaging analyses. Deviations from standard axillary dissection were only allowed when suggestive lymph nodes were located outside the anticipated surgical field of axillary exploration.

There was a high drop-out rate among patients in the study, for various reasons.

In the preliminary study only 9 cases (52 lymph nodes) could be evaluable.

Table 1 summarizes the results of lymph node evaluation by two radiologists and the investigating site pathologists.

<table>
<thead>
<tr>
<th>Size category</th>
<th>&lt; 5 mm</th>
<th>5 mm to &lt; 10 mm</th>
<th>10 mm to &lt; 15 mm</th>
<th>&gt;15 mm</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Benign</td>
<td>14</td>
<td>10</td>
<td>1</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Malignant</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>All</td>
<td>24</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>52</td>
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</tbody>
</table>
The evaluation procedure that gave the best results for combined pre- and postcontrast MRI was based on the following parameters:

- Transverse lymph node diameter ≤6 mm rather than >6 mm
- Visual assessment of signal change on T1 SE, T2 FSE and PSIF
- Quantitative ratios of signal change SCR to T1 SE, T2 FSE, and PSIF.

On the basis of these parameters, 88% of the lymph nodes were correctly classified with a sensitivity of 85% and a specificity of 92%.

Finally, an accuracy of 87% was obtained when transverse diameter, SCR T2 FSE and visual assessment of signal change on T2 FSE were used as classification parameters.

Among these single parameters, only the transverse diameter and the visual assessment of signal change on T2FSE proved to be significant discriminators of benign versus malignant lymph nodes \((P=0.013 \text{ and } P=0.007, \text{ respectively})\). The most suggestive area of the lymph nodes was determined visually.

The procedures for determination of these areas were as follows:

- Comparison of pre- and postcontrast scans revealed differences.

When no suspicious areas could be detected, areas showing either no change or signal intensification were chosen.

If neither of these applied, the areas of the lymph node with the widest transverse diameter were chosen.

For evaluation of significance of pre- and postcontrast results areas with iso- or hyperintense signal (referred to muscle) on T2 FSE were searched for. If this was not successful, areas with the same characteristics were searched for on FISP.

The signal intensity on the postcontrast T2 FSE scans and the change between pre- and postcontrast T1 SE, T2 FSE and the FISP was recorded as a signal increase, no change, or a signal decrease.

Quantitative evaluations were performed in regions of interest (ROIs):

- Measurement of the representative ROI, care being taken that ROIs were included only on tissue type
- As a control, a second ROI sited in the fatty tissue around the lymph node was examined, in order to normalize inhomogeneous reception of the surface coil and differences in the adjustment of the MR unit between the examinations.

The following ratios were calculated:

- Signal intensity ratio (SIR) in the precontrast study:
  - \(\text{SIR pre}=\text{(SIR lymph node) pre}\)
  - \(\text{SIR post}=\text{(SI lymph node) post}\)
  - \(\text{(SI adjacent fat) post}\)

The histopathological examination was based on systematic work-up of the entire dissection bloc in one site. In the other site the nodal sampling was performed by the surgeon, giving the exact position of the node to the pathologist.

The following features of each lymph node were included in the statistical evaluation in an SPSS for Windows, vers. 9.0 database:

Precontrast: homogeneity, SIR T1 SE, SIR T2 FSE, SIR FISP visual assessment of signal intensity

Postcontrast: homogeneity SIR T1 SE, SIR T2 FSE, SIR FISP, visual assessment of signal on T2 FSE

The histopathological classification of each single lymph node as

- Completely involved
- Partly involved
- Not involved

The data were entered in a logistic regression analysis. The best results were obtained with the following parameters:

- Transverse lymph node diameter \((≤6 \text{ mm rather than } >6 \text{ mm})\)
- Visual assessment of signal change on T1 SE, T2 FSE and PSIF
- Quantitative ratios concerning signal change SCR on T1 SE, T2 FSE, and PSIF

On the basis of these parameters 88% of the lymph nodes were correctly classified (sensitivity 85%, specificity 92%).

By backward selection the following parameters were eliminated:

- SCR of PSIF
- SCR of T1SE and visual assessment of signal change on T1-SE and on PSIF