Preoperative nodal staging of urinary bladder cancer with MRI using ultra small super paramagnetic iron oxide particles

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The status of the lymph node largely dictates the management of the primary tumor. In order to obtain the pre-operative lymph node status the physician now depends on CT, MRI or PET examinations which only have a low sensitivity. In this study we will prove that we can increase the sensitivity pre-operative by using a new imaging method: the MR-lymphography (MRL). With MRL we can increase sensitivity from 69% to 88% and the Negative Predictive Value from 73% to 82%. This gives us the opportunity to evaluate if we can replace the PLND by non-invasive MRL in the future.

1. Introduction

Detection of lymph node metastases has very important clinical consequences. If metastatic disease is present, usually curative cystectomy will not be performed anymore. Current imaging techniques can only show nodal size. Scheidler et al. have shown, that both CT and two-dimensional (2D) MRI perform better than lymphography, and that there is a trend towards better performance of 2D MRI versus CT [1].

Recently Jager and co-workers showed, that with three-dimensional (3D) high resolution MRI, not only nodal size but also nodal shape can be determined. Taking in account the nodal shape also, improved their results. However, in their study metastases in normal size lymph nodes (< 10 mm in flat-oval nodes, < 8 mm in round nodes) were still missed, resulting in low sensitivity [2].

On fast dynamic MRI normal size metastatic nodes show early enhancement, however, also non-metastatic nodes may enhance. Therefore, fast dynamic contrast enhanced MRI increases sensitivity, but decreases specificity [3].

Despite the fact that Ultra Small Super Paramagnetic Iron Oxide Particles (USPIO) have been reported to show internal lymph node morphology, metastases in nodes smaller than 10 mm could not be detected [4]. A possible explanation may be the fact that sequences and contrast dosage were not optimal in this study.

2. Purpose

The purpose of this study is to increase the sensitivity of MRI in detecting lymph node metastases, that is to recognize metastases in normal size nodes, with maintaining high specificity by using an optimal dose of USPIO and high resolution 3D T1-weighted and 2D T2*-weighted sequences.

3. Material and Method

In a prospective study 37 patients with histologically proven invasive Urinary Bladder (UBC) were examined at 1.5 T (Siemens Vision, Erlangen Germany) using a body phased-array coil. MRI was performed before and 24-36 hours after intravenous infusion of USPIO (particle size 20-50 nm; Sinerem, Guerbet, Paris, France) at a dose of 2.6 mg Fe/kg. MR images were acquired using high resolution 3D T1-weighted (MP-RAGE, pixel size 1.4 x 1.4 x1.4 mm) and 2D T2*-weighted sequences (MEDIC, pixel size 0.8 x 0.8 x 3.0 mm). The T2*-weighted MEDIC sequences were acquired in planes parallel to the iliac vessels ("obturator" planes) and in coronal planes parallel to the obturator nerve. The FLASH T2*-weighted sequences in the axial plane. The 3D sequences were evaluated by soft-copy reading using multiple planes.

On the pre-contrast MRI lymph nodes were rated positive based on size and shape criteria. described by Jager et al. [2], flat-oval node > 10 mm, round node > 8mm. On the post-contrast MRI lymph nodes were rated positive if they showed focal or total lack of signal loss on the T2*-weighted sequence. The MR-findings were prospectively evaluated by one experienced observer in each center (JOB, MGH* and MT**).

Results of pre- and post-USPIO MRI were compared with histopathology on patient-to-patient basis. 34 patients had lymphadenectomy, 3 had a positive image guided biopsy. Statistical analysis was performed to calculate differences in sensitivity, specificity, negative- and positive predictive value, using the χ^2-test.

4. Results

During the slow, 30 minute, infusion of the USPIO-contrast only one patient showed minor side effects (low back pain), which was due to a too rapid infusion. After slowing down the infusion rate the symptoms decreased, and no further treatment was needed.

Normal nodal tissue showed signal loss 24-36 hours post injection. Metastases showed equal or higher signal. On the 3D T1-weighted MP-RAGE sequence vessels, especially veins, showed high signal intensity, thus resulting in better separation from nodes. On the MEDIC sequence in most patients the vessels showed low SI.

Pre contrast MRI was true positive in 11 patients, true negative in 17, false negative in 5 and false positive in 4. With post-USPIO MRI 14 patients were true positive, 18 true negative, 2 false negative and 3 false positive. Sensitivity and negative predictive value showed a significant improvement using post-USPIO, respectively from 64% to 88%, and 73% to 82%, with both p values < 0.001. Five out of the 16 patients had metastases in normal size nodes (< 8 mm). In 3 of them metastases could be detected prospectively based on post-USPIO images only. The size of the metastases in these nodes ranged from 7 to 4 mm. All missed metastases were present in very small nodes, < 4 mm. Specificity and positive predictive value increased from 81% to 86% and 77% to 90% respectively, this increase was also significant (specificity $p<0.05$, PPV $p<0.001$). In 1 patient an enlarged reactive node could be correctly recognized as non-metatstatic by its decreased SI on the post-USPIO images.

5. Discussion

On post-USPIO MRI the internal nodal structure can be visualized even in small (< 8 mm) nodes. Thus it is possible to separate normal lymphatic tissue from metastases. This results in a significant better recognition of metastases in normal size nodes. Sensitivity improved from 69% to 88%. Possible explanations for these better results compared to earlier studies [4] are, the combination of the use of a 3D T1-weighted and a high resolution T2*weighted sequence, a higher contrast dose, and the use of non-axial "obturatur planes" both of sagittal and coronal orientation.

Thanks to the visualization on post-USPIO MRI of potential small metastatic nodes outside the routine surgical field-of-view in 5 patients lymph node dissection was positive, which otherwise would have been negative because the nodes were outside the "surgical field of view".

The findings of post-USPIO MRI have important clinical consequences. Determination of presence and location of small metastatic nodes, will improve accuracy of laparoscopic- and laparotomic lymph node dissection. Also, due to higher accuracy of biopsy and surgical node dissection, there may be a shift from laparotomic- towards laparoscopic node dissection and towards biopsy. Finally, the high NPV may result in replacement of surgical node dissection, which will lead to reduced morbidity and a reduction of costs

Future prospects

In the future only the post-USPIO examination may be sufficient to make an accurate diagnosis. Low SI normal nodes can be clearly separated from metastases on both post-USPIO 3D T1-weighted and high resolution T2*-weighted sequences without the need to compare with pre contrast images. A node is metastatic if on both sequences there is an area with absence of low SI.

6. Conclusions/Summary

1. This prospective study in 37 patients with UBC shows, that USPIO is well tolerated, and that post-USPIO MRI significantly improves sensitivity, and negative predictive value of nodal staging from 64% to 88%, 73% to 80% respectively.
2. In 3 out of 5 patients with USPIO MRI small metastases (7-4 mm) in small (< 8 mm) lymph nodes were detected.
3. USPIO MRI may be performed using only a combination of two sequences: a 3D T1-weighted, and a high resolution T2*-weighted sequence.
4. Further multi-center studies to reproduce these results are promising and needed.

7. References

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