Peripheral zone prostate cancer: Pre-treatment evaluation with MR and 3D $^1$H MR spectroscopic imaging - correlation with pathologic findings

Poster No.: C-1385  
Congress: ECR 2010  
Type: Scientific Exhibit  
Topic: Genitourinary  
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Keywords: Prostate Cancer, MR Spectroscopy, Endorectal MRI  
DOI: 10.1594/ecr2010/C-1385

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Purpose

The aims of this study were: to assess the sensitivity, specificity, and accuracy of endorectal MRI and 3D MRSI in the diagnosis of peripherical zone prostate cancer in patients with high PSA levels and biopsy-proven prostate carcinoma, candidate to radical prostatectomy; to find a cut-off value of [(Cho + Cr)/Cit ratio in order to discriminate between normal peripherical zone tissue and cancer; to dimostrate a correlation between (Cho+Cr)/Cit ratio and histologic Gleason score.

Methods and Materials

Our retrospective study included 70 consecutive patients with US biopsy-proven prostate carcinoma who were referred for endorectal MRI prior to radical prostatectomy between June 2006 and April 2007. Of these patients, 14 were excluded because of previous hormone/radiation therapy treatment or because MRI was not done. Step-section pathological specimens were available in 52 patients (median age 65 years; age range 48-77 years; median PSA 10.37 ng/mL; PSA range 4.2-39 ng/mL). MR image acquisition protocol MRI and MRS were performed on a 1.5-T-whole-body MR imager (Magnetom Symphony Maestro; Siemens Medical Solutions, Erlangen, Germany) with a pelvic phased-array coil and an endorectal coil (MRInnervu; Medrad, Indianola, USA) for signal reception. Sequences acquired included thin-section high-spatial-resolution sagittal, axial and coronal T2-weighted fast spin-echo images (FSE) of the prostate and seminal vesicle with the following parameter: TR 4500 ms; TE 107 ms; slice thickness 3.0 mm; FoV 160 mm; Gap 0.8 mm; matrix 256 9 256; NEX 2. Our protocol included also T1-weighted FSE sequence (TR 500 ms, TE 15 ms, slice thickness 3.0 mm, FoV 160 mm, Gap 0.8 mm, matrix 256 9 256, NEX 2) to detect nodal disease and post-biopsy intraglandular hemorrhage. After review of the axial T2-weighted images, an MRSI volume was selected by the radiologist to maximize coverage of the prostate while minimizing the inclusion of periprostatic fat and rectal air. Three dimensional MRSI data were acquired using a waterand lipid-suppressed double spin-echo point-resolved spectroscopy (PRESS) sequence that used spectral-spatial pulses for the two 180 excitation pulses. At the end of the examination the spectra were postprocessed and evaluated by two experienced radiologists (about 7 years of experience). For all voxels, the (Cho + Cr)/Cit was calculated.

At pathologic analysis, a Gleason score was assigned to the whole cancer in the specimen. Besides, cancer foci were outlined in ink by the pathologist on whole-mount, apical, and seminal vesicle slices in order to result grossly visible and photographed. These histological findings constituted our tumor maps. The radiologists, working together, matched the histopathologic step sections with the most closely corresponding
T2-weighted transverse MR images. The radiologist outlined the tumor on the registered MR and MRS images and indicated the voxels covering tumorous lesions as "malignant voxels" and voxels covering non-suspicious prostate tissue as "normal voxels".

**Results**

All patients, who underwent MRI and MRS followed by radical prostatectomy, were included in the final analysis of spectroscopy data. Step-section histopathology demonstrated stage pT2 disease in 18 patients and pT3 in eight patients (unilateral extracapsular extension n = 2, bilateral n = 0, seminal vesicle extension n = 0). In these 52 patients, a total of 86 locations of cancer were identified with step-section pathologic evaluation.

Biopsy correctly detected 74 locations with 12 false-negative and six false-positive findings (sensitivity of 86%, specificity of 67%, accuracy of 83%, NPV of 50%, and PPV of 92%); MRI correctly detected 72 locations with 14 false-negative and two false-positive findings (sensitivity of 84%, specificity of 90%, accuracy of 93%, NPV of 53%, and PPV of 97%); MRS correctly detected 72 locations with 14 false-negative and four false-positive findings (sensitivity of 84%, specificity of 78%, accuracy of 88%, NPV of 50%, and PPV of 95%); MRI + MRS correctly detected 78 locations with eight false-negative and four false-positive findings (sensitivity of 91%, specificity of 88%, accuracy of 90%, NPV of 50%, and PPV of 95%). Sensitivity, specificity, accuracy, and positive and NPVs of biopsy, MRI, MRS, and MRI + MRS for lobar localization of prostate cancer are listed in Table 1 and histogram in Fig. 1 shows the gain in sensitivity, specificity, accuracy, PPV and NPV of MRI + MRS than biopsy. Using Cohen’s test we compared the true positive values of the different diagnostic techniques (biopsy, MRI and MRS alone and MRI + MRS) with the histopathologic results, to evaluate the degree of agreement between the different diagnostic methods and the gold standard (histology). Cohen’s test showed that biopsy had a lower degree of agreement with histology than MRI + MRS combined (0.559, moderate agreement versus 0.735, good agreement) [8] (Table 2). Retrospectively, basing on whole-mount sections and using a dedicated software we merged histopathologic sections with the corresponding T2-w images in order to obtain "neoplastic spectra" (n = 74) from the malignant voxel exactly enclosed within the neoplastic area outlined.
in ink from the pathologist, and "control spectra" 
(n = 132) from the voxels out of the signed neoplastic 
areas(Fig 2). We obtained also related (Cho + Cr)/Cit 
ratios; the mean peak area ratio of (Cho + Cr)/Cit in 
tumorous lesions was 2.74 (±4,6) and in control voxels 
0.25 (±0.16). The difference regarding the (Cho + Cr)/ 
Cit ratio was highly significant between tumor and 
control voxels (P < 0.001).

We classified the obtained spectra as normal if 
(Cho + Cr)/Cit ratio was <2 SD, uncertain if ratio was 
<2-3 SD> and pathologic if ratio was >3 SD from the 
normal. On this basis we find a cut-off value (0.47) that 
may be used to discriminate between normal tissue (<2 
SD or <2-3 SD>) and cancer (>3 SD) in peripheral 
zone(Table 3).

The ROC curve confirmed our cut-off as a very good 
one (sensitivity 100%, specificity 89.4 (Fig. 3). 
Furthermore, we classified patients of our study based 
on Gleason score resulting from histologic analysis. We 
obtained five degrees of Gleason score (3 + 3, 3 + 4, 
4 + 3, 3 + 5, and 4 + 5). For each group we plotted 
the different values of Cho + Cr)/Cit ratio and we 
demonstrated (Fig. 4) a significant correlation between 
(Cho + Cr)/Cit ratio and Gleason score (r = 0.5816, 
P < 0.0001).
Fig. 1: Figure 1: The histogram shows true positive (TP), true negative (TN), false-positive (FP), and false-negative (FN) value of the different methods compared with histology. Combined MRI and MRS shows a gain in TP and reduction on FP and FN compared with biopsy.
**Fig. 2:** Fusion imaging of histology, MRI and MRS and related neoplastic spectrum.

**Table 1:**

<table>
<thead>
<tr>
<th></th>
<th>% Sensitivity</th>
<th>Specificity</th>
<th>% Accuracy</th>
<th>% PPV</th>
<th>% NPV</th>
</tr>
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<tbody>
<tr>
<td>Biopsy</td>
<td>86</td>
<td>67</td>
<td>83</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td>MRI</td>
<td>84</td>
<td>89</td>
<td>85</td>
<td>97</td>
<td>53</td>
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<tr>
<td>MRS</td>
<td>84</td>
<td>78</td>
<td>83</td>
<td>95</td>
<td>50</td>
</tr>
<tr>
<td>MRI + MRS</td>
<td>91</td>
<td>78</td>
<td>88</td>
<td>95</td>
<td>64</td>
</tr>
</tbody>
</table>

**Fig. 3:** Table 1: Sensitivity, specificity, accuracy, and positive and NPVs of biopsy, MRI, MRS, and MRI + MRS for lobar localization of prostate cancer
Table 2: Cohen’s test

<table>
<thead>
<tr>
<th></th>
<th>K-value</th>
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<tbody>
<tr>
<td>Biopsy</td>
<td>0.559</td>
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<tr>
<td>MRI</td>
<td>0.581</td>
</tr>
<tr>
<td>MRS</td>
<td>0.563</td>
</tr>
<tr>
<td>MRI + MRS</td>
<td>0.735</td>
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Fig. 4: Table 2: Cohen’s test

(Cho + Cr)/Cit

<table>
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<th>(Cho + Cr)/Cit</th>
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<tr>
<td>Normal</td>
<td>&lt;0.47</td>
</tr>
<tr>
<td>Cancer</td>
<td>&gt;0.47</td>
</tr>
</tbody>
</table>

Fig. 5: Table 3: the cut-off value for (Cho + Cr)/Cit ratio
Fig. 6: Fig. 3:Sensitivity and specificity of ROC curves
Fig. 7: Correlation between (Cho + Cr)/Cit ratio and Gleason score.
Conclusion

In our study, we evaluated the addition of MRS to clinical MRI to increase the specificity of MRI in tumor detection and localization[15] in patients who underwent prostatectomy. The accuracy we obtained using combined MRI and MRS for tumor lateralization(right or left prostatic lobe) was 88%, as indicated in the literature [6]. A negative result with combined MRI and MRS excluded the presence of cancer with high probability (NPV 64% vs. 53% of MRI alone)(Fig. 5).Our study showed also that we can use the cut-off value of (Cho + Cr)/Cit ratio of 0.47 to discriminate between cancer and normal prostatic tissue in the peripheral zone (sensitivity 89.2%; specificity 91%, P = 0.0001).Preliminary findings suggest that small (<5 mm),low-grade tumors may be undetected with MRS because the severity of metabolite alteration correlates with tumor aggressiveness. High-grade cancers (Gleason scores 7 and 8) revealed highly elevated choline resonances, whereas lower grade tumors (Gleason scores 4 and 5) showed slightly elevated choline levels only [16].We believe that clinical implications of improved prostate cancer localization with MRS apply (a) for patients with increasing PSA levels and results of negative US-guided biopsy (for suspicious lesions); (b) for evaluation of tumor location and of the distance to the neurovascular bundle and the prostate capsule to determine if nerve-sparing surgery is possible; and (c) for planning of intensity-modulated radiation therapy [22],which requires exact localization of the prostate cancer to administer an extra boost of radiation in addition to the normal dose.

In conclusion, findings in this study demonstrate the potential usefulness of combined morphologic and metabolic information about prostate cancer in clinical practice and provide an analysis of this new method. Our findings show that the addition of MRS to MRI provides better detection and localization of prostate cancer, with sensitivity, accuracy, and NPV higher than those with MRI alone determining which voxels contain cancer and which are benign. This suggests that if this technique is included in the MRI protocol, the localization of prostate cancer in patients will improve.

Images for this section:
Fig. 1: Axial T2-weighted images from an FSE sequence of a 61-year old patient with a PSA level of 8.7 ng/mL and a histologically proven prostate carcinoma of the right side (E) with demonstration of a tumor voxel (A, B) and a control benign voxel from the opposite side (C, D)
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