



# Combined MRI and MR Spectroscopy of the Prostate Before Radical Prostatectomy

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**OBJECTIVE.** The purpose of this study was to evaluate a routine protocol for combined MR and spectroscopic imaging of the prostate for staging accuracy.

**SUBJECTS AND METHODS.** Fifty patients with biopsy-proven prostate carcinoma were examined with our sequence protocol, which consisted of T2-weighted fast spin-echo sequences and a pelvic T1-weighted spin-echo sequence. For spectroscopy, we used a 3D chemical shift imaging (CSI) spin-echo sequence. Image interpretation was performed by two radiologists. The total number of tumor voxels and tumor voxels per slice were counted to estimate the tumor volume in every patient. The potential of MR spectroscopy to differentiate between T2 and T3 tumors, based on the estimated tumor volumes, was compared with the staging performance of MRI.

**RESULTS.** The MR measurement time was 19.01 minutes, and the total procedure time averaged 35 minutes. Seventy-six percent of the spectroscopic examinations were successful. Statistically significant differences in the number of tumor voxels per slice and tumor volumes were found between T2 and T3 tumors. The descriptive parameters of MRI and MR spectroscopy did not differ significantly; sensitivity and specificity were 75% and 87%, respectively, for MRI and 88% and 70%, respectively, for MR spectroscopy. The combination of both methods resulted in only a slight improvement in staging performance and was not statistically significant.

**CONCLUSION.** Combined MRI and MR spectroscopy of the prostate has no diagnostic advantage in staging performance over MRI alone. The mean tumor volumes, estimated by MR spectroscopy, differ statistically significantly between T2 and T3 tumors.

**M**RI of the prostate with a combined pelvic and endorectal coil has become an accepted method for staging prostate cancer [1, 2]. For the clinically important discrimination between T2 and T3 prostate carcinomas, MRI has proved to be a specific method, but it also reveals considerable variability in staging accuracy [3–8]. Proton MR spectroscopic imaging of the prostate with evaluation of the metabolites choline, creatine, and citrate is a promising method for detecting prostate carcinomas that show a higher choline and a reduced citrate level in comparison with healthy prostate tissue [9, 10]. Proton MR spectroscopy of the prostate is also useful for monitoring hormonal or irradiation therapies of prostate cancer [11, 12]. In a preliminary study, MR spectroscopy showed some advantage for the detection of transitional zone prostate cancers, which are difficult to detect by MRI alone [13]. In addition, 3D spectroscopy of the prostate is proposed as a means of improving the accu-

racy of diagnosis of extracapsular extension for the less experienced interpreter, compared with MRI alone, in consideration of tumor extent estimated by MR spectroscopic imaging [14]. A major disadvantage of MRI and MR spectroscopy of the prostate is the long examination time coupled with discomfort of the patient and a difficult integration in the clinical routine.

## Subjects and Methods

### Patients

The present study was approved by the local ethics committee and informed consent was obtained from all patients. In total, 50 patients with a biopsy-proven prostate carcinoma were examined with our combined imaging protocol before radical prostatectomy. The age range of the patients was 48 to 78 years; the median patient age was 66 years. The prostate-specific antigen (PSA) levels ranged from 3.23 ng/mL up to 36.1 ng/mL with a mean PSA level of 8.5 ng/mL ( $\pm$  5.9 ng/mL). The pathologic Gleason scores ranged from 4 to 9 with a median Gleason score of 6.

**Keywords:** genitourinary tract imaging, MRI, prostate

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## Inclusion and Exclusion Criteria

Patients with a histologically proven prostate carcinoma without any contraindications for an MRI examination of the prostate were included in our study. Patients with previous surgical or irradiation therapies or under ongoing hormonal therapy were not included. Patients who had undergone a prostate biopsy up to 3 weeks before MRI and spectroscopy were also not included.

## MRI

Imaging of the prostate was performed on a 1.5-T scanner (Magnetom Sonata; Siemens Medical Solutions) using a combined phased-array coil and endorectal coil (MRInnervu, Medrad). The whole prostate and the seminal vesicals were visualized in every patient. The sequence protocol consisted of unenhanced axial, coronal, and sagittal T2-weighted fast spin-echo sequences and a T1-weighted spin-echo sequence for the pelvis.

## Sequence Data

Sequence data were as follows. For fast spin-echo transversal: TR/TE, 4,400/109; echo-train length, 23; slice thickness, 3 mm; field of view, 180 mm; interslice gap, 0.3 mm; matrix,  $205 \times 256$ . For fast spin-echo sagittal: 4,290/109; echo-train length, 25; slice thickness, 4 mm; field of view, 200 mm; interslice gap, 0.4 mm; matrix,  $205 \times 256$ . For fast spin-echo coronal: 4,160/106; echo-train length, 25; slice thickness, 3 mm; field of view, 200 mm; interslice gap, 0.3 mm; matrix,  $205 \times 256$ . For T1 spin-echo: 591/14; slice thickness, 5.5 mm; field of view, 350 mm; interslice gap, 0.6 mm; matrix,  $215 \times 512$ .

## Three-Dimensional Proton MR Spectroscopy

MR spectroscopy data were acquired with a 3D chemical shift imaging spin-echo sequence [15] on a Magnetom Sonata 1.5-T scanner (Siemens Medical Solutions). An endorectal coil was used for signal reception allowing a maximum signal-to-noise ratio. In-phase detection of the citrate signal was obtained with a TE of 120 milliseconds. By choosing k-space-weighted acquisition, the scanning time was 10 minutes 45 seconds for a  $12 \times 12 \times 8$  scan with a TR of 1,300 milliseconds and four averages. With the application of a Hamming filter, the voxel size was increased from a nominal  $6.7 \times 6.7 \times 10$  mm to an effective size of  $10 \times 10 \times 15$  mm [16]. The nominal voxel size was  $0.45 \text{ cm}^3$ . Shimming was performed by applying the field map-based automatic shimming procedure of the system. The volume of interest was positioned closely around the prostate, using a reference frequency corresponding to 2.9 parts per million. Simultaneous spectral suppression of the water and the lipid signals was performed as described by Mescher et al. [17]. Six spatially selective saturation bands were interactively positioned. After post-

processing of the time domain by zero filling from 1 to 1,024 data points, multiplication by a Hanning filter, Fourier transformation, and phase and baseline correction, integral values were obtained by fitting gaussian lineshape functions to the resulting absorption spectra. For further analysis, the integral ratios of (choline + creatine) / citrate were used. By using the reported ratios, interpatient normalization is achieved because all the systematic variabilities, the most prominent influence of which is the coil loading, are cancelled out. All obtained image planes were used as reference images for an exact positioning of the volume of interest and the selective saturation bands.

## MR Image Analysis

All images were analyzed prospectively by two independent interpreters with 7 and 2 years of experience in endorectal MRI, who were not aware of the patients' clinical data except that all patients had biopsy-proven prostate cancer. For evaluation of image quality, a scoring system was applied as follows: 1 = poor image quality, imaging should be repeated; 2 = moderate image quality but sufficient for analysis; and 3 = good image quality. The criteria for the diagnosis of extracapsular extension were an irregular shape of the capsule, a large tumor with a broad contact to the capsule, and an obliteration of the retroprostatic angle. These criteria were included in a general impression to the interpreter. Radiologic staging was performed according to the international TNM classification, and diagnosis was made in consensus. The detailed written histopathologic results of the transversely sectioned prostate gland served as the gold standard for the verification of the radiologic staging.

## Three-Dimensional MR Spectroscopic Imaging Evaluation

After staging by means of imaging was completed, the spectroscopic data sets of every patient were provided and analyzed retrospectively. The data of spectroscopic imaging were overlaid on the T2-weighted transverse reference images, and voxels covering tumorous lesions were identified. Voxels were considered to be sufficient for analysis if one of the metabolites had a signal-to-noise ratio of at least 4:1. According to a previous study by our group [18], tumor voxels were identified when the ratio of (choline + creatine) / citrate was equal to or higher than 1.1.

The number of tumor voxels per slice was counted and served as a basis for the estimation of the tumor extent. A receiver operating characteristic (ROC) analysis was calculated to identify the best cut-point value of the number of tumor voxels to be most predictive for a T3 carcinoma.

Tumor volumes were calculated by multiplication of the nominal voxel size ( $0.45 \text{ cm}^3$ ) with the number of tumor voxels. The histopathologic results, pro-

vided as written reports and including the pathologic TNM result, served as the gold standard.

## Statistical Analysis

All statistical analyses were performed with the Bias software and SPSS (version 12.0, Statistical Package for the Social Sciences) for Windows (Microsoft). Descriptive statistical data, including sensitivity, specificity, positive and negative predictive values, and Youden indexes, were determined for MRI and MR spectroscopy.

The McNemar test was used to compare sensitivities and specificities of MRI with MR spectroscopy. Preoperative PSA levels, pathologic Gleason scores, total amount of tumor voxels, and tumor voxels per slice of patients with T2 and T3 tumors were compared by using the Mann-Whitney *U* test.

To evaluate the accuracy of the diagnostic variable tumor voxels per slice, ROC analysis was performed. The optimal cut point value was determined as the number of tumor voxels per slice yielding the highest Youden index (sensitivity + specificity - 1).

## Results

### Histopathologic Findings

Of 50 patients included in this study, nine had extracapsular extension of the prostate carcinoma (stage T3 prostate carcinoma) and 41 patients had cancer confined to the prostatic gland (stage T2 prostate carcinoma).

### Image Quality and Spectral Quality

All images were of good quality, so no examination had to be repeated. MR spectroscopic imaging was sufficient for analysis in 38 patients, in whom one of the metabolites—choline, creatine, or citrate—had a signal-to-noise ratio of at least 4:1. Thus, for the comparison of MRI with MR spectroscopy, 38 patients were evaluated. Of these 38 patients, eight had extracapsular extension of the tumor (stage T3 prostate carcinoma) and 30 had cancer confined to the gland (stage T2 prostate carcinoma).

### Duration of Examination and Postprocessing

The net examination time for imaging was 8 minutes 56 seconds and the net examination time for spectroscopy was 10 minutes 45 seconds, resulting in a complete duration of 19 minutes 1 second for combined imaging and spectroscopy. The preparation of the patients for the examination, including the exact positioning of the endorectal coil and fitting of the body coil, took 15 minutes on average, so the complete duration for the whole examination procedure

**TABLE 1: Descriptive Statistical Data of MRI and MR Spectroscopic Imaging**

|                                                      | Sensitivity (%) | Specificity (%) | False-Positive Results (%) | False-Negative Results (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Youden Index (%) |
|------------------------------------------------------|-----------------|-----------------|----------------------------|----------------------------|-------------------------------|-------------------------------|------------------|
| MRI alone                                            | 75              | 87              | 13                         | 25                         | 60                            | 93                            | 62               |
| MR spectroscopy (3.88-voxel threshold)               | 88              | 70              | 30                         | 13                         | 44                            | 95                            | 58               |
| MR spectroscopy (6.25-voxel threshold)               | 63              | 93              | 7                          | 38                         | 71                            | 90                            | 56               |
| Combined MRI and spectroscopy (3.88-voxel threshold) | 75              | 93              | 7                          | 25                         | 75                            | 93                            | 68               |
| Combined MRI and spectroscopy (6.25-voxel threshold) | 50              | 100             | 0                          | 50                         | 100                           | 88                            | 50               |

was roughly 35 minutes. For postprocessing of the spectroscopic data sets, a mean time of 30 minutes per patient was estimated. This included the identification of voxels covering tumorous prostate tissue, manual phase correction, and calculation of the choline + creatine / citrate ratio.

#### Results of Imaging Alone

Six of the eight patients with T3 prostate cancer were correctly identified by MRI, resulting in a sensitivity of 75%. Of the 30 patients with T2 prostate carcinoma, 26 were correctly identified, resulting in a specificity of 87%. The rate of false-positive results was 13%; the rate of false-negative results was 25%. The positive and negative predictive values were 60% and 93%, respectively. The Youden index was 62%. Three patients (all without extracapsular extension) had no visible tumors on T2-weighted imaging and were classified as stage T2 tumors (Table 1).

#### Results of MR Spectroscopy

The same 38 patients described in the previous paragraph were evaluated using MR spectroscopy. The total number of tumor voxels per prostate ranged from zero to 39; the number of tumor voxels per slice ranged from zero to 13.

The group of patients with a T3 tumor had a higher total amount of tumor voxels than the group of patients without extracapsular extension (median, 13 vs 7.5) and a significantly higher voxel per slice ratio (median, 6.5 vs 3.0) (Table 2 and Fig. 1). Four patients (three with a T2 tumor, one with a T3 tumor) displayed no tumor voxels despite a histologically proven tumor (Fig. 2).

ROC analyses were performed to identify the optimal cut-point value of the number of tumor voxels per slice and the total number of tumor voxels most suitable to differentiate between a T2 and T3 tumor stage. The

area under the curve for tumor voxel per slice (0.79) was higher than for total number of tumor voxel (0.70), indicating that the variable tumor voxel per slice was more suitable to discriminate between T2 and T3 tumors than the variable total number of tumor voxel. For that reason, we chose tumor voxel per slice for further calculations.

The cut-point value resulting in the highest Youden index was 3.88 (i.e., 3.88 or more tumor voxels per slice are taken as predictive for a T3 tumor stage). For this cut point, sensitivity was 88% and specificity was 70%, resulting in a Youden index of 58%. If only values with a specificity of more than 90% were taken into account to avoid too many false-positive results, 6.25 voxels per slice was the optimal cut-point, yielding a sensitivity of 63% and a specificity of 93% (Youden index, 56%). The differences of the descriptive parameters between MRI and MR spectroscopy with different cut-point values were not statistically significant ( $p = 0.27$ – $1.0$ ; McNemar test). A sample size calculation was performed to estimate the number of patients with T3 tumors needed to result in a significant difference of sensitivity between MRI and spectroscopy; the number obtained was 172. The sample size of patients needed to produce a significant difference in specificity was calculated as 195.

#### Results of Combined Visual and Spectroscopic Diagnosis

The results of visual and spectroscopic diagnosis were combined in a way that both techniques were equally weighted. Diagnosis of a T3 tumor was only made if each visual diagnosis and spectroscopy diagnosed a T3 tumor; otherwise, the tumors were classified as T2. For the cut-point value of 3.88 voxels per slice, the combined diagnosis resulted in a sensitivity of 75% and a specificity of 93% (Youden index, 68%). For the cut-point value of 6.25 vox-

**TABLE 2: Comparison of Total Amount of Tumor Voxels and Tumor Voxels per Slice of T2 and T3 Tumors**

|          | Total Amount of Tumor Voxels (median) | Tumor Voxels per Slice (median) |
|----------|---------------------------------------|---------------------------------|
| T2 tumor | 7.5                                   | 3.0                             |
| T3 tumor | 13                                    | 6.5                             |
| <i>p</i> | 0.08                                  | 0.01                            |

els per slice, the combined diagnosis resulted in a specificity of 100% and a sensitivity of 50% (Youden index, 50%) (Table 1).

#### Tumor Volumes

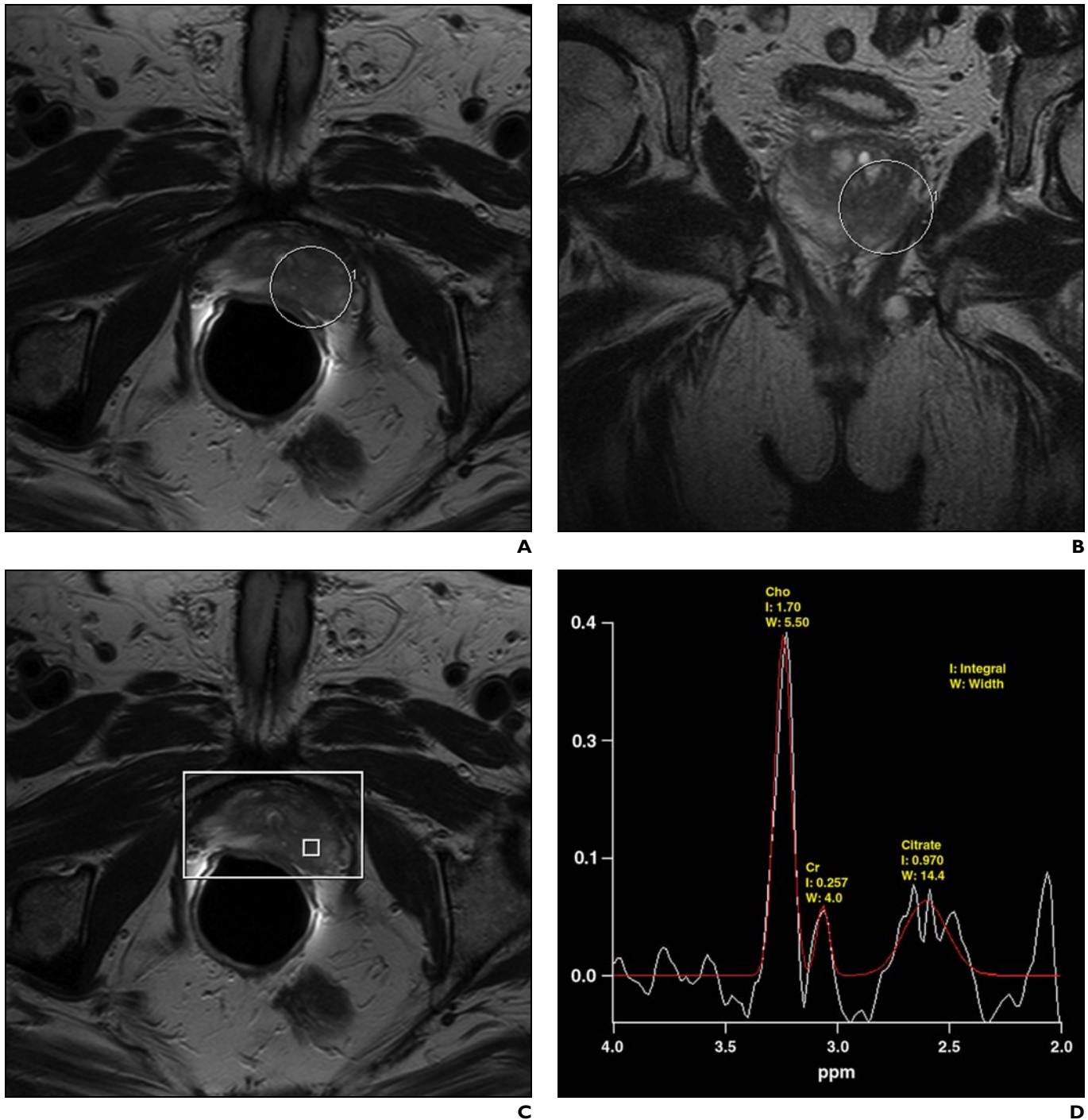
The corresponding mean tumor volumes that were estimated by the total number of tumor voxels were  $4.0 \text{ cm}^3 (\pm 3.3 \text{ cm}^3)$  for patients with a T2 tumor and  $7.5 \text{ cm}^3 (\pm 5.8 \text{ cm}^3)$  for patients with a T3 tumor. The corresponding tumor volumes per slice were  $1.3 \text{ cm}^3 (\pm 1.0 \text{ cm}^3)$  for T2 tumors and  $2.7 \text{ cm}^3 (\pm 1.7 \text{ cm}^3)$  for T3 tumors. The corresponding values for 3.88 and 6.25 voxels per slice that were yielding the highest Youden index or a specificity of more than 90% were  $1.75 \text{ cm}^3$  or  $2.81 \text{ cm}^3$ , respectively.

#### Discussion

MR spectroscopy of the prostate is a non-invasive approach for the detection of prostate tumors, and the potential of MR spectroscopy to identify intraprostatic tumor foci in addition to MRI with a high sensitivity and specificity has already been proven in several studies [9, 10, 19–21]. Yu et al. [14] proposed the estimation of the tumor extent by MR spectroscopy as a means of predicting extracapsular extension.

The total procedure time of the combined sequence protocol accounted for 35 minutes, which is an acceptable time under routine conditions. Nevertheless, 12 spectro-

## MRI of the Prostate for Staging Accuracy



**Fig. 1**—70-year-old man with histopathologically proven T3a prostate cancer with prostate-specific antigen level of 10 ng/mL and Gleason score of 6 (3 + 3). Tumor extended over four spectroscopic slices. Patient had total number of 31 tumor voxels and 7.75 voxels per slice. Note: Endorectal coil is rotated to left, but tumor is clearly visible because it is located on same side.

**A and B**, Transverse (**A**) and coronal (**B**) T2-weighted MR image from fast spin-echo sequence showing hypointense lesion (circle) of left peripheral zone with obliteration of retroprostatic angle.

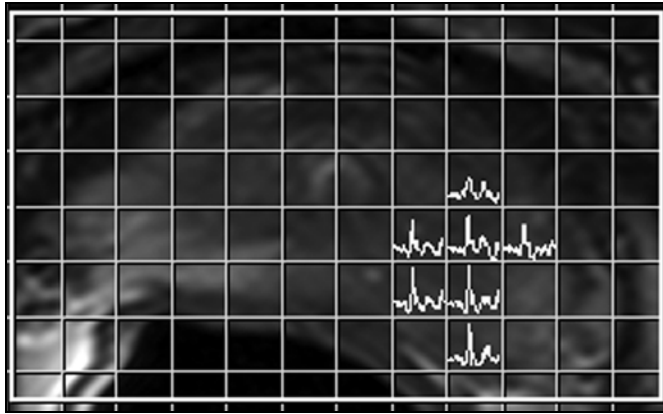
**C and D**, Tumor voxel from center of lesion showing pathologic ratio of (choline + creatine) / citrate (rectangle denotes **E**).

(Fig. 1 continues on next page)

scopic examinations in our study group were nondiagnostic, which shows the interference liability of this procedure and is a

clear limitation in the clinical practice. One explanation could be the application of the field map-based automatic shimming pro-

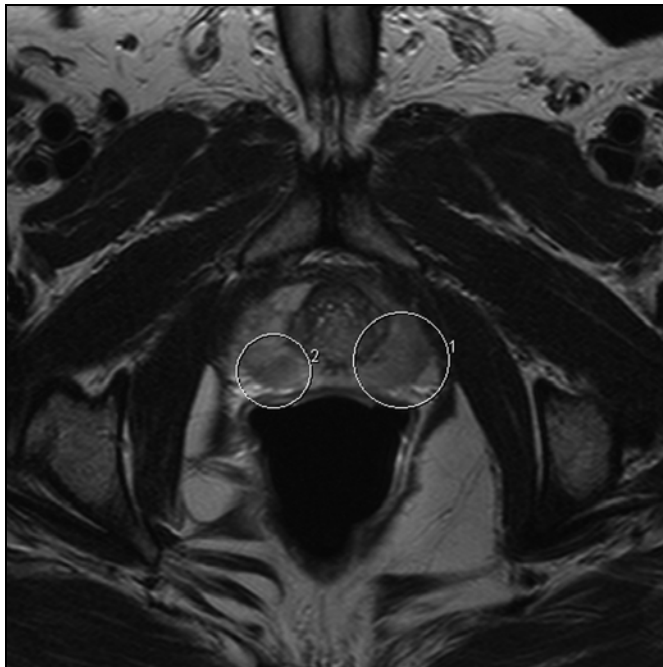
cedure of the system, which allows a quick examination but might also be affected with a higher failure rate of MR spectroscopy.



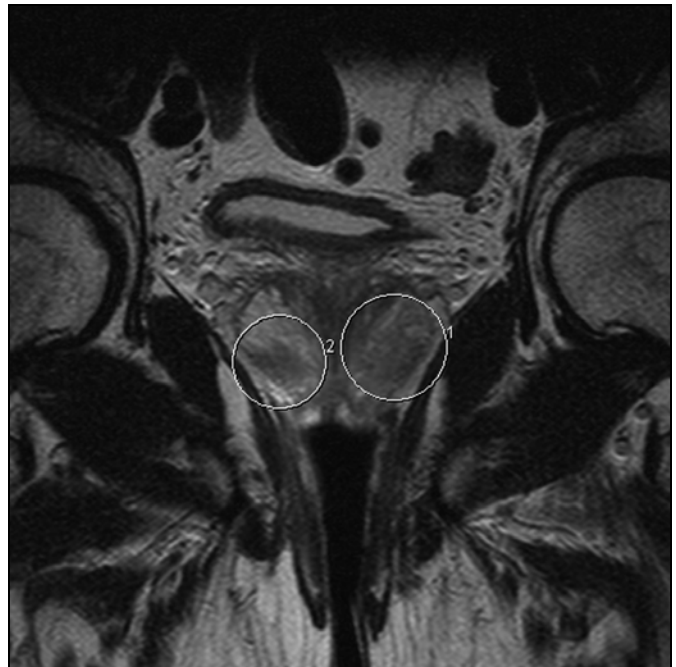
E

**Fig. 1 (continued)**—70-year-old man with histopathologically proven T3a prostate cancer with prostate-specific antigen level of 10 ng/mL and Gleason score of 6 (3 + 3). Tumor extended over four spectroscopic slices. Patient had total number of 31 tumor voxels and 7.75 voxels per slice. Note: Endorectal coil is rotated to left, but tumor is clearly visible because it is located on same side.

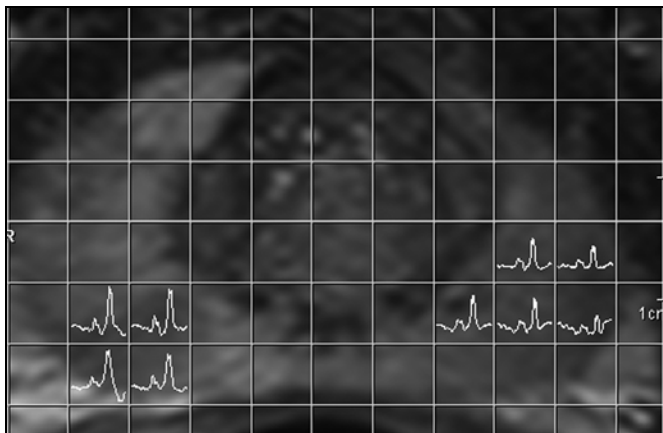
**E**, Overlaid spectral grid covering tumorous lesion with voxels of nominal size of 0.45 cm<sup>3</sup>. Volume of interest (*white*) is close around prostate. Voxels covering tumorous lesion have pathologic metabolite ratio with high choline and low citrate value.



A



B



C

**Fig. 2**—58-year-old man with histopathologically proven T3a prostate cancer with prostate-specific antigen level of 7.7 ng/mL and Gleason score of 6 (2 + 4). Spectroscopy showed no tumor voxels despite histologically proven prostate carcinoma.

**A and B**, Transverse (**A**) and coronal (**B**) T2-weighted MR image from fast spin-echo sequence showing hypointense lesion (*circles 1 and 2*) of both peripheral zones.

**C**, Overlaid spectral grid and voxels covering suspicious lesions showing normal metabolite levels with high citrate and low choline values.

We did not evaluate whether manual shimming can improve the outcome of spectroscopic studies or not. The results of the MR spectroscopy would perhaps have been better if the sequence had contained more averages or a longer TR. However, this would have prolonged the examination time of the spectroscopic sequence.

Previous histopathologic studies [22, 23] have shown a correlation between tumor extent and extracapsular extension and a correlation between tumor volume and loss of differentiation and thereby with the probability of distant spread [22].

In our study, the results of MR spectroscopic imaging showed statistically significant differences between the median values of tumor voxels and tumor voxels per slice between T3 and T2 tumors (6.5 vs 3). In the group of patients with T3 tumors, seven of eight displayed at least four tumor voxels per slice.

Interestingly, we found altogether four patients who did not show any tumor voxels at all, despite a histologically proven tumor. One of them was a patient with a T3 tumor and a clearly visible hypointense lesion on the T2-weighted images.

False-negative spectroscopic results are reported in a study of Lee et al. [24], who performed choline measurements in patients with different entities of malignant tumors. They showed an example of a patient with a histologically proven T2 prostate carcinoma and a normal spectroscopic pattern. The existence of false-negative spectroscopic results is problematic because it will lead to a false-negative diagnosis if MRI is not suspicious. In addition to this, tumor volume measurement by MR spectroscopy, which consists of the existence of voxels with an abnormal metabolite ratio, will be inaccurate.

Calculated by the number of total tumor voxels, we found a mean tumor volume of 4.0 cm<sup>3</sup> in patients with a T2 tumor and a mean tumor volume of 7.5 cm<sup>3</sup> in patients with a T3 tumor. The data about tumor volumes in the literature are not uniform. Stamey et al. [25] found that capsular penetration was present in 79% of prostates with cancer volumes greater than 3 cm<sup>3</sup>. Another study reports mean tumor volumes of 9 cm<sup>3</sup> in prostates with capsular penetration [23]. Lencioni et al. [26], who performed MR measurements of tumor volumes with MRI, used an MR tumor volume of 2 cm<sup>3</sup> as a cut-point value for extracapsular spread and achieved a sensitivity of 81.2% and a specificity of 100%. We did not evaluate how far our results of tumor volumes

represented the real tumor volumes because we did not correlate our results with histopathologic tumor volume measurements. In a study by Coakley et al. [27], tumor volume measurement by MR spectroscopy was found to overestimate tumor volume and showed only a statistically significant correlation with histopathologic tumor volume when tumor nodules greater than 0.50 cm<sup>3</sup> were considered. Conversely, histopathologically estimated tumor volumes might not represent the real tumor volumes because tissue fixation, staining, and slicing might cause substantial changes in tumor size.

MRI alone had a better overall performance than MR spectroscopy alone, with a sensitivity of 0.75, a specificity of 0.87, and a corresponding Youden index of 0.62. The comparison of MRI alone with combined MRI and spectroscopy showed differences in sensitivity and specificity that were not statistically significant. One could argue that the small number of patients with a T3 tumor is the reason the results are not statistically significant, and indeed the fact that there were only eight patients with extracapsular extension makes a comparison between the two methods problematic. But a sample size calculation indicated that even a much larger sample size probably would not have resulted in significant differences.

In our study, MRI evaluation was performed by two radiologists with 7 and 2 years of experience in prostate MRI interpretation for whom the possible advantages of additional MR spectroscopy might not be as relevant as for inexperienced radiologists. In fact, Yu et al. [14] showed that the combination of MRI and MR spectroscopy provides statistically significant improvements of accuracy only in the less experienced interpreter. We did not test the impact of MR spectroscopy on the staging accuracy of inexperienced interpreters; we believe a scenario involving a truly inexperienced interpreter is not realistic and only of theoretic interest.

MR spectroscopy is an indirect method of diagnosing extracapsular extension based on measurements of tumor volumes. Therefore, as mentioned earlier, an accurate diagnosis is not possible if patients display no tumor voxels at all despite a histologically proven prostate carcinoma. Another restraint is the observation of a large variety of the number of tumor voxels in both T2 and T3 prostate carcinomas. Our results show a wide range of the number of tumor voxels per slice in both groups of patients, starting from zero to 9.33

in patients with T2 tumors and zero to 13 in patients with T3 tumors, with substantial overlap in both groups. To obtain a specificity of more than 90%, the cut-point value of the number of tumor voxels must be equal to or above 6.25, corresponding to a sensitivity of only 63% (and a corresponding Youden index of 56%). Conversely, to achieve a higher sensitivity by using a lower cut-point value of tumor voxels per slice, one has to tolerate a lower specificity because a considerable number of patients with a T2 tumor display more than 3.88 tumor voxels per slice. These considerations explain the only moderate results of the staging performance of MR spectroscopy in our study.

In conclusion, we observed statistically significant differences between the mean and median values of tumor volumes and tumor voxels per slice between T3 and T2 tumors. Using MR spectroscopy we were able to stage prostate carcinomas with an acceptable sensitivity or high specificity, depending on the chosen threshold of tumor voxels per slice. However, the differences of the staging performance between MRI and MR spectroscopy were not statistically significant. The combined information of both methods resulted only in a slight improvement of the staging performance. In a prospective evaluation, MR spectroscopy was found to have a relatively high failure rate and quite a long postprocessing time. Based on these results, we cannot recommend the routine use of our combined sequence protocol for staging purposes of patients with histologically proven prostate carcinoma.

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