MRI Spectroscopy in Screening of Prostate Cancer

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Abstract. Background: The purpose of this study was to evaluate the suitability of MR Spectroscopy in screening for prostate cancer in comparison to T2-weighted MR imaging. Materials and Methods: Forty-six patients with biopsy confirmed prostate cancer underwent combined endorectal-body-phased-array MRI at 1.5T (Tesla). Twelve patients were additionally examined with 3D-spectroscopy sequence. The results of the spectroscopy were compared with the findings of T2-weighted MR imaging and the histological examination of radical prostatectomy specimens. Results: With 3D-spectroscopy, a choline+creatine/citrate-ratio of 0.45 for healthy tissue and a ratio of 1.90 for tumor tissue were found and a significant difference between the groups was demonstrated. In 6 cases diagnosis of tumor localization was improved with spectroscopy in comparison with T2-weighted imaging alone. Conclusion: 3D-spectroscopy is a suitable technique for improving MR imaging of prostate cancer. This method can improve the diagnostic accuracy of T2-weighted imaging alone. At present, 3D-CSI spectroscopy alone can not be recommended with sufficient validity.

In industrialized countries, such as the United States or Germany, prostate carcinoma is the most common form of malignancy and the second leading cause of cancer related death in men. In order to facilitate the earliest possible detection of the tumor, improvements in the initial diagnosis are required. Early detection of a tumor located within the prostate gland can often lead to an effective cure of this carcinoma.

Prostate cancer most often occurs in the outer glands in which the tumor can be detected via a digital rectal examination (DRE). Nevertheless, approximately 23 to 45% of carcinomas still remain undetected by this method. Fifteen to 20% of the prostate cancers are located in the transitional zone and are thereby difficult to access via the palpate examination (1).

The PSA level (prostate specific antigen) introduces another possibility for early detection of prostate carcinoma. It should be noted that an inflammation of the prostate gland (prostatitis) or a benign enlargement of the prostate gland (nodular hyperplasia) can also increase the PSA levels. Moreover, prostatic carcinoma was also present in 25% of patients with a PSA level below the critical 4 ng/ml threshold. In order to facilitate a more comprehensive early detection of the carcinoma, additional diagnostic imaging methods should be utilized (1). Transrectal ultrasound (TRUS) can be considered another method to confirm the existence of a suspected tumor. An ultrasound steered sextant biopsy could also be advised. This method offers a sensitivity of 17 to 53% and a specificity of 40 to 63% depending on the study. Of the patients who underwent a sextant biopsy, 64 to 78% experienced minimal side-effects such as urinary tract infections, gross hematuria, hemospermia or acute retention of urine. The spreading of tumor cells along the puncture path produced no relevant clinical sequelae (1).

Magnetic resonance imaging (MRI) of the prostate in combination with a dedicated endorectal coil is a valid method for the visualization of the prostate and its associated neoplasm. The coil can be positioned close to the target tissue and thereby produce highly detailed images of the target and surrounding area, thus allowing for an accurate interpretation. Suspected tumor areas in the peripheral zones are typically characterized by low signal, while these are often not easily visualized in the central gland due to pre-existing benign prostate hyperplasia that presents as mostly inhomogeneous (2). Moreover, in many patients receiving hormone treatments, the prostate gland experiences a signal loss, therefore making it very difficult to distinguish a suspected tumor area from that of a healthy area (3). The experience level of the examiner plays a...
critical role in these cases (4, 5). H-spectroscopy (magnetic resonance spectroscopy=MRS) of the prostate is a method that can be combined with standard imaging in order to minimize or reduce these factors (2). The purpose of this study was to test the significance of endorectal MRI using T2 weighted imaging as compared to MR spectroscopy of the prostate as well as verify in the spectrogram a significant difference of the attained quantitative values of tumor and healthy tissue of the prostate.

Materials and Methods

Patient population. Endorectal MRI examinations were conducted on 46 patients from 23.03.2001 to 20.11.2005. The average age at the time of the MRI examination was 65.1 years (49-77). All patients previously received a biopsy confirming the presence of prostate carcinoma. Four patients, as indicated in their case history, also received transurethral resections (TUR) of the prostate. Thirty-one patients received a pre-operative hormone treatment with an anti-androgen therapy which caused the previously increased PSA levels to drop off. The initial PSA level was on average 11.24 ng/ml and the pre-operative levels averaged at 3.49 ng/ml. All patients were treated by radical prostatectomy. Twelve patients (average age of 63.3 years) also received a 3D-spectroscopy of the prostate; all of them received total cross sections.

MRI examination. The MRI examination was conducted on a 1.5T system (Siemens Medical Solutions, Erlangen, Germany: "Symphony") combined with an endorectal-body phased array coil (Medrad, Pittsburgh, PA, USA). A T2 weighted Turbo Spin Echo (TSE) sequence in the axial, coronal and sagittal planes with an slice thickness of 3 mm was implemented in order to cover the total prostate from the apex to the base, including the seminal vesicle. Additionally, T1 weighted axial images of the complete pelvis including the promontory (slice thickness 7 mm) were utilized in order to localize hemorrhage after previous biopsy or suspected lymph nodes.

The axial, coronal and sagittal T2 weighted images enabled the positioning for the measurement of the volume of the prostate (VOI=volume of interest) for the 3D spectroscopy which was accompanied only by the endorectal receiver coil. The examiner positioned the VOI of the MRS examination on the images showing the largest diameter of the prostate in all three planes. Presats (satbands) were positioned in all directions around the prostate. Outer volume suppression in directions around the prostate must be utilized in order to eliminate disturbances of the spectra caused by periprostatic tissue, fat, rectum or the coil. The VOI presented a typical shape of the prostate with a slice thickness of 8 mm. Additionally, a manual shim (tuning of the gradients) was performed in order to compensate for inhomogeneities of the magnet field.

The scan for the spectroscopy lasted approximately 8 to 10 min. The entire examination including the preparation of the patient and the measurement required about 1 hour. Additionally, the individual spectra were evaluated via an interactive post processing computer program.

The 3D-spectroscopy resulted from the excitation of hydrogen molecules that were induced by the HF pulses. Thereby, a 3D version of a PRESS sequence (point resolved spectroscopy) was utilized to exactly localize the VOI. The VOI was then subdivided into a matrix of voxels using phase encoding in 3 dimensions (chemical shift imaging-CSI or MR spectroscopic imaging MRSI). The different metabolites in the examined tissue were excited through wide band RF pulses. The attained signal was composed of a mixed frequency (FID) which, via the Fourier transform, could be separated according to their frequencies and into a spectrum which was then depicted by a diagram.

The clinical MRS of the prostate is able to clearly image substances containing choline, citrate and creatine. They appeared in definite locations on the X-axis: citrate at 2.6 ppm, creatine at 3.00 ppm and choline at 3.2 ppm (4, 6).

In tumorous tissue, it is characteristic to see a reduction of the citrate and an increase of the choline and creatine concentrations (Figure 1b) in contrast to healthy tissue, where a high citrate and a lower choline and creatine (Figure 2) are normally seen (6).

The choline and creatine peaks typically lay close to one another. For this reason, choline and creatine often combine to one value and this total was then evaluated as a relationship to citrate (choline + creatine/citrate ratio=cho+cr/cit-ratio). The integral of these peaks was then calculated and the ratio of both integrals was applied. The resulting area under the spectrum was proportional to the concentration of the spins and the metabolites. Post processing of these points was performed in order to facilitate a quantified spectrum (6).

Pathology. In all 46 patients, pelvic lymph nodes were removed together with radical prostatectomy including capsule, seminal vesicles and ampules. Twenty-eight specimens were available for histopathological examination using total cross sections and slices that contained the largest area of tumor growth were analyzed. Histological sections were scanned and the extent of tumor growth was indicated, so that a comparison to the MRI images and the spectroscopy was possible. In 18 remaining cases, only histopathology reports were available for analysis. Prostatic carcinoma was restricted to one lobe (pT2a/b) in 19 cases, both lobes were affected by disease (pT2c) in 10 cases, 5 tumors showed growth outside the capsule (pT3a), 8 an infiltration of the seminal vesicle (pT3b) and 4 expanded beyond the organ (pT4). In 7 patients regional lymph node metastases were present (N1). The Gleason Score was on the average of 6.5 (Gleason 3-9).

Comparison of the MRI images and the spectroscopy with the pathology. The images of the examined patients were analyzed by two independent radiologists experienced in prostate MRI. The estimation of the tumor and the subsequent staging of the cancer were agreed upon by the professionals. The MRI findings were compared with the pathological findings and the results were shown in a four field chart. The evaluation of the spectroscopy was performed on a voxel-by-voxel basis so that each voxel could be defined with its appropriate cho+cr/cit-ratio. Voxels positioned outside the margins of the prostate, voxels not displaying the typical characteristics and voxels which did not clearly refer to pathology or normal tissue were not considered. In addition, the spectroscopic data of 12 patients, the image findings and the pathology were correlated.

The examiner of the specimens marked within the tumor area 2 to 7 voxels (depending upon the size of the tumor) as pathological. In order to create a comparison with the tissues showing pathology, the same number of voxels was required from normal tissue (Figure 2).
Statistics. The comparison of the MRI images and the pathology were shown in a four field chart. The sensitivity, specificity and the total accuracy were then calculated. The results from imaging were then compared with the spectroscopy and the pathology. The values from the 3D spectroscopy of the pathological and healthy tissues were checked for a significant difference as indicated by the $t$-test for independent random samples and the pre-performed Levene test. In addition, the values for the cho+cr/cit ratio were categorized and correlated.

Results

**Endorectal MRI.** A sensitivity of 59%, a specificity of 66% and a total accuracy of 63% for the growth of the tumor outside the capsule was attained. The infiltration of seminal vesicle was determined to have a sensitivity of 27%, a specificity of 89% and a total accuracy of 74%. The involvement of the lymph nodes was diagnosed with a sensitivity of 29%, a specificity of 97% and a total accuracy of 86%.

**3D spectroscopy.** In a comparison of the spectroscopy to the pathological findings of the biopsy specimen, it was determined that 44 voxels contained healthy tissue and 44 contained tumor tissue. The average value for healthy tissue was 0.45 with a standard deviation of 0.21. The tissue containing cancer cells had an average value of 1.90 with a standard deviation of 0.95. Both groups were examined using the $t$-test for independent random samples to determine the differences in their average values. A highly significant conclusion was that the two groups differentiated themselves with an error probability of $p<0.001$. In addition, the results of the 3D spectroscopy were dispersed in different categories and the number of occurrences was calculated (Table I). Category 1 included the voxels containing a cho+cr/cit-ratio of 0.00 - 0.50 (n=30), category 2 a range of 0.51-1.00 (n=29), category 3 with 1.01-1.50 (n=16), category 4 with 1.51-2.00 (n=10), category 5 with 2.01-2.50 (n=8) and category 6 with values greater than 2.50 (n=11). Based on the Pearson correlation coefficient of
r=0.7, a highly significant relationship could be calculated between the tissue containing pathology and the size of the cho+cr/cit-ratio.

The outcome of the imaging was compared to the results of 3D spectroscopy and to the histopathological findings. The prostate was subdivided into areas of the central gland and the right and left peripheral zones. The agreement with the pathology report was verified with the results from imaging and spectroscopy (Table II). In the event that one of the three gland areas presented more than 2 or more dependent voxels with a cho+cr/cit-ratio greater than 0.95 (in reference to the above mentioned value for pathological tissue of 1.90 and a standard deviation of 0.95), then the spectrogram for this area was considered pathological.

In 4 cases, the T2 weighted image correctly showed the tumor location and the spectroscopy showed the correct location of the tumor in 6 cases (this was not demonstrated in three cases). In 6 cases, spectroscopy improved the estimation of the tumor location. In 4 patients, spectroscopic data did not correspond to the imaging (Figure 3 a-c).
Discussion

The prostate tumor staging results obtained in this study were less accurate, in comparison with the results of other researchers. For tumor growth outside the prostate capsule and tumour invasion into the seminal vesicle, a sensitivity of 59% and 27%, respectively, a specificity of 66% and 89%, respectively, and a total accuracy of 63% and 74%, respectively were obtained. Pegios et al. (7) achieved higher values for tumor growth (sensitivity 100%, specificity 87-93% and a target accuracy of 94-97%) as well as for the seminal vesicle (sensitivity 100%, specificity 84% and a target accuracy of 88%). Comet-Batlle et al. attained a sensitivity of 80%, a specificity of 76.12% and a total accuracy of 77.17%, although only needle biopsies but not large sections of radical prostatectomy specimens were available for comparison (8). It is important to note that needle biopsies for cancer confirmation can be inaccurate in grading. Another cause for our lower staging results could be due to the fact that 31 patients at the time of the MRI examination had undergone hormone treatment. As a result, of an involution of the gland caused a signal loss of the organ which can render recognition of the tumor very difficult (3).

The involvement of the lymph nodes was determined with results (sensitivity 29%, specificity 97%) similar to those reported by Pegios et al. (7) who reported a sensitivity of 25% and a specificity of 95%. The question arises as to whether or not it is possible to use spectroscopy as a method to improve tumor diagnosis during the MRI exam. First, the validity of the method was verified. 3-D spectroscopy verified the middle values of the cho+cr/cit-ratio of the spectrum for healthy and tumorous areas of the prostate, revealing a significant difference in these values. In healthy tissue values of 0.45 (±0.21) were obtained, while in cancerous tissue a value of 1.90 (±0.95) was obtained and was somewhat elevated compared to other studies. Joung et al. used the textbook value of 0.22±0.013 as the gold standard for normal tissue, which was also confirmed by their examination (0.25±0.12) (9). Tissues defined by values
greater than 0.22 + 3 standard deviations were highly suspected as tumorous. Mueller-Lisse et al. (10) concluded that 0.24±0.13 were values for healthy tissue and those tissues with 3 standard deviations were considered tumorous. Scheidler et al. (4) reported results somewhat less accurate and stated that tissue with a ratio less than 0.75 was healthy and tissue greater than 0.75 was tumorous. Nevertheless, these studies only considered high quality voxels for the spectroscopy, which would explain the higher values obtained in our examination (spectroscopy was not always optimal). In particular, elderly patients could not always be positioned comfortably in order to minimize the motion effect artefact. Another criterion for the quality of the measurement was the positioning of the presets in the periprostatic space in order to mask disturbing fat signals (outer volume suppression). Depending on the form and size of the prostate, complete suppression could not always be guaranteed. Gradient shimming could not compensate for all of the inhomogenities inherent to the magnet field. As a result, the bandwidth of the spectrum caused a loss in the accuracy.

Another limitation was the voxel selection. In the above mentioned studies (9, 10) only the voxels from the peripheral zone were selected. In this location, 60 to 75% of the prostate carcinomas are generally found, while 10 to 15% of tumors are located in the transitional zone (1). Kaji et al. confirmed with healthy volunteers a normal cho+cr/cit-ratio range from 0.58±0.38 for the peripheral zone and from 0.72±0.51 for the transitional zone of the gland (11). Similar conclusions were reported by Kurhanewicz et al. with 0.54±0.11 and 0.83±0.34 for the peripheral zones and central gland, respectively (12). We can thus expect to obtain lower values for the cho+cr/cit-ratio in the peripheral areas than in the central glands. For this reason, our results including high values from the central gland and low values from the peripheral zone comply with those values previously reported.

Since a significant difference could be proved regarding the metabolic ratio of healthy and tumorous tissue, it appears that 3D spectroscopy was an appropriate tool for the discovery of primary tumors in the prostate.

Compared to a standard T2 weighted examination, a combination of 3D spectroscopy and the pathology clearly improved the accuracy of the interpretation in 6 out of 12 cases (50%). Scheidler et al. (4) was also increased the MRSI sensitivity and specificity for tumor identification by combining these techniques, as opposed to using a single imaging technique.

Kurhanewicz et al. increased the target accuracy with the confirmation of the tumor volume and location using spectroscopy (4). The tumor volume could also provide information regarding the extent of the tumor beyond the capsule. Since the MRSI aids in differentiating of the staging of the tumor between T2 and T3 (5). Differentiation in the central zone of the BHP of a prostate carcinoma can become meaningful with spectroscopy as a tumor can easily be interpreted as a BHP if only the single imaging technique is used (13). Therefore, the spectroscopy study can help to more accurately make the differentiation between tumor and BHP. MR spectroscopy can also provide helpful diagnostic information in defining the location of tumors in patients with excessive bleeding following biopsy procedures (14).

However, 3 cases (12.25%) showed no correlation between the tumor location by spectroscopy and the pathology, leading to a false positive result (Figure 3a-c). Jung et al. (9) demonstrated that the specificity of 69.2% (207 out of 299 voxels) to 89.3% (267 out of 299 voxels) as malignant or benign depended upon the examiner as well as the grouping criteria. This group also reported false positive indications (92 in 32 out of 299 voxels).

Stanka et al. (13) only confirmed tumor size with both the images and histology in only 6 out of 18 cases, in which the size was lower than the actual size in three cases and where the size was greater than the actual size in nine. In the metabolite map, 7 out of 18 cases were correctly estimated while in 8 cases the size were overestimated. Despite the fact that the imaging was improved, there were false positive results regarding the overestimation of tumor size. Spectroscopy should not be used alone to determine tumor size since false positive results can also be obtained due to the inaccuracy of the measurement or a large hyperplastic nodule in the inner gland. (Kurhanewicz et al. (12): small overlaps of the cho+cr/cit-ratio of normal tissue of the peripheral zone and BHP).

Our calculations ignored single voxels with increased cho+cr/cit-ratio and only regions containing 2 or more voxels suspected as pathological were considered. Therefore, small tumours which could influence the spectrum of single voxels were not identified by spectroscopy.

Spectroscopy in combination with MRI appears to be an appropriate method for determining the location and diagnosis of prostate carcinoma. Based on our examinations, we do not recommend the use of spectroscopy alone as the primary tool for the recognition of prostate carcinomas.

References


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