

Determination of cut-off value of metabolite ratio in prostate cancer prior to biopsy - A 3D MRSI study

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Introduction: It is estimated that 30% of patients of prostate cancer have organ confined disease and are curable by radical prostatectomy. Digital rectal examination (DRE) and prostate specific antigen (PSA) is used as screening methods while ultrasound guided systematic sextant needle biopsy is used for diagnosis of prostate cancer. The present biopsy scheme has a false negative rate between 15% and 34% (1). It is reported that metabolite ratio with 2 or 3 standard deviations above the mean value (3SD method) of normal peripheral zone may be used to identify cancer (2,3). In the present study, using the receiver operating characteristic (ROC) curve analysis, we report a cut-off value of metabolite ratio [Cit/(Cho+Cr)] determined for the entire peripheral zone (PZ) in a large cohort of men (n = 62). The cut-off value thus determined was applied to another group of men (n = 61) to determine the sensitivity and specificity. In addition, a cut-off value of metabolite ratio was determined using the criteria of the ratio being 3SD above the mean value observed for the histologically proved cancer patients.

Materials and Methods: Men having raised PSA (> 4 ng/mL) or abnormal DRE were included in the study: Group I (n=62, mean age = 65.1±8.1 years, mean PSA = 18.9±30.2 ng/mL) and Group II (n = 61, mean age = 65.3±9.32 years, mean PSA = 16.5±29.3 ng/mL). The cut-off value determined from ROC analysis and by using the 3SD method for Group I patients, were tested on patients of Group II to determine the sensitivity and specificity. Normal controls (n = 7) below age of 40 years were recruited. MR investigations were carried out at 1.5 T using pelvic phased array coil in combination with endorectal coil (Medrad Inc., USA) and were performed and analyzed two days prior to biopsy. T1-weighted transverse and T2-weighted images in transverse, sagittal and coronal planes were acquired covering the entire prostate. For ¹H MRS, point resolved spectroscopy (PRESS) localized 3D-MRSI sequence was used. MEGA pulse (4) was used for simultaneous suppression of lipid and water. Six to 8 outer volume saturation bands were used to suppress signal originating from peri-prostatic fatty tissue. The parameters used for MRSI were: TR = 1300 ms, TE = 120 ms. Spectroscopic data obtained was superimposed on transverse T2-weighted MR images. Metabolite ratio Cit/Cho+Cr was calculated from peak integral values determined for each peak. All patients were managed as per clinical and histopathology findings.

Results and Discussion: ROC analysis of metabolite ratio of patients of Group I gave a value of 1.2 (area under the curve = 0.89, sensitivity = 87%, specificity = 85%). The cut-off value thus determined was tested on patients of Group II. Accordingly, 10/61 were predicted as suspicious for malignancy on MRSI and were positive on biopsy. Three patients predicted as negative for malignancy on MRSI were positive on biopsy; the biopsy report of one patient was equivocal and no definite conclusion could be made on the presence of malignancy. In addition, 7 patients who were positive for malignancy on biopsy in Group I, had their mean value of the metabolite ratio from voxels which are cancerous was 0.33 ± 0.24. Therefore the cut-off metabolite ratio value 3SD above the mean is 1.05, which is well below the lowest observed value of the metabolite ratio of 1.56 for normal controls. Using the cut-off determined from ROC analysis, a sensitivity of 77%, and specificity of 83% with an accuracy of 82% was calculated for patients of Group II. A sensitivity of 100% with a negative predictive value of 100% was calculated using the 3SD method. In the present study we used the average metabolite ratio for whole of PZ from each patient to arrive at a cut-off to predict malignancy. The 3 cases predicted as not suspicious of malignant had low grade tumor as evident from Gleason score. This may be due the fact that the tumor may occupy only a part of the PZ while the overall metabolite ratio may fall in the normal range. Analysis of the individual data (voxels) of these three patients revealed voxels suspicious for malignancy with reduced citrate and increased choline (Fig. 1). Higher specificity and higher negative predictive value observed using the cut-off value determined in the present study indicate that this cut-off value is sensitive in predicting malignancy. However, the ideal comparison would be to use histopathology results of radical prostatectomy on voxel by voxel basis. Thus, the cut-off value reported by us using ROC results in predicting some false negative cases, which decreases the sensitivity of the method. However, the advantage is that there is less chance of false positive cases since if the average metabolite ratio for whole of the PZ is below the cut-off value of 1.2; it means that the number of voxels suspicious of malignancy is less than the number of voxels showing normal levels of citrate and choline. ROC analysis of metabolite ratio values with the corresponding histopathology report on voxel by voxel basis would be more accurate and is the subject for our future studies.

The three cases which were predicted negative for malignancy from ROC analysis were correctly predicted as positive for malignancy by the 3SD method with certain voxels showing metabolite ratio less than 1.05. However, with the cut-off value from 3SD method, more number of patients was predicted as suspicious of malignancy, but they were negative on biopsy. This may be because these patients may harbor cancer, which may not have been detected due to sampling error inherent to biopsy. In spite of the limitations of sextant biopsy, this is the only gold standard available in the absence of radical prostatectomy specimens and radical prostatectomy can not be carried out unless the patient is proven to have cancer by biopsy.

Conclusion: In conclusion, our study shows (a) patients who were suspicious for malignancy on MRSI [(average metabolite ratio of the PZ less than the cut-off determined by ROC analysis (<1.2)] may be subjected to biopsy to prove the presence of cancer, and (b) patients who were predicted as negative for malignancy by 3SD method may be categorized as patients for 'watchful waiting'.

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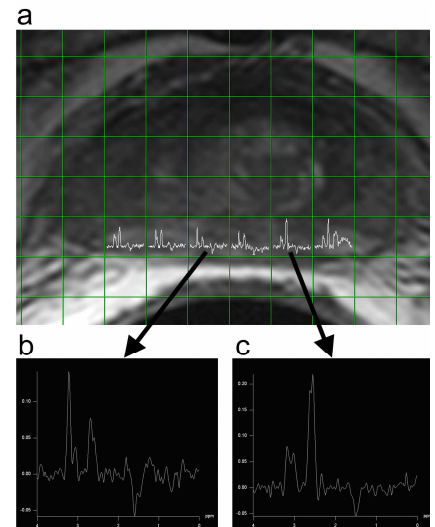


Figure 1. Representative example of MRSI result of a patient predicted correctly as suspicious for malignancy by 3SD method but not by ROC analysis. (a) MRSI grid overlaid on axial T2-weighted image showing spectra obtained from PZ. (b) and (c) are enlarged spectrum showing changes in choline and citrate levels.