Regression analysis of defined mixtures of cancer and benign tissue in prostate biopsies

R. Somorjai[1], R. Bourne[2], A. Nikulin[1], B. Dolenko[1], S. Fairy[2], P. Russell[2], C. Mountford[2]

[1]Institute for Biodiagnostics, National Research Council, Winnipeg, Manitoba, Canada, [2]Institute for Magnetic Resonance Research, Sydney, NSW, Australia

Synopsis For *in-vivo* MRS the assessment of disease extent and progression is limited by the relatively poor spatial resolution of the method. Many of the voxels from which spectra are derived contain a mixture of tissues of different pathological status. To address this problem we performed a regression analysis on ^{1}H MR spectra (8.5 T) of prostate biopsy tissue in which the partial volumes of malignant and benign tissue were estimated by histopathology of serial sections. Using six spectral subregions linear regression analysis enabled the prediction of cancer volume with an overall accuracy of 97% for an independent test set.

Introduction MRS-based detection of cancer and other diseases depends on assignment of particular MR spectral patterns to tissue types of particular pathological status. A high sensitivity and specificity for detection of disease is the primary clinical goal of MR-based diagnosis (see Lean et al [1]). For *in-vivo* MRS the assessment of disease extent and progression are limited by the relatively poor spatial resolution of the method. Many of the voxels from which spectra are derived are likely to contain a mixture of tissues of different pathological status. Diagnostic interpretation of the spectra from such mixed tissue voxels would ideally report not only the presence of disease, but also the extent or partial volume of disease within the volume of interest. To this end, we performed a robust regression analysis on prostate biopsy tissue, in which the presence and volume fraction of cancer was quantified by serial section histopathology.

Materials and Methods Tissue specimens (n=125) were obtained from 34 prostates immediately after radical retropubic prostatectomy. Sextant peripheral zone punch biopsies (5mm Steifel) were taken through the posterior side of the organ through a small incision in the prostatic capsule. Each biopsy was divided in half lengthwise, placed in 0.3 ml phosphate buffered saline (PBS/D_2O), and frozen in liquid nitrogen. Specimens were stored at -70^{o}C for up to 6 weeks. One dimensional MRS experiments (8.5 Tesla) were performed on a Bruker Avance 360 MHz spectrometer and a standard 5 mm dedicated proton probehead over a sweep width of 3597 Hz (10.0 ppm) using a 90^o pulse, 8192 data points, 256 accumulations with an acquisition time of 0.8 sec and relaxation delay of 1 sec. Water suppression was effected by a field gradient method. Spectra were processed using Bruker XWINNMR software.

The 125 spectra were spilt into a Training Set (83 spectra) and an independent Test Set (42 spectra). A genetic algorithm-driven optimal region selector [2] (GA_ORS) was used to determine the best spectral regions. We modified the robust least trimmed squares (LTS) regression method [3] (20% trimming) by optimizing not only the 80% subset composition, but also the allowed spectral shifts. The latter compensates for possible misalignments of the spectra. Accuracies were assessed as 100% minus the average of the absolute deviations of MRS-estimated cancer volumes from cancer volumes estimated by serial section histopathology.

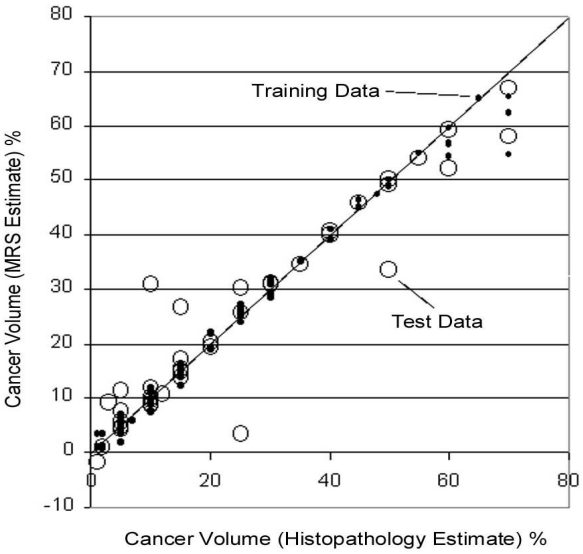

Figure 1: the regression results (ordinate) vs. the histopathology estimates of cancer volume fraction

Histopathology. Five consecutive 5 µm sections were taken every 100 µm with the intervening tissue discarded. Each set of five sections was placed on a single slide. The volume percentage of carcinoma and of stromal and glandular elements were reported in all specimens. All histological examinations were performed blinded.

Results and Discussion Using six optimal spectral subregions and allowed spectral shifts of ±15 data points (ca. ±0.04ppm), robust regression analysis of the MR spectra from tissue containing defined volume fractions of cancer enabled the prediction of cancer volume with an overall accuracy of 98.6 ± 2.0% for the training set and 96.6 ± 5.5% for the independent test set. All accuracies were assessed as 100% minus the average of the absolute deviations of MRS-estimated cancer volumes from cancer volumes estimated by serial section histopathology. When the worst 10% of outliers are excluded (8 from the training set, 4 from the test set), the results are 99.0 ± 0.7% for the training set and 98.2 ± 2.5% for the test set. In Figure 1 the regression results (ordinate) vs. the histopathology estimates of cancer volume fraction are shown. The power of the analysis is reflected in the high accuracy obtained for the independent test despite the number of spectra included low.

Conclusions Robust regression analysis of MRS data can accurately predict the volume fraction of cancer present in tissue. The method may be useful for the more accurate determination of cancer extent *in-vivo*.

References

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