Tumour Grade, estrogen receptor status and progesterone receptor status determined from a single fine-needle aspiration breast biopsy using ^{1}H MRS and a statistical classification strategy

S. T. Doran[1], C. Lean[1], B. Dolenko[2], P. Malycha[1], D. Clark[1], L. Gluch[1], U. Himmelreich[1], R. Somorjai[2], C. Mountford[1]

[1]Department of Magnetic Resonance in Medicine, University of Sydney, Institute for Magnetic Resonance Research, Sydney, NSW, Australia, [2]National Research Council Canada, Institute for Biodiagnostics, Winnipeg, Manitoba, Canada

Introduction

Local therapy alone will cure approximately half of patients with early breast cancer [1]. For the other half, it is necessary to ascertain the likelihood of disease recurrence, and whether systemic therapy will be of benefit. Tumour grade, estrogen receptor (ER) and progesterone receptor (PgR) status are important in the management of breast cancer as they are good indicators for risk of disease recurrence. ER and PgR status are also used as indicators of responsiveness to endocrine therapy. To quantify these prognostic factors pathologists must prepare cell blocks and perform time-intensive immuno-histochemistry on sections. Magnetic Resonance Spectroscopy (MRS) on a fine-needle aspiration biopsy (FNAB) discriminates between invasive carcinoma and normal or benign breast tissue with a sensitivity and specificity of 95% and 96%, respectively, based on the amounts of creatine and choline [2]. Application of a statistical classification strategy (SCS), developed to analyse biomedical data [3,4], improved the distinction between benign and malignant (sensitivity 98%, specificity 94%) and importantly, allowed the presence or absence of lymph node involvement (sensitivity 96%, specificity 97%); and presence or absence of vascular invasion (sensitivity 82%, specificity 100%) to be determined from a FNAB of the primary lesion [5]. Here we apply the SCS to the analysis of ^{1}H MR spectra of FNABs from primary breast lesions to determine further prognostic information, specifically tumour grade, ER status and PgR status.

Materials and Methods

FNABs (21/23 gauge needle, 15-20 passes) of palpable and/or radiologically localised breast lesions were collected for MRS study immediately prior to the cytology sample by the breast surgeon. MRS experiments were carried out on a Bruker AM-360 wide-bore spectrometer (360 MHz or 8.5 Tesla) with an Aspect 3000 computer and a 5 mm dedicated proton probehead. Samples were spun at 20 Hz and the temperature maintained at 37^{o}C. Unprocessed (apart from normalization) MRS data were transferred electronically from Sydney, Australia to the Institute for Biodiagnostics (IBD), Winnipeg, Canada where the SCS was applied. After simple preprocessing that included taking first derivatives and rank-ordering, IBD's genetic algorithm-based Optimal Region Selection (ORS_GA) software was used to find maximally discriminatory spectral sub-regions. The averages of the intensities comprising these sub-regions were used to develop Linear Discriminant Analysis (LDA) classifiers made robust by IBD's bootstrap-based crossvalidation method. This involves randomly selecting ~half of the spectra from each class and using these to train an LDA classifier. The remaining spectra are used to validate this classifier. The process is repeated B=1000 times (with replacement). The weighted average of the B sets of coefficients produces the final classifier; the weights reflect classifier accuracies of the test sets.

Results

Three 2-class SCS-based classifiers were generated using the MR spectra of FNABs from primary breast tumours. A total of 131 MR spectra were used in the study. Each classification problem was based on a different subset. For determining tumour grade, there were 52 spectra from Grades 1 and 2 which were combined to represent “low grade” tumours and 42 from Grade 3 (high grade). For assessing ER status, 90 ER positive and 38 ER negative spectra (as determined by immuno-histochemistry) were available. For assessing PgR status, there were 77 PgR-positve and 51 PgR-negative spectra (as determined by immuno-histochemistry). The results are summarised in Table 1. In the Table we display, for each of the three classifiers, the number of spectral regions used by the classifier, the sensitivity, specificity, overall accuracy and the crispness of the classification (percentage of samples assigned with a class probability >75%).

Table 1: Classification Results: Tumour Grade, ER status and PgR status from FNAB of primary breast cancers

	Number of Spectral Regions	Sensitivity%	Specificity%	Overall Accuracy%	Crispness%*
Grade 1 & 2 versus Grade 3	**5**	**96.2**	**95.2**	**94.7**	**78.7**
ER positive versus ER negative	**5**	**91.1**	**89.5**	**90.6**	**75.8**
PgR positive versus PgR negative	**6**	**90.9**	**86.3**	**86.7**	**64.1**

ER: Estrogen receptor; PgR: Progesterone receptor.

Discussion and Conclusions

Applying the SCS to 1D proton MRS of FNABs of primary breast cancers provides for a classification-based diagnosis with a relative high degree of accuracy for tumour grade, ER status and PgR status. Proton MRS, combined with the SCS, offers the potential for a rapid and cost effective method for determining these prognostic indicators simultaneously with the diagnosis of the primary pathology and lymph node involvement.

References

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