MR determind metabolites may serve as prognostic factors in breast cancer

T. F. Bathen[1], B. Sitter[1], G. F. Giskeødegård[1], L. Buydens[2], G. Postma[2], H. Fjøsne[3], S. Lundgren[1,4], and I. S. Gribbestad[1]
[1]Dept. of Circulation and Medical Imaging, NTNU, Trondheim, Norway, [2]Dept. of Analytical Chemistry, Radboud University Nijmegen, Nijmegen, Netherlands, [3]Dept. of Surgery, St. Olavs University Hospital, Trondheim, Norway, [4]Dept. of Oncology, St.Olavs University Hospital, Trondheim, Norway

Introduction

Breast cancer has the highest incidence and mortality of all malignant diseases among women globally (1). Patients' treatment is currently based on clinical assessment, histopathological evaluation of tumour biopsies and on lymph node status, which is the strongest prognostic factor. Adding prognostic information using molecular methods could move to a more personalized medicine concept, where treatment of each patient is based on individual tumour biology. Biochemical properties described by magnetic resonance (MR) characterise breast cancer (2,3), and the metabolic profiles of breast cancer tissue correlate to clinical parameters such as lymphatic spread and hormone status (4). The purpose of the current study was to define new prognostic factors for breast cancer based on HR MAS MRS.

Methods

Breast cancer tissue was excised from patients with palpable breast cancer (Invasive ductal carcinoma (IDC)). Tissue specimens were analysed in D2O-PBS, and HR MAS MR spectra were recorded on a Bruker Avance DRX600 spectrometer. Proton MR spin echo spectra were acquired with a total echo time of 285 ms and water presaturation (4 °C, spin rate 5 kHz). A pathologist scored the relative areas of normal and neoplastic epithelial elements. Only patients without neoadjuvant chemotherapy before the surgery were included. For those surviving less than 5 years, death was proven cancer related. At least 5-years follow-up were available for all. Furthermore, to ensure a strong cancer signature in the spectra, only biopsies containing more than 20% tumour cells were used for further analysis. This resulted in a dataset consisting of 61 spectra (44 patients, whereof 11 patients survived less than 5 years).
A region of interest containing the spectral intensities in the 3.0-4.6 ppm region was selected. Baseline offset was adjusted, and the spectra were further SNV scaled, peak aligned and smoothed (moving average). The spectra were analysed with principal component analysis (PCA). Using ROC curve analysis, a cut-off value of PC2 was found and used in a Kaplan-Meyer survival analysis.

Results and discussion

A major proportion of the long term survivors are associated with higher values for PC2 in the score plot (A, survival>5 years: blue coding). Based on this intriguing finding, we wanted to investigate the possibility of detecting clusters with different prognostic outcome. The ROC curve analysis suggested a cut-off value of -5 for PC2 (Sensitivity: 0.77, specificity: 0.54. AUC: 0.71). This defined two groups of initially 18 and 43 patients, with a significant different cumulative survival (B). The loading profile of PC2 suggests that good prognosis is related to higher levels of glycerophosphocholine, betaine and creatine, and lower levels of lactate and glycine (C).

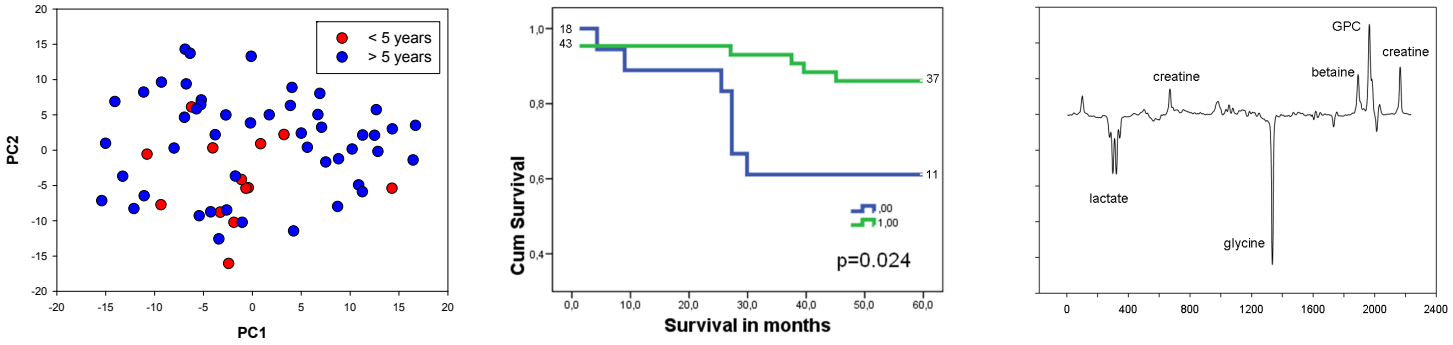

Figure: (A) Scoreplot of PC1 versus PC2. (B) Kaplan-Meyer survival plot. (C) Loading profile of PC2

Conclusion

We suggest that a combination of MR determined metabolites may serve as an additional prognostic factor in breast cancer. The feasibility should be further investigated with a larger number of samples.

References:

(1) Parkin DM Lancet Oncol 2006 . (2) Gribbestad et al. NMR Biomed 1994;7:181. (3) Sitter et al. NMR Biomed 2002;15:327. (4) Bathen et al. Breast Cancer Res Treat 2007;104:181