Correlation of in vivo MRS and ex vivo HR MAS metabolic profiles and clinical outcome for brain metastases patients

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Introduction

Brain metastases (BM) are a common oncologic challenge. The overall prognosis of survival for these patients is generally poor. Recent treatment strategies focus more on individualized patient protocols depending on the biological characterization of the BM and extracranial tumors. Furthermore, the need for early evaluation of response is increasing in order to optimize and avoid ineffective treatment. Both in vivo and ex vivo MR spectroscopy provides biochemical profiles of tissue and has been reported to differentiate brain tumors in several studies [1-4]. The objectives of this study were to characterize BM using ex vivo and in vivo MR spectroscopy, and to correlate tumor metabolic profiles with clinical outcome for the patients.

Experimental

In vivo ^{1}H MR spectra were obtained from patients (n=21) with BM (n=27) using a 3T clinical MR system (Philips Intera) prior to treatment. The MRS volume was located using PRESS (TR 2000 ms, TE 33 ms). Ex vivo HR MAS MR spectra (n=26 biopsies from 15 patients) were obtained using a Bruker Avance DRX600 (4°C, spin rate of 5 kHz). Standard pulse-acquired ^{1}H spectra and spin echo spectra (TE 32 and 285 ms) were acquired. In seven of the patients, more than one biopsy from the same tumour was analyzed, and the mean spectra were used for multivariate analysis. All data was analyzed using partial least squares regression (PLS) with full cross validation, relating spectral data to the clinical outcome after 5 months. Classification of the patients was also made by using recursive partitioning analysis (RPA) [5].

Results and discussion

Twelve of the 21 patients examined by in vivo MRS and 11 of the 15 patients examined by HR MAS lived after 5 months. The PLS results for the in vivo MR spectra are presented in Figure 1A. The score plot of the two first principal components (PC1 and PC2) are shown with the corresponding weighted regression coefficients, summarizing the correlation of spectral data from untreated metastases and survival 5 months after treatment. PC1 and PC2 explained totally 85 % of the spectral data and 53 % of the y-variable (survival data). The correlation coefficient obtained between measured and predicted survival was 0.73 (p < 0.01) for the calibration run and 0.76 (p < 0.05) for the corresponding validation (seven test samples). The spectra of patients who survived 5 months after first MRS (**O**) are clustered in the upper right quadrant of the score plot, while the spectra of patients who passed away before 5 months (**†**) are clustered on the opposite side. The intermediate area defined by two dotted lines, enclose patients with different outcome, spectral information and RPA.

The HR MAS spectra with short echo time gave the best PLS results regarding numbers of valid PC's and the significance of correlation coefficients. The displayed score plot in Figure 1B shows PC1 versus PC2, which explained totally 81 % of the spectra and 77 % of the y-variable. The correlation coefficient between measured and predicted survival was 0.88 (p < 0.01) and 0.65 (p < 0.01) for calibration and validation, respectively. Spectra of patients who survived 5 months after surgery (**O**) were linearly separable from patients surviving < 5 months (**†**).The RPA classification of the patients were not in accordance to their corresponding spectrum's location in the PLS score plot. In conclusion**,** the MRS determined metabolic profiles might be valuable information when planning treatment of BM, and also in the decision for termination of further therapies.
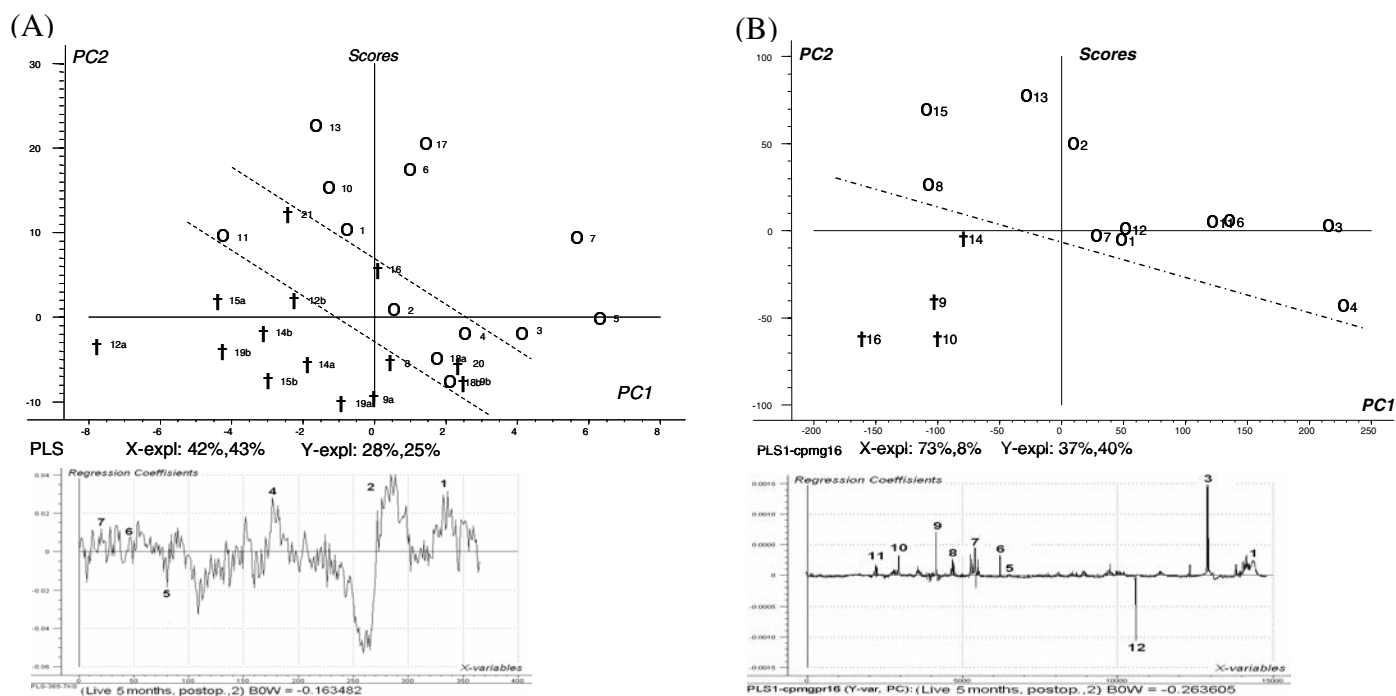
Figure 1.
PLS score plots showing the dispersion of **A**) in vivo MR spectra (n=27) and **B**) ex vivo HR MAS spin echo spectra (n=15) from patients who lived longer than 5 months after the first MR examination, marked as **O**, and those who passed away before 5 months, marked as **†**. The two first principal components are shown with the corresponding regression coefficients; PC1 and PC2. The numbers represent following metabolites: 1: Lipid (0.9 ppm), 2: Lipid (1.3 ppm), 3: Lactate (1.3 ppm), 4: Lipid (2 ppm), 5: Lipid (2.8 ppm), 6: Creatine (3.0 ppm), 7: Choline containing compounds (3.2 ppm), 8: Taurine (3.4 ppm), 9: Glycine (3.6 ppm), 10:Creatine (3.9 ppm), 11: Lactate 4.1 ppm), 12: Acetate (1.9 ppm)

References
1. Barton, S.J. et al. MAGMA, 8, 1999, **2.** Howe, F.A. et.al., NMR Biomed., 16, 2003, **3.** Ishimaru, H. et.al., Eur.Radiol., 11, 2001, **4.** Martinez-Bisbal, M.C. et.al., NMR Biomed., 17, 2004, **5.** Gaspar et al., Int J Radiat Oncol Biol Phys, 47, 2000.