

Subclassification of brain tumors based on ex vivo MRS metabolic profiles

T. E. Sjøbakk^{1,2}, S. Gulati³, M. Gulati¹, S. Lundgren^{1,4}, S. H. Torp^{5,6}, and I. S. Gribbestad¹

¹Dept. of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway, ²St. Olavs University Hospital, Trondheim, Norway, ³Dept. of Neurosurgery, St. Olavs University Hospital, Trondheim, Norway, ⁴Dept. of Oncology, St. Olavs University Hospital, Trondheim, Norway, ⁵Dept. of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway, ⁶Dept. of Pathology and Medical Genetics, St. Olavs University Hospital, Trondheim, Norway

Introduction: The main groups of brain tumors can be classified using MR spectroscopy in vivo and ex vivo [1, 2]. Subclassification of these groups could provide more unique and individual biological information of value for patient treatment. Meningiomas are the second most common central nervous system tumor, accounting for approximately 20% of all primary adult intracranial tumors. Meningiomas are histopathological classified into three groups; grade I-III, where grade I is benign and grade II and III are malignant types. Brain metastases, the most common intracranial tumor, can originate from primary lung, breast, skin and colon carcinomas. Previous work suggests that a discrimination of origin may be achieved by their metabolic profile examined by multivariate analyses [3]. The objective of the present study was to examine if meningiomas and brain metastasis could be characterized in subgroups based on their metabolic profiles and whether these subgroups correlate to histopathological features.

Samples and methods: Resected tumor tissue from patients scheduled for brain tumor surgery were immediately stored in liquid nitrogen. HR MAS MR spectra were obtained using a Bruker Avance DRX600 instrument using standard pulse-acquired and spin echo (TE 32) pulse sequences as previously described [3]. The spectra were examined using principal component analysis (PCA) and partial least square (PLS) regression with full cross-validation and mean-centered data. Histopathology data (diagnoses, grading) were obtained using standard clinical procedures. The study was approved by the local ethics committee.

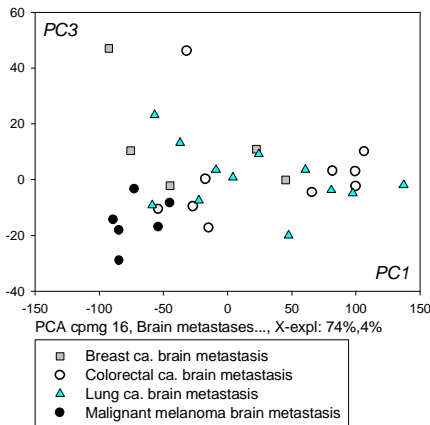


Figure 1. PCA score plot of PC1 and PC3 showing the dispersion of spin echo spectra (TE32) of brain metastases from 33 patients with different primary cancer.

Results and discussion: MRS determined metabolic profiles and histopathology were obtained from brain metastases (n=33) and meningiomas (n=22). The spectral region 4.7-0.7 ppm of spin echo spectra was selected for the PCA analysis. The score plot of principal component PC1 and PC3 for brain metastases spectra (n=33) is shown in Figure 1. PC1 and PC3 account for nearly 80 % of the total variation of the spectra. PC1 is mainly based on variations in the level of lipid signals compared to metabolite levels. PC3 separates both due to metabolite differences in the spectrum region 3.0 – 4.7 ppm and the lactate signal at 1.3 ppm. Brain metastases from malignant melanomas tend to cluster as one group; however, the other groups are overlapping. Mean spectra from two sub-classes of metastases from malignant melanomas and colorectal cancer (Figure 2) show differences in both lipid content, metabolite level and composition. The PLS analysis of spectra from meningiomas (n=22) using the spectral region 4.7 – 1.5 ppm as input x-variables, is shown in Figure 3. The score plot shows a separation of meningiomas based on their histopathological grading (only grade I and II represented), in accordance with previous findings [4]. The PLS model results in three valid PCs, where the correlation between actual and predicted class is 0.94 (p-value) and 0.62 (p-value) for calibration and validation, respectively. We found no correlation between subclasses of meningiomas and lipid content.

Conclusions: Using HR MAS metabolic profiles, a subclassification of meningiomas correlating to histopathological grading was found. The spectra of brain metastases showed a subgroup of malignant melanoma metastases. The other groups of metastases appeared with overlapping metabolic profiles.

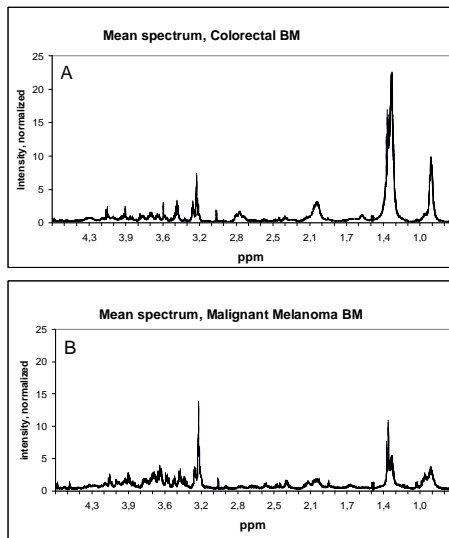


Figure 2. Mean spin echo spectra (TE32) of brain metastases (BM) from colorectal carcinomas (A, n=10) and malignant melanomas (B, n=6). The spectrum region 4.7 – 0.7 ppm region is shown.

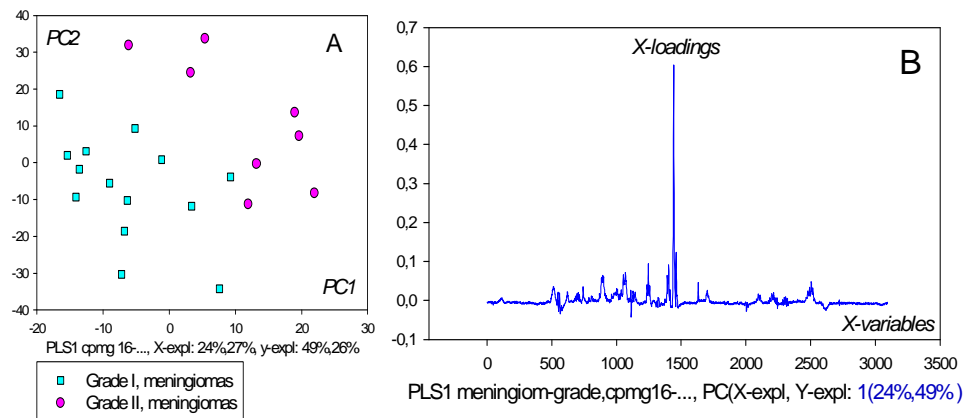


Figure 3. A: PLS score plot of PC1 and PC2 of spin echo spectra (4.7-1.4 ppm) of meningiomas (n=22). The samples are dispersed according to tumor grade I and II. B: Loading profile of PC1 showing metabolites which contribute to the dispersion.

References

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3. Sjøbakk T, et al. *NMR Biomed*. 2008, 4. Monleon D, et al. *J Proteome Research* 2008