MR CHARACTERIZATION OF TWO EXPERIMENTAL MODELS OF OVARIAN CANCER: METABOLITE QUANTIFICATION AND DIFFUSION AND PERFUSION ASSESSMENT

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Introduction

Ovary cancer is the gynaecological malignancy at highest death rate. It is often discovered only at advanced stages, with frequent occurrence of relapse and onset of drug resistance. MRI combined with MRS has demonstrated its usefulness in tumour diagnosis, prognosis and treatment evaluation in vivo. An abnormal pool of choline-containing compounds (tCho) is detected in MRS spectra of cultured ovarian carcinoma cells and in patient ovarian cancer masses (1-4). Proper animal models would greatly contribute to evaluate the significance and biological role of these and other alterations during tumour growth or following treatment in ovarian cancer. In this work two models of human ovarian carcinoma were implemented and characterised by quantitative MRS and ADC analyses.

Methods

In vivo MRS measurements were performed on a Varian Inova system, equipped with a 200/183 horizontal magnet at 4.7 T. MRI/MRS analyses were performed on tumour xenografts 7-16 days following 1) sc implantation in the dorsum and 2) ip implantation in the peritoneum of SKOV3ip cells in SCID mice. The SKOV3ip cell variant was obtained by in vivo intraperitoneal passage of SKOV3 cells and was chosen because of its high in vivo tumorigenity associated with elevated PCho content. MRI evaluation was performed by T1W (TR/TE=500/20ms), T2W (TR/TE=3000/70ms) and PD (TR/TE=3000/20ms) multislice spin echo images with an in plane resolution as high as 47 x 94 μm^2 and a thickness of 600 µm. ADC measurements were performed by acquiring DW images (TR/TE=2000/50 ms, b ranging from 123 to 1105 s/mm^2). Perfusion fraction (i.e. the component attributed to flowing spins) was calculated by extrapolating the intensity value for the b=0 image and subtracting the real images acquired with b=0 (5). Quantitative ^1H MRS analyses were performed by using a PRESS sequence (TR =4000 ms, in order to minimise T1 relaxation losses and TE ranging from 23 to 256 ms) and assuming 80% of tumour water content. LCModel was used for the spectral fitting.

Results and Conclusions

Both models developed solid tumour masses (Fig1a) already detectable at 7-10 days post injection (dpi). The ip injection produced solid pelvic masses preferentially in the proximity of the uterus. At 14-16 dpi they are homogenous and large enough to position voxels of 6-10 µl for MRS. Both models have similar spectral patterns composed by two prominent signals, due to tCho and inositol (Ino) metabolites (Fig1b). The assignment of Ino derived from the characteristic multiplet profile at 3.55 ppm, whose intensity was modulated by TE in our in vivo spectra. In vitro MR analyses of tissue extracts confirmed the presence of Ino at 3.55 ppm and PCho as the main constituent of the tCho peak. In some cases, especially in intrapelvic implants, a large lipid (Lip, 1.3 ppm) signal was often observed, probably due to contamination by surrounding tissue. In sc implants the Lip signal (likely due to intratumoral lipids) appeared only at late stages of tumour growth. Quantitative results are summarised below:

	Water T2 (ms)	Cho T2 (ms)	ADC (x $10^{-4}mm^2/s$)	% Perfusion	Cho (mM)	Ino (mM)
ip	57 ± 4 ms	377 ± 50 ms	16.4 ± 1.1	3.7 ± 2.3	3.9 ± 0.7	16 ± 3
sc	55 ± 1 ms	316 ± 43 ms	15.8 ± 0.3	2.4 ± 2.1	3.9 ± 0.7	13 ± 2

In vivo quantification of the Cho signal in both types of xenografts gave the same average concentration value, consistent with those measured in aqueous extracts of similar tumours (1). The slight, although not significant difference in Ino content may be related to the proximity of its signals to the water peak and therefore to a worse spectral fitting. ADC values were consistent with those measured in ovarian carcinoma patients (5), while the perfusion fraction was lower.

In conclusion, both ortho- and heterotopic ovarian cancer models gave reasonable values for the measured parameters and can represent valuable tools to detect possible biochemical and physiopathological changes during tumour growth and/or in response to therapy.

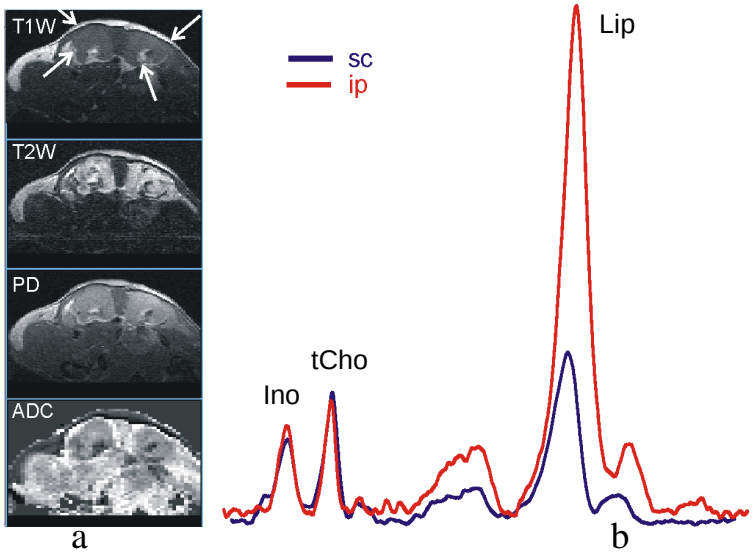

Figure 1 a) MRI of pelvic human ovarian cell xenograft (15 dpi) inSCID mouse; b) MR spectra of sc and ip ovarian carcinoma xenografts.

References : 1) Iorio E et al, 2005,Cancer Res,65,9369; 2) Podo et al, 2007,Current Med Imaging Rev, 3, 123; 3) Iorio E et al, ISMRM Cancer Study Group, Nice, Sept 2008; 4) Stanwell P et al, 2008, Invest Radiol, 43, 745; 5) Priest AN et al., 2008, Proc Intl Soc Mag Reson Med 16.

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