^{31}P MRS at 7T can be more sensitive and specific than ^{1}H MRS in monitoring breast cancer treatment.

D. Klomp[1], W. van der Kemp[1], M. Korteweg[1], J. Wijnen[1], M. van de Bosch[1], and P. Luijten[1]
[1]University Medical Center Utrecht, Utrecht, Netherlands

Introduction

The choline signal in proton MR spectroscopy is a sensitive measure to monitor treatment in breast cancer[1]. Unfortunately, the detection technique used for a quantitative assessment of choline concentrations can be quite challenging. The intensity of the choline signal is four orders of magnitude smaller than the signals from the surrounding lipids and the location of the tumor has to be known in advance as in general only single voxel MRS can be applied robustly (i.e. without being contaminated with signals from lipid tissue). In addition to these sensitivity limiting factors, specificity may be hampered by insufficient spectral resolution in ^{1}H MRS in vivo to discriminate between multiple compounds involved in choline and ethanolamine metabolism. With ^{31}P MRS, no signals are observed from lipid tissue, making the technique very simple and robust to apply in breast tissue for metabolic imaging. In addition, ^{31}P MRS provides a higher chemical shift dispersion, enabling the detection of phosphocholine (PC), phosphoethanolamine (PE) and their glycerol compounds (GPC, GPE), which may give a more detailed insight in the biology of cell proliferation. In fact, animal and cell studies have shown that particularly the ratio between phosphomonoesters (PE+PC) and diesters (GPE+GPC) can be used as markers for treatment evaluation of breast cancer[2,3]. This study is designed to assess the feasibility of detecting phospholipid metabolites in the human breast at spatial resolutions of 10ml using ^{31}P MRSI at 7T in patients. Additionally, we want to validate the substantially higher PE and GPE levels compared to PC and GPC in breast tumor tissue, and report alterations in phopholipid metabolism that could not be observed with ^{1}H MRS during the course of neoadjuvant chemotherapy.

Methods

A two-channel double-tuned unilateral RF coil was designed for ^{31}P and ^{1}H MRI and MRS of the human breast and interfaced to a whole body 7T MR system (Philips, Cleveland, USA). In vivo single voxel MR spectra of $(2.0\ cm)^3$ were obtained from the tumor (invasive ductal carcinoma) in three patients with breast cancer and from glandular tissue in a healthy volunteer (semi-LASER sequence, MEGA water and lipid suppression, TR = 4 s, 32 averages). The MR spectra were obtained at a TE of 56ms and 118ms to correct for T2 relaxation and water referencing was used for quantification. In addition, ^{31}P MR spectra were obtained from 10 ml voxels over the entire breast using pulse acquired 3D CSI (with a TR of 1.5s and a nominal flip angle of 39 degrees) from all subjects.

Results

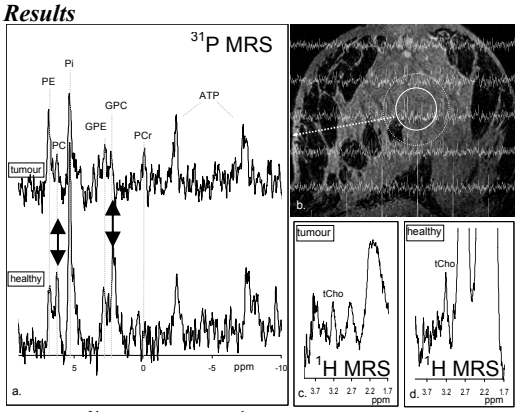

Figure 1. ^{31}P (3D CSI) and ^{1}H (single voxel) MR spectra obtained from human breasts (patient versus age matched healthy control) at 7T in vivo. Note that all choline compounds (PC, GPC and "total choline") are even lower in the tumor ($0.4mM_{tCho}/kg_{wate}$),(c) versus the healthy control ($0.7mM_{tCho}/kg_{wate}$) (d), whereas the ratio between phosphomonoesters (PC+PE) and diesters (GPE+GPC), which can only be observed in the ^{31}P MRS, is substantially different (a).

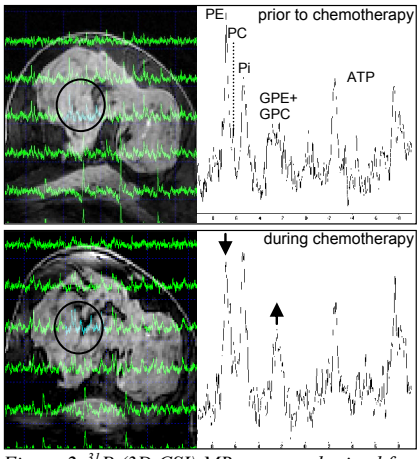

Figure 2. ^{31}P (3D CSI) MR spectra obtained from a breast tumor prior to (top) and during (lower) chemotherapy. Note the reduced phospomonoesters and elevated diesters, while the total level remains comparable. Also note that the increased contribution of lipids (see MRI) during chemotherapy does not effect the detection of the phospholipid metabolites. The only noticeable effect is line broadening

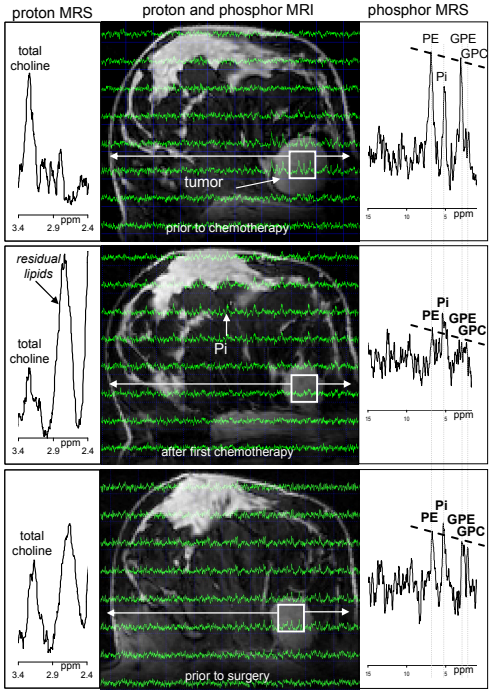

Figure 3. ^{31}P (3D CSI) and ^{1}H MR spectra obtained from a breast tumor prior to (top), during (middle) and after (lower) a, by histopathology proven, ineffective chemotherapy. Although "total choline" levels are reduced from 4.2 via 0.7 to $2.6mM/kg_{water}$ during the treatment, the ratio between phoshomonoesters and diesters remained constant (see slope of dashed line).

Conclusion and discussion

In this work we demonstrate the ability to detect phospholipid metabolites in vivo in the human breast using ^{31}P MRS at 7T. Incorporation of lipid tissue in the selected voxel does not effect the detection of phospholipids (Fig. 2), which opens up the ability of applying metabolic imaging to the entire breast. In contrast to healthy tissue, substantially higher levels of PE and GPE are observed in tumor tissue relative to PC and GPC. As both PE and GPE contain two protons with exactly the same chemical shift as the 9 tri-methyl choline protons, increased signal strength in tumor tissue at 3.2 ppm may be assigned to increased (PE + GPE) rather than to changes in the total choline pool as shown in figure 1. This will have a substantial impact on the interpretation of quantitative spectroscopic data in tumors. The balance between phosphomonoesters and diesters can be altered independent of the total choline pool (Fig. 2) or visa versa (Fig. 3), which could lead to a false negative or false positive evaluation of treatment efficacy when only performing ^{1}H MRS. In conclusion we therefore state that ^{31}P MRS at 7T seems a promising technique for monitoring breast cancer treatments with potentially a higher sensitivity and specificity than ^{1}H MRS .

References

[1] Haddadin et al. NMR in Biomed 2009;22(1). [2] Katz-Brull et al. Cancer Res 2002;62(7). [3] Sterin et al. Cancer Res. 2001;61(20).