Inherently decoupled $^1$H antennas and $^{31}$P loops for metabolic imaging of liver metastasis at 7 T

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Abstract
High field $^{31}$P spectroscopy has thus far been limited to diffuse liver disease. Unlike lower field-strength scanners, there is no body coil in the bore of the 7 T and despite inadequate penetration depth (<10 cm), surface coils are the current state-of-the-art for acquiring anatomical images to support multinuclear studies. We present a system of proton antennas and phosphorus loops for $^{31}$P spectroscopy and provide the first ultrahigh-field phosphorus metabolic imaging of a tumor in the abdomen. Herein we characterize the degree to which antennas are isolated from underlying loops. Next, we evaluate the penetration depth of the two antennas available during multinuclear examinations. Finally, we combine phosphorus spectroscopy (two loops) with parallel transmit imaging (eight antennas) in a patient. The loops and antennas are inherently decoupled (no added circuitry, <0.1% power coupling). The penetration depth of two antennas gives twice that of conventional loops. The liver and full axial slice of the abdomen were imaged with eight transmit/receive antennas using parallel transmit B1-shimming to overcome image voids. Phosphorus spectroscopy from a liver metastasis resolved individual peaks for phosphocholine and phosphoethanolamine. Proton antennas are inherently decoupled from phosphorus loops. By using two proton antennas it is possible to perform region-of-interest image-based shimming in over 80% of the liver volume, thereby enabling phosphorus spectroscopy of localized disease. Shimming of the full extent of the abdominal cross-section is feasible using a parallel transmit array of eight antennas. A system architecture capable of supporting eight-channel parallel transmit and multinuclear spectroscopy is optimal for supporting multiparametric body imaging, including metabolic imaging, for monitoring the response of patients with liver metastases to cancer treatments and for patient risk stratification. In the meantime, the existing infrastructure using two antennas is sufficient for preliminary studies in metabolic imaging of tumors in the liver.

Abbreviations used: A, anterior; BMI, body mass index; BW, bandwidth; B0, static magnetic field; CSI, chemical shift imaging; F, foot; FOV, field of view; GE, gradient echo; GPC, glycerophosphocholine; GPE, glycerophosphoethanolamine; H, head; $^1$H, proton nucleus; L, left; NMR, nuclear magnetic resonance; P, posterior; PC, phosphocholine; PCr, phosphocreatine; PDE, phosphodiester; PE, phosphoethanolamine; Pi, inorganic phosphate; PME, phosphomonoester; Ptc, phosphotidylcholine; $^{31}$P, phosphorus nucleus; R, right; RF, radio frequency; ROI, region of interest; SNR, signal-to-noise ratio; $S_{21}$, transmission coefficient; T, Tesla; TE, echo time; TR, repetition time; T1, longitudinal relaxation; T2, transverse relaxation.

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1 | INTRODUCTION

1.1 | Towards spectroscopy for cancer treatment monitoring in the liver

The translation of nuclear magnetic resonance (NMR) techniques from test tubes to patients was motivated by a required paradigm shift in cancer treatment, with an early focus on phosphorus spectroscopy. To date, NMR remains a mainstay for the development and evaluation of new therapeutics. The pioneers of MR underestimated the difficulty and necessity of creating a stable high field magnet on the human scale. With the emergence of ultrahigh field (>4 T) magnetic resonance imaging, phosphorus spectroscopy (\(^{31}\)P) becomes possible on clinically relevant spatial and temporal resolutions (<30 minutes, <30 mL) and allows for differentiation of relevant metabolites, opening up the possibility of \(^{31}\)P spectroscopy as a nonionizing method of metabolic tracking of tumor response to therapeutics in patients.

The liver is a frequent site for metastases of solid tumors, such as breast, colon, oesophago-gastric and pancreatic cancers. Once metastasized, most cancers are incurable, although overall survival and quality of life may be extended by systemic treatment. Unfortunately, response to treatment varies greatly between patients, even when suffering from the same primary tumor. New tools to predict or measure treatment response before or shortly after the start of treatment are urgently needed to prevent the long-term exposure of patients to ineffective treatments.

In the preclinical setting, \(^{31}\)P spectroscopy is already a key tool for elucidating cancer metabolism and quantitative evaluation of new treatments. As such, clinical \(^{31}\)P spectroscopy is of great interest as a potential tool for tracking treatment response. Phosphorus spectroscopy provides a multitude of information on cancer metabolism and the local environment, such as phospholipid metabolism (phosphoethanolamine [PE], phosphocholine [PC], glycerophosphoethanolamine [GPE] and glycerophosphocholine [GPC]), cellular energetics and intracellular and extracellular pH (via inorganic phosphate [Pi]). These may all be related to early treatment response. For example, in the case of secondary hepatic lymphoma, decreases in the phosphomonoesters (PMEs), comprising predominantly PE and PC, occur within 1 to 14 days of the beginning of treatment.

Until recently, at 7 T (300 MHz), collecting a proton image of the liver presented a challenge as the wavelength for proton imaging at 300 MHz approaches the dimensions of the abdomen. Therefore, conventional approaches using volume coils (eg, birdcage) or loop coils for acquiring scout images for preparing \(^{31}\)P scans (B0 shim and voxel placement), or anatomical images on which to overlay spectra results (localizer images), fail to provide sufficient penetration depth for proton imaging at high field. There is no body coil in the bore of the 7 T and no receive loops are present in the bed.

1.2 | Antennas for ultrahigh field body imaging

Antennas propagate electromagnetic fields directly into the tissue and thus enable improved penetration depths over loops and microstrip elements, overcoming the challenges associated with body imaging at 300 MHz. In addition to poor penetration depth, at high field destructive interference causes inhomogeneity of the transmit field, which can be minimized by a technique known as B1 shimming. In B1 shimming, the transmit profiles of each element are mapped in order to determine the required input phase (and optionally the magnitude) of the excitation pulses sent to individual transmit elements in order to reduce destructive interference in the region of interest (ROI). In practice, B1 shimming requires a system capable of independent control of multiple transmit channels which can operate simultaneously, namely, a parallel-transmit system or "multix" system.

1.3 | Antennas in combination with loops for ultrahigh field multinuclear spectroscopy

The fields generated by an antenna and an underlying loop are orthogonal and therefore inherently decoupled (<0.1% power transferred). Therefore, the antennas provide an opportunity for two simultaneously present although independent hardware systems. The typical compromises of combining frequencies are avoided. Such methods either incorporate additional circuit components (eg, decoupling, dual-tuning) or require the hardware to be exchanged mid scan session. The use of an eight-element array of fractionated dipoles at 7 T is a well-known method within the high field community. However, the state-of-the-art for proton imaging to support multinuclear experiments remains surface coils, and typically...
dual-tuned surface coils. Due to this reliance on surface loops thus far, high field phosphorus spectroscopy in the human liver in vivo has been limited to diffuse disease, due to the difficulty of obtaining proton images to enable ROI B0 shimming and voxel placement in preparation for the phosphorus chemical shift imaging (CSI). In the current study, we demonstrate the inherently decoupled nature and use of simultaneously present phosphorus loops (120 MHz) and proton antennas (300 MHz), and explore the application of the fractionated antennas as a means of overcoming the limitations in ultra-high field x-nuclei spectroscopy for oncology due to the complexity of performing routine imaging tasks (\( ^1H \)) in the abdomen at high field. As proof-in-concept, we demonstrate a novel coil combination of antennas (\( ^1H \)) and loop coils (\( ^31P \)) for targeting organs within the abdomen by obtaining the first 7 T phosphorus dataset in a patient with liver metastasis. The goal is to share this method with those working on multinuclear 7 T studies, as well as to demonstrate to MR spectroscopists working at lower field strength that the necessary imaging requirements can now be met at high field for body applications by simply using two \( ^1H \) antennas and two \( ^31P \) loops. Proceeding towards clinical applications, we also make a case for a new 7 T system architecture capable of combining parallel transmit imaging (\( ^1H \)) with multinuclear (\( ^31P \)) spectroscopy at 7 T.

2 | METHODS

2.1 | Hardware setup and quantification

A customized liver coil (MR Coils, BV, Zaltbommel, the Netherlands) was built for use with a 7 T Philips system (Philips, Cleveland, OH, USA) consisting of eight fractionated dipole antennas (30 cm from end to end of the conductors—according to Raaijmakers et al. for transmit and receive of the proton (300 MHz) signal—and two partially overlapping loops (20 cm in diameter) for transmitting and receiving the \( ^31P \) (120 MHz) signal.

In order to demonstrate the inherently decoupled nature of proton antennas and phosphorus loops, we conducted a series of benchtop measurements to characterize the magnitude of the transmission coefficient (\( |S_{21}| \)),

\[ |S_{21}| \text{ (dB)} = 20 \log_{10} \left( \frac{v_2}{v_1} \right) = 10 \log_{10} \left( \frac{P_2}{P_1} \right), \]

where \( v_1, P_1, v_2, \) and \( P_2 \) are the voltages and powers measured at ports 1 and 2 of a vector network analyzer. A phosphorus loop was attached to port 1 and the antenna was attached to port 2. Note that \( |S_{12}| = |S_{21}| \). Markers were placed at the operating frequencies of both devices and recorded for five volunteers with various body mass index (BMI) measurements (20–34 kg/m\(^2\)). For each of the five volunteers, three measurements were made at each frequency and recorded. The mean and standard deviation of the individual subject means were calculated for both frequencies.

The commercially available system does not support multinuclear spectroscopy and parallel transmit (\( ^1H \)) during the same scan session. Therefore, the multinuclear experiment and associated proton imaging were conducted with two (out of eight) antennas (300 MHz) and the two overlapping loops (120 MHz). For each frequency, the pairs of elements were combined with quadrature hybrids (+90 degrees for transmit, −90 degrees for receive).

2.2 | Scanning

The study was approved by the internal review board and written informed consent was obtained from all participants. Power was optimized for the \( ^31P \) sequence by using a flip-angle sweep to identify the maximum signal intensity in a phantom (55% solution of alcohol in water with 4.8 g/L salt; permittivity of 36 and a conductivity of 0.43 S/m) and verified in a participant. Similarly, the optimal power level was found for the proton antennas as evaluated in a phantom and verified in vivo, to verify that the desired flip-angle matched the actual flip-angle. Adiabatic pulse-acquire scans were performed for the multinuclear experiments; therefore, we did not further optimize the transmit power.

The scanner was rebooted (5 minutes) mid-session in order to access the transmit chain for the multinuclear experiment (classic mode) for half of the examination, and the parallel-transmit capable transmit chain (multix mode) during the other half of the experiment. The multinuclear power amplifier is used for proton imaging during parallel transmit.

2.2.1 | Classic-mode protocol

Proton (\( ^1H \)) localizer images were obtained using two antennas in quadrature for ROI-based B0-shimming (2nd order) with a gradient echo MRI (parameters listed below). As eight-channel parallel transmit was unavailable during this mode, six of the antennas were unused during this part of the examination and instead terminated with 50 Ω load resistors. Phosphorus spectroscopy data were acquired with quadrature-combined
overlapping loops. A pulse-acquire sequence (block pulse, 30° flip angle, 2048 samples, 8192 Hz BW, TR 1 second, 24 averages) was used to set the center frequency to correspond with PE. We obtained 3D CSI scans with a field of view (FOV) of 240 × 240 × 240 mm, TR/TE 700/0.4 ms, and 30 mm isotropic voxels, with a total imaging time of 5 minutes per average. An adiabatic half passage RF pulse was used for pulse-acquire 3D CSI with a tanh/tan shape, 2 ms pulse duration, and maximum frequency modulation of 21 kHz (174 ppm).

2.2.2 | Multix-mode protocol

With the 31P loops remaining in place below the antenna array, eight antennas were connected to an interface box with transmit/receive switches to allow use of the antennas for transmit and receive. The parallel transmit protocol was adapted from previous work using the same antenna elements for imaging the prostate, pancreas, and kidneys (eg, Hoogduin et al24). B1 and B0 shimming were performed using an image-based shim tool (MR Code, BV, Zaltbommel, the Netherlands). ROI B0 shimming (2nd order) was performed on a reference scan, and B1-shimming was conducted by mapping the B1 of each transmit antenna and calculating the relative phase offsets using a third-party software application running on the scanner host (MR Code).

Images were acquired with a gradient echo using TR/TE 4.97/2.42 ms, 40° flip angle, 300 × 330 × 330 mm FOV and voxels of 0.8 × 0.9 × 5 mm. Dixon images were collected in both modes (multislice gradient echo, 20 slices, TE1/TE2/TR 2.65/3.15/10 ms, 15° flip angle, 250 × 300 × 80 mm FOV, 276 × 276 encoding in 4 mm thick slices, three averages, 109 seconds acquisition).25 The FOV for obtaining water images with the Dixon method in the patient was adjusted to 234 × 359 × 80 mm.

2.3 | Data processing and analysis

2.3.1 | Penetration depth

While considerable work has been done to characterize the use of eight-antenna arrays for body imaging, this is the first time that two antennas have been used as a means of ROI-based shimming and localizing an anatomical target for multinuclear spectroscopy. Again, the scanner architecture does not currently support multinuclear spectroscopy and parallel transmit (eight-channel) imaging during the same scan session, thus we used two antennas combined in quadrature for localizing and ROI-based shimming in preparation for the phosphorus spectroscopy 3D CSI. Therefore, we characterized the depth of the sensitivity profile for the two antennas in quadrature (signal calculated as 1.5-fold greater than mean background signal) for nine participants of various sizes and BMI (~ 20–30 kg/m²) along three axes: anterior/posterior (A/P), left/right (L/R) and head/foot (H/F). In order to evaluate the needed depth to provide full coverage of the liver, we characterized the depth of the liver along the same three axes for young (aged <40 years) healthy volunteers. All length measurements are reported as the mean accompanied by standard deviation of the sample population in parentheses.

2.3.2 | Spectroscopy

Voxels were selected for postprocessing from 3DiCSI (Hatch Center for MR Research, Columbia University, NY, USA) and Hamming-filtered, uploaded into JMRUI26 and filtered with a 40 Hz Lorentzian, zero-filled to double the number of points (from 512 to 1024), zero-order phase corrected, and 1st order (0.4 ms) phase-corrected. In order to support a comparison with the literature in the Discussion section, estimates of SNR for the PE and PC peaks of the patient were derived from peak heights and noise floor estimates. The estimation process was tested for convergence through comparison of known and estimated SNR in the phosphorus spectroscopy dataset under discussion from Schmitz et al.27

3 | RESULTS

3.1 | Inherent decoupling between antennas and loops

The conducted benchtop measurements confirmed that the antennas and loops were inherently decoupled. The transmission coefficients across the five volunteers were − 40 (+/− 5) dB at the phosphorus frequency and − 56 (+/− 4) dB for the proton frequency. These measurements indicated that the power coupling was of the order of hundredths of a percent for the phosphorus experiments, and less than one thousandth of a percent for the proton experiments. This confirmed that neither decoupling nor detuning circuitry was required and that the two systems could be used independently and simultaneously.
3.2 Penetration depth of antennas

The penetration depth of a two-antenna system in vivo exceeds 15 cm in the A/P direction and approaches 30 cm in the R/L direction. Aggregate data compare penetration depth (n = 9) with liver depth (n = 5) as four of the livers were not fully visualized for each direction (Table 1). The penetration depth in both the R/L and H/F direction exceeded the required depths for visualizing the liver, although the A/P penetration was approximately equal to the liver depth. The liver coverage achieved by two antennas was sufficient to visualize the boundaries of five out of nine (55%) of the healthy volunteers scanned, and was within 1 cm of the necessary A/P coverage for the remaining volunteers. The coverage in the H/F axis exceeded the required coverage by 2-fold. As can be seen from Figure 1, while a conventional loop approach provides less than 50% liver coverage (Figure 1A), the presented two-antenna system provides upwards of 80% liver coverage (Figure 1B).

3.3 Liver imaging and spectroscopy

We successfully combined 7 T multinuclear spectroscopy and parallel-transmit anatomical data in a single exam, and demonstrated the first documented application in a patient. The two-antenna system in combination with the loops allowed for phosphorus 3D CSI with ROI-based shimming. Two antennas with fixed-transmit phases allowed the Couinaud system left and right hemi-livers to be visualized (Figure 1B). While the right and left hemi-livers (Couinaud system) can be imaged with two antennas combined in quadrature, full visualization of the liver is not possible due to voids in the image (observable in Figure 1B). Parallel transmit with eight antennas allows for B1-shimming to overcome these image voids. Figure 1 presents the identical slice with voids (Figure 1C) and with B1-phase shimming (Figure 1D). The eight transmit/receive antennas provide coverage of the complete ROI, allowing visualization of the liver and full axial slice of the abdomen (Figure 2).

| TABLE 1 | Measurements of penetration depths and needed coverage for liver in the anterior/posterior (A/P), right/left (R/L) and head/foot (H/F) directions. Aggregate values are displayed as mean (std) across participants. *Four of the nine participants were excluded in estimating the needed coverage, as the A/P boundary was insufficiently imaged. |
| A/P [cm] | R/L [cm] | H/F [cm] |
|---|---|---|
| penetration (n=9) | 16.4 (1.5) | 27.9 (2.7) | 30.0 (2.7) |
| needed coverage (n=5*) | 14.8 (1.4) | 20.0 (2.4) | 15.1 (1.3) |

**FIGURE 1** A, Two overlapping loops (position indicated in gray) are the state-of-the-art for localizer images for multinuclear experiments at 7 T, adapted from Runge et al.22; B, by using two antennas for 1H (boxes labeled 1H) centered over 31P loops (position indicated in gray), the coverage of the liver is extended to include the anatomical left and right hemi-livers. Eight antennas distributed in one row encircling the abdomen: the signal voids due to destructive interference are C, present before B1-shimming and D, gone after adjusting relative phases of the transmit pulses (B1+ phase shimming).
In this study we perform, to our knowledge, the first application of high field phosphorus spectroscopy in a liver tumor, and do so in combination with parallel transmit imaging. Figure 3 shows results from a patient with liver metastasis with the $^{31}$P 3D CSI projected onto a Dixon image collected with eight antennas using parallel transmit. Phosphorus spectra from the liver and from the metastasis of oesophago-gastric cancer allow differentiation of PE and PC. The PE and PC appear with equal peak heights in the liver volume, whereas in the tumor, the PE peak is greater than the PC peak and the phosphodiesters (PDEs).

**FIGURE 2**
A, Dixon image (see text for parameters) of a healthy female participant (body mass index = 23 kg/m$^2$, age = 38 years) using eight antennas and parallel transmit, with anatomical labels provided on the identical image (right) so as to not obscure features. B, Survey in coronal (left) and sagittal (right) planes (2D gradient echo, TR 10 ms, 15° flip angle, 280 × 280 × 464 mm field of view (FOV); 257 phase encoding steps, 516 frequency encoding steps; 30 slices, each 10 mm thick, 78 seconds acquisition), demonstrating FOV provided by the eight antennas.

**FIGURE 3**
Spectroscopic data from A-C, a patient with one average and D, a healthy volunteer with five averages scaled to the Pi peak. (A) Phosphorus spectra 3D CSI with 30mm isotropic voxels from a patient with liver metastasis (gastric primary), displayed on a B1-shimmed Dixon image obtained with eight antennas. Spectra collected with $^{31}$P loops from characteristic voxels (B) inside the tumor and (C) inside the liver. The phosphoethanolamine (PE) of tumor (B) is greater than the phosphocholine (PC), glycerophosphoethanolamine (GPE), glycerophosphocholine (GPC) and inorganic phosphate (Pi), while the peak height of PE is less than or equal to those of PC, GPE, GPC and Pi in the liver voxel (B). As can be seen from a healthy volunteer, in the healthy liver (D), the phosphodiesters (GPC and GPE) dominate the phosphomonoesters (PE and PC). PCR, phosphocreatine; PtC, phosphotidylcholine.
By leveraging the ability of antennas to propagate signal into the body and the inherent decoupling between antennas and loops, we present what is, to our knowledge, the first 7 T phosphorus spectroscopy of a tumor in the liver, as well as in the abdomen. First, we demonstrate the inherent decoupling of the antennas and proton systems, with less than a tenth of a percent of power coupling between the antennas and coils at both operating frequencies. Subsequently, we characterize the penetration depth and liver coverage provided by two antennas used in quadrature. The antennas provide penetration depths ranging from 15–28 cm (90%–100% liver coverage) for 7 T proton imaging compared with loops (6–12 cm; <50% liver coverage), as illustrated in Figure 1. Finally, we demonstrate the combined use of the antennas and loops for phosphorus spectroscopy in the liver. The FOV of two 1H antennas centered over a pair of 31P loops allowed for gradient echo imaging of the liver for ROI-based B0 shimming (50% liver coverage), as illustrated in Figure 1. Finally, we demonstrate the combined use of the antennas and loops for phosphorus spectroscopy in the liver. The two-antenna two-loop setup is adequate for collecting multinuclear spectra from tumors in the liver. With two antennas it is possible to perform ROI-based B0 shimming over the majority of the liver. However, there are signal voids inside the liver as well as at the edges of the liver. Therefore, for multiparametric imaging (eg, dynamic contrast-enhanced, T1 maps, T2 maps, diffusion-weighted imaging, quantitative susceptibility maps) of the entire liver, it becomes necessary to boot into parallel transmit mode. In the best case scenario, it takes less than 5 minutes to switch into parallel transmit mode. There are also scan preparations that must be repeated (scouts, B0-shimming and verification), which take an additional 5–10 minutes. In order to have anatomical reference points, and to provide the full cross-section of the abdomen to which radiologists are accustomed, it is preferable to display spectroscopic voxels on the parallel transmit images. We conducted the protocol in a range of volunteers including men and women of different sizes (BMI ~ 20 kg/m2). The liver coverage values reflect that variation. In petite women, full liver coverage is possible with only two antennas; however, a signal void remains. In larger males, the majority (>90%) of the liver boundaries are covered, and still a signal void in the liver remains. While it may be necessary with extreme BMIs to conduct a power optimization check, the coil design and protocol are intended for use with a range of BMIs and body sizes observed in the clinic. Extensive use of the eight-antenna setup on individuals with diverse BMIs has been explored and reported.

We present, what we believe is, the first high field phosphorus spectroscopy of a tumor in the abdomen (Figure 3), with the spectral resolution to differentiate PME and PDE metabolites. As a result, the spectra from the patient with liver metastases appears to exhibit a metabolic phenotype with PE > GPE while the peak height of PC is reduced compared with PE. A similar metabolic phenotype has been identified and prototyped in PME and PDE metabolites. As a result, the spectra from the patient with liver metastases appears to exhibit a metabolic phenotype with PE > GPE while the peak height of PC is reduced compared with PE. A similar metabolic phenotype has been identified and reported. Further investigation within the liver and other tumor sites are warranted to explore the clinical relevance of such a metabolic phenotype. There is an additional and known background signal in the liver not present in breast or prostate phosphorous spectroscopy at 2.06 ppm, corresponding to phosphatidylcholine (Pc) that is present in the liver and in high concentrations in the gall bladder. As the spectra presented in Figure 3 come from voxels near the gall bladder, there are large peaks from Pc (2.06 ppm). Likewise, phosphocreatine (PCr) peaks are present due to contamination from neighboring muscle tissue.

In the current study, a local coil was used to excite the phosphorus signal. In order to overcome transmit inhomogeneity associated with surface coils, we combined adiabatic pulses with 3D CSI for localization, as this is known to be less B1-sensitive than other methods. Breathing-belt triggering would have stretched a 3D CSI single average acquisition to 25 minutes (a 5-fold increase), and was therefore deemed impractical. The TR of the current study was insufficient to overcome saturation effects in the absence of a spoiler gradient due to the widely varying longitudinal relaxation (T1) of relevant metabolites. Spectral quality could be improved through B1 calibration per individual and volume depth, which has the added benefit of allowing for T1-saturation correction. The use of a B1-calibration reference
marker (such as in Purvis et al.) would also facilitate quantification of metabolite concentration. Further improvements in spectral SNR are possible through implementation of various imaging techniques including AMESISING, DIMEPT, and proton observed phosphorus editing. Purvis et al. used a 16-channel phosphorus receive array to acquire $^{31}$P of the liver and Valkovic et al. have demonstrated the use of a $^{31}$P birdcage for transmit in combination with a $^{31}$P receive array for cardiac studies. In such an approach, both the SNR and the homogeneity of the transmit pulse can be improved.

### 4.2 Perspective

The optimal setup for multiparametric imaging including spectroscopy would benefit from (a) a scanner architecture capable of supporting multinuclear spectroscopy and a parallel transmit array of antennas, (b) a separate volume transmit coil for phosphorus spectroscopy, and (c) an array of receive loops for accelerated phosphorous spectroscopy.

The intended use of the presented technology is for treatment monitoring and ongoing research into the possible application of patient risk stratification. In vitro evaluations of phospholipid metabolism in primary (hepatocellular carcinomas) and secondary (adenocarcinomas and squamous cell carcinomas) malignant tumors of the liver can clearly differentiate between tumor-containing and nontumor-containing samples from a patient. Although in vivo $^{31}$P at lower field strengths is limited to large tumors (>5 cm, eg Laufs et al.), $^{31}$P as a marker for treatment response in hepatic primary (hepatocellular carcinomas) and liver metastases (adenocarcinomas and squamous cell carcinomas) has proven useful for early identification of responders and nonresponders, even in the absence of evidence of treatment response in anatomical images. At lower field strengths, providing reliable measures which differentiate between controls and tumors is challenging due to partial volume affects and the overlap in the peaks of the PMEs PC and PE, and the PDEs GPC and GPE, due to the limited spectral resolution.

In a recent human breast cancer study, the $^{31}$P metabolite concentrations (PE, PC, GPE, and GPE) clearly differentiated tumor tissue from healthy controls in vivo at 7 T. Ultra-highfield in vivo $^{31}$P spectroscopy has also been shown to relate to histological markers of aggressiveness such as mitotic count, and aid in the decision tree for determining which breast cancer patients require systemic therapy (eg, chemotherapy or radiation). In vivo animal models at 7 T have also demonstrated that the ratio of PE to $\beta$-adenosine triphosphate (NTP) with 1.5 × 1.5 × 2 cm voxels clearly differentiated between tumor-containing volumes and liver volumes with no macroscopic tumor.

The tumor size that is possible to investigate with 7 T depends on the location of the tumor. For example, a sub mL volume (<0.1 mL) of signal-generating tissue with <2 mmol concentrations of PMEs has been detected above the noise floor in healthy axilla lymph nodes. In the breast, a < 2 mL volume tumor was monitored for treatment tracking using $^{31}$P at 7 T. In related work in breast cancers, we have looked at spectra with SNRs of the PE peak as low as 2 and were successfully able to differentiate what appeared to be different metabolic phenotypes, which correlated with mitotic count (dataset from Schmitz et al. and Rivera et al.).

In the case of the presented spectra, we have an SNR of roughly 17 for PE and 10 for the PC peak, with a voxel size of 30 x 30 x 30 mm. Therefore, assuming the PE concentration does not vary with tumor size, a 17mm isotropic voxel would suffice (representing an estimated SNR for PE of 3 and 1.8 for PC). However, the tumor growth rate slows with increasing size, and as we have seen in the patient cohorts from the same breast cancer data, the aggressive phenotype (corresponding to the higher mitotic counts) peak in mitotic count below 10 mm and typically have lower mitotic counts as the maximum dimension of the tumor exceeds 13 mm. This is predicted by growth models that take into account growth slow down as the vasculature is unable to maintain steady nutrient flow to the whole tumor (eg. Gompertzian). The PME/PE ratio was also seen to decrease with increasing tumor size by Daly et al. Analysis of the presented dataset suggests that treatment monitoring would be possible in a 3–5 mL volume tumor, and smaller tumors with elevated PE concentrations may also be observable. Given that these estimates are based on a shallow tumor and the SNR of the current setup decreases with depth, we have kept the estimated range conservative. With boosts in SNR provided by receive arrays and accelerated spectroscopic imaging, sensitivity to tumors of 2 mL even at depth is likely to be possible.

Typical liver metastatic tumor sizes range from 2 mm to 20 cm in diameter, with the largest tumor in a given patient corresponding to a typical diameter of 1–19 cm (as calculated from 60 colorectal carcinomas and assuming spherical tumors) with means exceeding 10 mL. Therefore, the presented sensitivity is applicable for the majority of patients undergoing treatment.

### 5 Conclusions

We have presented the technology and protocols appropriate for phosphorus spectroscopy as a potential means of early treatment response tracking for tumors in the abdomen. As an improvement over conventionally used surface loops, we have demonstrated that the antennas are inherently decoupled from loops, and that two antennas combined in quadrature can provide nearly full coverage (90%–100%) of the liver, facilitating tumor localization and ROI B0 shimming. While two antennas can provide near-complete coverage of the liver for gradient echo scans, parallel transmit systems for B1-shimming are required for obtaining radiological grade images that benefit from uniform contrast weighting in T1-
and T2-weighted MRI. Through the use of antennas for proton imaging and parallel transmit in combination with $^{31}$P coil loops, we can begin to explore the potential of adapting treatments to patients using full-radiological grade images and multiparametric imaging.

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