Feasibility of $^{31}$P spectroscopic imaging at 7 T in lung carcinoma patients

Quincy (Q.). van Houtum$^1$ | Firdaus (F.A.A.). Mohamed Hoesein$^1$ | Joost (J.J.C.). Verhoeff$^2$ | Peter (P.S.N.). van Rossum$^2$ | Anne (A.S.R.). van Lindert$^3$ | Tijl (T.A.). van der Velden$^1$ | Wybe (W.J.M.). van der Kemp$^1$ | Dennis (D.W.J.). Klomp$^1$ | Catalina (C.S.). Arteaga de Castro$^1$

1 Radiology Department, University Medical Center Utrecht, Netherlands
2 Radiotherapy Department, University Medical Center Utrecht, Netherlands
3 Respiratory Medicine Department, University Medical Center Utrecht, Netherlands

Correspondence
Quincy van Houtum, MSc., University Medical Center Utrecht, Netherlands, Heidelberglaan 100, 3584 CX.
Email: qhoutum2@umcutrecht.nl, quincyvanhoutum@gmail.com

Currently, it is difficult to predict effective therapy response to molecular therapies for the treatment of lung cancer based solely on anatomical images. $^{31}$P MR spectroscopic imaging could provide as a non-invasive method to monitor potential biomarkers for early therapy evaluation, a necessity to improve personalized care and reduce cost. However, surface coils limit the imaging volume in conventional $^{31}$P MRSI. High-energetic adiabatic RF pulses are required to achieve flip angle homogeneity but lead to high SAR. Birdcage coils permit use of conventional amplitude modulated pulses, even over large FOV, potentially decreasing overall SAR massively.

Here, we investigate the feasibility of 3D $^{31}$P MRSI at 7 T in lung carcinoma patients using an integrated $^{31}$P birdcage body coil in combination with either a dual-coil or a 16-channel receiver.

Simulations showed a maximum decrease in SNR per unit of time of 8% for flip angle deviations in short TR low flip-angle excitation 3D CSI. The minimal SNR loss allowed for fast 3D CSI without time-consuming calibration steps (>10:00 min.). $^{31}$P spectra from four lung carcinoma patients were acquired within 29:00 minutes and with high SNR using both receivers. The latter allowed discrimination of individual phosphodiester, inorganic phosphate, phosphocreatine and ATP. The receiver array allowed for an increased FOV compared to the dual-coil receiver.

3D $^{31}$P-CXI were acquired successfully in four lung carcinoma patients using the integrated $^{31}$P body coil at ultra-high field. The increased spectral resolution at 7 T allowed differentiation of multiple $^{31}$P metabolites related to phospholipid and energy metabolism. Simulations provide motivation to exclude $^{31}$P B$_1$ calibrations, potentially decreasing total scan duration. Employing large receiver arrays improves the field of view allowing for full organ coverage. $^{31}$P MRSI is feasible in lung carcinoma patients

Abbreviations: $^{31}$P, Phosphorus; ATP, Adenosine triphosphate; CSI, Chemical Shift Imaging; FID, Free induction decay; GPC, Glycerophosphocholine; GPE, Glycerophosphoethanolamine; MRSI, Magnetic Resonance Spectroscopic Imaging; NADPH, Nicotinamide adenine dinucleotide phosphate; PC, Phosphocholine; PCr, Phosphocreatine; PDE, Phosphodiester; PE, Phosphoethanolamine; Pi, Inorganic Phosphate; PME, Phosphomonoesters; Rx, Receiver; SAR, specific absorption rate; TR, repetition time; UDPG, uridine diphosphoglucone

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1 | INTRODUCTION

In recent years, many new molecular therapies, such as immunotherapy, have been introduced for the treatment of lung cancer. Tumor cells generally use antigens to mask themselves from the immune system and immunotherapy exploits this mechanism by administering antibodies which specifically target tumor antigens. This labels the cell which allows it to be recognized by the own defense mechanisms of the body. The immune system responds by inhibiting or attacking the tumor cells, resulting in stalled tumor growth not necessarily accompanied by a decrease of tumor volume on imaging modalities.

Currently, it is difficult to predict which patients show an effective response to immunotherapy based on anatomical images like computed tomography only. Although a promising new treatment strategy for non-small cell lung carcinoma, immunotherapy is expensive and severe drug side effects are observed accompanied by an apparent decrease in quality of life. Therefore, there is an unmet need for a non-invasive method that can be used to predict tumor metabolic response which is crucial for early therapy effect evaluation. By adjusting the therapy strategy accordingly, such a tool would allow for more personalized curative care with less side effects, and reduced costs.

A recent study in breast cancer showed that changes in the phospholipid metabolism in responsive tumors can be detected after a single chemotherapy session using 31-phosphorous (31P) magnetic resonance spectroscopic imaging (MRSI). 31P MRSI can detect the phospholipid and energy metabolites, which provides possibilities to monitor tissue metabolism non-invasively during treatment. Inorganic phosphate (Pi), phosphocreatine (PCr) and ATP (with the \( \alpha,\beta, \gamma \) resonances) allow assessment of the energy metabolism and the phosphomonoesters (PME) and phosphodiesters (PDE) provide insight into the phospholipid metabolism. Enhanced ratios of phosphocholine (PC) to glycerophosphocholine (GPC) and phosphoethanolamine (PE) to glycerophosphoethanolamine (GPE), are frequently observed in tumor tissue and correlated with proliferation. Another study in breast cancer demonstrated the feasibility of the phospholipid metabolism as biomarker for therapy follow-up and additionally reported shortening of the transverse relaxation time of Pi as a biomarker. As the physiological changes are present before any morphological changes have occurred, these metabolites, their ratios and individual MR properties are potential (bio-)markers for therapy response monitoring.

However, the individual detection of 31P metabolites is hampered at lower magnetic field strengths (3 T and below) due to the restricted spectral bandwidth and the low detection sensitivity. By going to higher magnetic field strengths (e.g. 7 T and higher), the SNR and spectral resolution are intrinsically enhanced. These properties have a tremendous advantage for the low abundant 31P metabolites and even allow detection of the individual phosphomonoesters, (i.e. PE, PC) and diesters (i.e. GPE, GPC).

Unfortunately, the imaging volume in conventional 31P MRSI is limited as small birdcage or surface coils are used. Surface coils generally require the use of high-energetic adiabatic RF pulses to achieve flip angle homogeneity as inhomogeneous excitations lead to signal variation in the acquired spectra over the large field of view. Adiabatic RF pulses usually result in high specific absorption rates (SAR), leading to longer repetition times (TR), clinically impractical scan times for a single protocol and a limiting number of consecutive scans. Full spectroscopic coverage of large organs such as the lungs is therefore challenging due to inhomogeneous \( B_0 \) fields and inhomogeneous excitation which increase with magnetic field strength.

In addition, MR imaging and spectroscopy are challenging near the lungs due to the presence of air, the relatively small amount of tissue and respiratory motion. Yet, previous studies claim that from a technical point of view MR imaging on clinical field strengths is a feasible method for screening lung cancer.

Recent studies from Loring et al. and van Houtum et al. have presented a 31P whole-body birdcage coil designed for 7 T. Using the body coil in combination with the conventional adiabatic pulses for high and low flip angle excitations requires adiabatic half passage or BIR4 pulses respectively and would increase the cost effective \( B_1^+ \). This results in a narrow bandwidth leading to multiple acquisition to capture the full spectra. By design this coil results in an improved homogeneous excitation, comparable to the \( H \)-whole-body birdcage coils of clinical 3 T MR systems. This allows the use of rectangular pulses, which decreases global and local SAR, creating opportunities for fast spectroscopic imaging methods. In addition, they demonstrated that this 31P-body coil even allows quantification of transverse relaxation times and the feasibility of obtaining high flip angle chemical shift imaging (CSI), over a large field of view. However, the use of this coil was revealed with a 30% inter-subject variation of the flip angle using a single power setting for multiple volunteers. This raises questions for the need for individual 31P calibration, especially at low flip angles, as only the effective flip angle and not \( B_1^+ \)-field homogeneity is affected. Low flip angle excitations accompanied with short repetition...
times (TR) can be used for fast 3D CSI. The optimal SNR per unit of time at lower flip angles is acquired when the Ernst angle ($\alpha_E$) is used and any deviation from this flip angle result in additional $T_1$ weighting and a lower SNR per unit of time. The effects of a 30% flip angle deviation to the SNR per unit of time and consequently the acquired spectra can be evaluated by simulations. Excluding $B_1$ calibrations can decrease the total scan duration by 10 minutes or more, subsequently increasing patient comfort or allowing for additional scans or additional sampled averages to improve SNR.

The primary aim of this study was to investigate the feasibility of 3D $^{31}$P MR spectroscopic imaging at ultra-high field in combination with a $^{31}$P whole-body birdcage coil in four lung carcinomas.

2 | MATERIALS & METHODS

2.1 | Simulations

The effect of an uncalibrated excitation, that leads to a deviation from the Ernst angle ($\alpha_E$) was assessed by simulating the SNR per unit of time for the $\alpha_E$ and for $\alpha_E$ with a ± 30% and ± 50% deviation over a TR/$T_1$-ratios range of 10⁻⁶ to 0.3. The latter is chosen with respect to a short TR of 60 ms and the longitudinal relaxation times ($T_1$) for $^{31}$P metabolites of interest possibly ranging from 450 ms ($\alpha$-ATP) to 7000 ms (GPE). The simulated spectroscopy signal shown in equation [1] was corrected for time differences by dividing with the square root of TR. The SNR per unit of time for all the calculated TR/$T_1$-ratios were normalized to the maximum signal at $\alpha_E$.

$$signal = \frac{\sin(\alpha) \left(1 - e^{-\frac{\alpha}{T_1}}\right)}{1 - \cos(\alpha) e^{-\frac{\alpha}{T_1}}}$$  (1)

2.2 | Materials

$^{31}$P MRSI was performed using an in-house designed $^{31}$P whole body birdcage coil integrated in a 7 T MR system (Philips Healthcare, Best, Netherlands). The body coil, tuned at 120.6 MHz, was powered by a 25 kW amplifier (PID: 53-S26B-128, MKS Technologies, Shenzhen, Republic of China) resulting in a $B_1^+$ field-magnitude of 15μT at the isocentre. Two 1H-TxRx/$^{31}$P-Rx arrays were constructed for the experiments. Array 1 (A1) contained a $^{31}$P dual-coil receiver ($10 \times 16 \text{ cm}^2$, Figure 1A) and two fractionated 1H dipole antennas (30 cm) used as transceivers, both driven in quadrature mode. Array 2 (A2) contained a 16-channel $^{31}$P body array with eight integrated 1H dipole antennas, shown in Figure 1B and C.

Spectroscopic imaging data and anatomical proton images for localization were acquired in four patients using one of the two different setups.

2.3 | Patients & setup

Four stage III-IV non-small cell lung carcinoma patients (ages: 53-63 years; BMI: 17.7-29.5 Kg/m²) were included in this feasibility study and signed informed consent prior to scanning. Two patients participated after their palliative chemo- and/or radiotherapy sessions and two patients...
participated after the first immunotherapy cycle (see Table 1 for details). Patients were scanned in supine position. Scans of two patients were acquired with the $^{31}$P dual coil Rx (A1) placed on the location closest to the tumor based on previously acquired clinical CT images for tumor localization. The other two patients were scanned with the $^{31}$P Rx array (A2), that was wrapped around the upper part of their torso. The two separate dipole antennas in A1 are positioned on the side and the top of the lung of interest. Maximum tumor dimension ranged from 25 mm to 75 mm and other clinical details per patient are shown in Table 1.

2.4 | MR data acquisition

No $B_0$ shimming was performed nor was the $^{31}$P $B_0^+$ calibration. Phosphorus ($^{31}$P) spectra were acquired using a 3D $^{31}$P acquisition weighted CSI protocol including elliptical k-space sampling. Excitation was performed using rectangular RF pulses only and the carrier frequency was set to $PCr$. The isotropic resolution ranged from 20 to 30 mm and other parameters are summarized in Table 2.

2.5 | Data processing

Spectroscopic data from the 3D CSI protocol were processed in Matlab 2018b (The Mathworks Inc., Natick, MA) using an open source in-house designed processing tool (CSIgui v1.1, http://www.csigui.tk, April 2019). $^{31}$P spectroscopy data were averaged and spatially filtered using a 3D hamming window followed by an inverse Fourier transformation to the spatial domain. All free induction decays (FID) were apodized using a 24 Hz gaussian filter and zero filled to 512 samples. Coil data was combined using the whitened singular value decomposition (WSVD) algorithm as reported by Rodgers et al. Zereth order phase correction was applied automatically, and first order phase correction was applied manually, thereafter. No additional nor aesthetic baseline corrections were performed. Spectra from tumors exceeding the voxel resolution were aligned to the metabolite peak with the highest SNR followed by averaging, excluding voxels with a 50% or less partial tumor tissue volume on available MR images. The SNR of metabolites was calculated using equation [2] with $S_{max}$, the real part of the maximum signal intensity and the noise defined as the absolute standard deviation of the last 50 samples points of the spectrum.

$$\text{SNR} = \frac{\text{real}(S_{max})}{\text{std}(S_{noise})}$$

Table 1

| Patient | Age (years) | BMI (kg/m²) | Tumor size (cm³|cc) | Therapy | Remarks |
|---------|-------------|-------------|----------------------|---------|---------|
| #1      | 59          | 20.4        | 7.25 x 1.75 x 1.00| 12.69   | Seq. Chemoradiation Stent in SVC close to tumor |
| #2      | 60          | 17.7        | 3.75 x 4.80 x 2.00| 36.00   | Thoracic SBRT - |
| #3      | 63          | 24.2        | 3.60 x 3.20 x 3.60| 41.47   | Erlotinib - |
| #4      | 53          | 29.5        | 3.60 x 3.00 x 2.50| 27.00   | Pembrolizumab - |

Table 2

| Patient | Resolution nominal (mm³)| nominal voxel volume corrected for weighted acquisition$^{24}$ |
|---------|--------------------------|---------------------------------------------------------------|
| #1      | 26 x 26 x 26| 31 | 7 x 5 x 6 | 60/0.54 | 20° | 4800 | 320 | 256 | 23:00 | 2 |
| #2      | 20 x 20 x 20| 14 | 12 x 7 x 9 | 60/0.54 | 12° | 4800 | 80 | 256 | 23:00 | 2 |
| #3      | 30 x 30 x 30| 48 | 12 x 6 x 6 | 60/0.51 | 9° | 5000 | 60 | 256 | 25:55 | 16 |
| #4      | 30 x 30 x 30| 48 | 15 x 11 x 8 | 60/0.44 | 10° | 4800 | 60 | 256 | 28:15 | 16 |
3 | RESULTS

Simulations resulted in a maximum decrease of 8% in SNR per unit of time within the used TR/T₂ range for + and − 30% deviating flip angles, as can be seen in Figure 2. In addition, the αₑ + 30% variation showed a lower decrease in SNR per unit of time compared to the αₑ − 30% variation. A similar trend is seen for a αₑ ± 50% variation showing a maximum decrease of 23% in SNR per unit of time within the same TR/T₁ range for the αₑ − 50% variation. According to the B₁ maps available for the ³¹P body coil, we could expect a maximum of 30% deviation in flip angle in the in-vivo measurements using equal power settings between subjects and, in addition, a maximum decrease in SNR per unit of time of less than 6% is seen for the TR/T₁-ratios range that corresponds to the ³¹P metabolites of interest (0.009; 0.13) and the proposed protocol TR (60 ms)²³.

All patients were imaged within an hour of scan time with one of the two setups. Positioning the ¹H transmit coils for patient #1 was limited due to a stent in the superior vena cava (SVC) located close to the tumor. No other patient related difficulties were experienced during the scan sessions. Images obtained with the dipole antenna in A1 were adequate for tumor localization and planning (Figure 3A), when tumor location was known from previous CT images (Figure 3B).

Images and tumor localization using A2 were improved compared to A1 as is depicted in Figure 3A and 3E. Spectroscopic imaging acquisitions could be obtained with both setups as shown in figures 3C & E, where a single spectroscopy slice from the 3D imaging set for patient #1 and #4 are shown respectively. Tumor voxels in the slice used for averaging are marked by the red and yellow rectangles, showing 8 out of 20 voxels for patient #1 and all tumor voxels for patient #4. In addition, the signal intensity of the voxels located at the posterior side of the patient in the spectroscopic imaging array in Figure 3E have higher SNR compared to the anterior side.

Obtained ³¹P lung carcinoma spectra were acquired with high SNR for PCr (9.5) and the ATP resonances (>4.7) using A1, the ³¹P dual-coil Rx (Figure 4A) and with high SNR ranging from 3.9 (PME) to 13.2 (α-ATP) using A2, the ³¹P 16-channel Rx array (Figure 4B). It allowed discrimination of PME, Pi, PDE, PCr in all patients, the three ATP resonances and UDPG in all subjects except for patient #1 and NADPH in patient #4. Moreover, the SNR of the phospholipid- and energy- metabolites was found higher with A2 compared to A1. The lack of B₀ shimming and partial volume effects over the large field of view is visible in the spectra with measured linewidths ranging from 0.20 ppm to 1.1 ppm after apodization when using either coil setup.

4 | DISCUSSION

3D ³¹P spectroscopic imaging was successfully obtained in four lung carcinoma patients with either the ³¹P dual-coil receiver or the 16-channel receiver array in combination with the integrated ³¹P body coil at 7 tesla. Both Rx setups allowed the acquisition of phosphorous metabolic information from the lung carcinoma via a non-invasive method, while targeting the full organ for evaluation. The increased spectral resolution at the ultra-high magnetic field strength of 7 T allowed differentiation of multiple phosphorous metabolites related to cell membrane and energy metabolism. A minimal decrease in SNR per unit of time was apparent from the simulations performed to study the effect of a +/- 30% deviation from the Ernst angle due to the lack of individual body coil power calibrations in this patient population. This minimal SNR loss of at maximum 8% allowed for 3D fast spectroscopic imaging with short TR and low flip angle excitation without time-consuming calibration steps during the scan session.

![FIGURE 2](image-url) Simulation of the SNR per unit of time for the 3D ³¹P spectroscopic imaging at Ernst angle (αₑ) and with a 30% and 50% deviation for the TR/T₁ ratio ranging from 10⁻⁶ to 0.3. The SNR per unit of time at αₑ is marked by the solid black line, the increased and decreased angles for both the 30% (red) and 50% (blue) deviations are displayed as dashed and dash-dotted lines respectively.
Increasing the number of receiver coils improved the field of view coverage of $^{31}$P MRS images expanding the available metabolic information over a larger field of view. This agrees with previous demonstrations in literature. In addition, the SNR increase gained with the 16-channel receiver array used in patient #3 and #4 not only allowed discrimination of PME, Pi, GPE, GPC, PCr, ATP (with $\alpha$, $\beta$, and $\gamma$-resonances) and uridine-diphosphate glucose (UDPG) as with the dual-coil receiver but also nicotinamide-adenine dinucleotide phosphate (NADPH) in patient #4. UPDG is a known liver metabolite and indicates minor liver signal contamination, however SNR was insignificant (SNR < 3). NADPH (SNR > 3) however, though also found in the liver, is a cofactor involved with anabolic reactions, already linked to tumor tissue. In addition, the highest SNR of the dual-coil receiver was measured for PCr (Figure 4A, Patient #1) which is not directly associated with tumor tissue, but rather muscle tissue. This can be explained by signal contamination from chest muscle signals contained in neighbouring voxels that bled in the tumor.

**FIGURE 3**

A) Coronal MR image including labels for the tumor, neck and lungs plus B) a coronal CT image with PET scan overlay, both from patient #1 and used for tumor localization. C) Single transverse slice of the 3D spectroscopic imaging data from patient #1 with the tumor voxels indicated by the red rectangle. D) Transverse and coronal CT images from patient #4 for tumor localization and planning. E) the MR image from patient #4 with an overlay of a single slice of the 3D spectroscopic imaging data. Tumor voxel is highlighted by the yellow rectangle.

**FIGURE 4**

Spectra of lung tumor tissue for all four patients acquired with the $^{31}$P chemical shift imaging protocol using a) A1, the $^{31}$P dual coil Rx and B) A2, the $^{31}$P 16-channel Rx array. Phosphomonoesters (PME), phosphodiesters (PDE), glycerophosphoethanolamine (GPE) plus glycerophosphocholine (GPC), inorganic phosphate (Pi), phosphocreatine (PCr) and the $\alpha$, $\beta$, and $\gamma$-ATP resonances are labelled where applicable. The number of tumor voxels used for averaging is denoted by N in the right top corner of the spectrum except for single voxel spectra. Notice the increase in PDE with respect to PME in patient #4 that might indicate tumor response to immunotherapy.
We conclude that $^{31}$P MRSI in lung carcinoma is feasible at 7 T. Employing large receiver arrays that can cover the whole torso, improves the field of view coverage allowing full organ $^{31}$P-MRSI acquisition. With only minor signal contamination to overcome, $^{31}$P MRSI shows great potential as tumor biomarker for treatment response monitoring in lung cancer.

5 | CONCLUSION

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ORCID
Quincy (.Q.). van Houtum https://orcid.org/0000-0002-6690-1018
Catalina (.C.S.). Arteaga de Castro https://orcid.org/0000-0002-1055-2672

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