Debate *on* Clinical Utility of MRS in Oncology: Contra-MRS

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Highlights
- Despite numerous research studies showing its potential, MR spectroscopy is not widely used in clinical oncology
- MRS is technically challenging to acquire, analyze and interpret – more so than any routine MR imaging method
- Without a "killer application", MRS will remain an investigational tool for the foreseeable future

Target Audience
Clinicians and imaging scientists interested in using MR spectroscopy for clinical cancer imaging

Outcome/Objectives
As a result of attending this course, participants should be able to:
- Understand the current role of MRS in clinical cancer imaging
- Understand technical and non-technical barriers to greater adoption of MRS
- Assess the future potential of MRS in clinical oncology

Purpose
- To present a *Devil's Advocate* position on the futility of working on MRS methods and applications
- To highlight the current problems with MRS, with the intent of accelerating their resolution

Overview
Why is MR spectroscopy not widely used in clinical oncology? For more than 20 years, it has been possible to perform MR spectroscopy on clinical MR scanners. Thousands of research studies have shown that the metabolic information MRS provides is useful for identifying and characterizing cancers: choline is a reliable marker of malignancy, and many organs exhibit metabolic markers of normalcy such as NAA and citrate that can be help separate cancer from healthy tissues. MR spectroscopy is approved for clinical use by the FDA and other regulatory bodies, and the major MR vendors all sell commercial spectroscopy software packages. In spite of this, MR spectroscopy is still considered an investigational tool in clinical oncology, and its use is predominantly limited to research hospitals and medical centers.

The short explanation for this is that 1) MR spectroscopy is too difficult to perform in a routine clinical setting, and 2) there is not yet a sufficiently compelling clinical need to justify fixing #1. This presentation will cover these explanations in greater detail; discuss the role of MRS in brain, prostate, and breast cancer; and prognosticate on the future of MRS in clinical oncology.

Challenges in Advancing MRS for Clinical Oncology
Clinical MR systems have been designed for and are optimized for MR *imaging*. It is feasible to perform MR spectroscopy with these systems, but, arguably, MRS is more difficult to implement than any MR imaging method currently used in clinical practice. This difficulty stems from both practical implementation issues as well as fundamental physical limitations.

The most fundamental limitation with MRS is its low sensitivity compared to imaging. This is not due to differences in acquisition techniques; rather it is because MRS seeks to measure the signal from low concentration (~1mM) metabolites, whereas imaging uses the signal from abundant water and lipid species. The signal given by metabolites is typically ~10,000 smaller than that of the water and lipid signals that are the basis of clinical MRI. Because of this difference, MRS is acquired at lower spatial

resolutions and with longer acquisition times. This gap between MRS and MRI will not be overcome by better software, higher fields, or improved coil technologies.

A second fundamental limitation is the need for fine spectral resolution. In typical cancer MRS applications, it is necessary to resolve signals with frequencies only ~0.2 ppm (25 Hz at 3T) apart (e.g., choline and creatine). In imaging, the predominant species of interest (water and $-CH_2-$ lipid) are much further apart (3.4 ppm, 435 Hz at 3T). This need for frequency precision makes MRS less robust than MRI, because it can be more easily impacted by system miscalibration, system instability, and physiologic motion. For these two reasons, at least, MRS is and will continue to be more challenging than MRI. However, there are a substantial number of addressable factors that currently impede greater adoption of MRS methods in clinical oncology.

The **acquisition** methods currently available on commercial MR systems limit the ability to collect quality spectra. Advances in pulse sequences, including better localization strategies (semi-LASER, SPECIAL, SEAD, etc.) and fast spectroscopic imaging techniques (EPSI), are widely used in the research community but are uncommon on commercial systems. The performance and consistency of B0 shimming techniques can be improved by optimizing for specific body regions to better accommodate motion and lipids, and adjust higher-order shims as needed. Spectroscopy acquisitions often require additional calibrations, such as adjustment of water suppression pulses, which do not fit in the standard imaging workflow of commercial MR systems. Acquisition planning for MRS (single voxel prescription, saturation band placement) is time-consuming and subjective, and could be greatly improved using automated guidance as is now available for many image acquisition protocols. Motion correction techniques using navigators and/or external signals from physiologic monitoring and cameras can also reduce the effect of motion during long MR scans.

A lack of suitable **analysis** methods also hinders greater use of MRS in clinical practice. Commercially-available software for spectroscopy analysis software packages are limited in functionality and transparency. Sophisticated spectroscopic processing and fitting software such as LC Model and JMRUI are widely used in research, but are not approved for clinical use by regulatory bodies. The standardization of spectroscopy analysis is further hindered by the use of proprietary spectroscopy file formats, which are prevalent in spite of the availability (since 2002) of a standard and flexible DICOM MR Spectroscopy file format definition. Today, most vendors' spectroscopy software cannot view or process data from other vendors – a situation similar to imaging in the early 1990's.

For all the above reasons, it requires special **expertise** to consistently acquire and analyze MR spectroscopic data (1). Clinical sites that do perform MRS routinely often have dedicated personnel (physicists, technologists, and/or radiologists) who specialize in spectroscopic acquisition and interpretation.

Other, non-technical factors also pose barriers to greater use of MRS in clinical oncology. Economic forces in healthcare are favoring shorter, more efficient imaging studies, placing pressure on radiologists and managers to eliminate longer MRI/MRS acquisitions that are not deemed essential. The advancement of evidence-based medicine (EBM) has also been impactful, as many early MRS studies did not provide the level of evidence needed to justify the additional costs of MRS (2). This has reduced the ability for radiology practices to bill insurance and Medicare/Medicaid for MRS studies, and thus decreased the commercial interest in advance MRS technology (3,4).

Specific Oncologic Applications of MRS
Brain Cancer
The brain is by far the easiest region for performing MR spectroscopy. The RF and shim coils are optimal, there is minimal motion, and there are minimal lipids to hinder B0 shim adjustment. The MR spectroscopy analysis packages available, while limited, are optimized for analyzing brain spectra. Biologically, the brain exhibits more measurable metabolites than any other body region, providing rich spectral content. Cancers typically exhibit higher choline and reduced NAA, and in some circumstances, higher lipid or lactate resonances. Clinically, non-invasive scans such as brain MRS are compelling because the morbidity of biopsy is higher than in other regions.

Despite these advantages, and despite numerous research studies showing benefit in specific clinical situations (5,6), MRS is still not used as a primary tool in brain cancer. Some clinical neuroradiologists use MRS extensively, others not at all, and others employ it sparingly to address a few specific questions (e.g., radiation necrosis vs recurrence). To date, the clinical information that MRS can provide has not yet been perceived as sufficiently valuable to warrant the investment needed by vendors and medical educators to make this technology clinically routine.

Prostate Cancer

Prostate spectra exhibit fewer metabolites than can be found in the brain, but typically show choline, creatine, citrate, and polyamines (particularly spermine). Choline is elevated in cancerous regions, whereas citrate and polyamines are indicators of normal prostatic function and are diminished in malignancy. The prostate is a relatively small organ, and is typically studied using an endorectal coil and MR spectroscopic imaging methods to allow assessment of the whole organ. B0 shimming is not overly difficulty, as the prostate is near the magnet isocenter and does not contain large lipid signals; however, bowel air and physiologic motion make B0 shimming somewhat more difficult than in the brain. The major MR vendors all provide some tailored pulse sequences and analysis software for prostate MRSI.

MRSI has been shown useful for identifying, localizing, staging, and grading prostate cancer (7,8). MRSI is not typically used independently; rather it is part of a multiparametric approach incorporating T2-weighted anatomical imaging, contrast-enhanced imaging, and (more recently) diffusion-weighted imaging. This multiparametric approach is likely to continue, but the value of MRSI's contribution to the multiparametric assessment is not yet clear. There are clinical trials underway (e.g., NCT01138527), but the only multisite trial reported to date showed that MRSI did not provide additional clinical value over imaging alone (9).

Breast Cancer

In the breast, MR spectroscopy can be used to measure the total choline resonance, which is typically elevated in cancer. Single-voxel spectroscopy has been commonly used, but use of spectroscopic imaging for improved spatial coverage is increasing, which may help reduce the subjectivity of voxel placement. Breast spectroscopy is more challenging than either brain or prostate MRS. This is primarily due to the large lipid resonances which can distort spectra and mask the small choline peaks, but also because the anatomy is highly variable, and B0 shimming is challenging due to lipids, respiration, and off-center position.

MRS has been used for both diagnosis and monitoring treatment response in breast cancer (10,11). For diagnosis, MRS has shown consistent results (12) in larger lesions, but reduced accuracy in smaller lesions (13,14). This trend limits its clinical utility, as larger lesions are easier to biopsy and characterize morphologically with contrast-enhanced MRI. Using MRS for detecting early response to treatment appears promising, but requires that choline can be measured pre-treatment (15), again limiting the use of MRS to larger lesions. It is also not yet clear if MRS can detect early response/nonresponse better than contrast-enhanced imaging, which is easier and has shown promising results (16).

Discussion

The two primary reasons why MRS does not currently have a greater impact in clinical oncology today are 1) technical difficultly of performing MRS (largely due to lack of better tools, expertise, and standardization) and 2) lack of demand for MRS by referring clinicians. The two factors are interdependent – vendors will not invest heavily in better MRS support unless there is greater clinical (and thus financial) demand; conversely, clinicians will not demand MRS unless it can be performed more easily *and* evidence for its clinical value is stronger. This chicken-and-egg situation has led to slow progress in advancing MRS methods for ~10 years. For these reasons, the near-term future of MRS in clinical oncology will likely continue to be characterized by incremental improvements in

technology, driven primarily by the research community, and gradually improved understanding of the relative clinical value of using MRS to address specific clinical questions.

In the modern healthcare environment, MRS needs to be better than its alternatives – MRI, PET, biopsy, and *doing nothing* – in terms of both clinical efficacy and cost effectiveness. There are two plausible scenarios could produce dramatic accelerations of MRS adoption. The most likely would be a so-called "killer application": an important and relatively frequent clinical question for which only MRS provided an unambiguous answer. The diffusion response in early stroke is an example of such a scenario, but one has not yet emerged for MRS. Alternatively, an unanticipated "disruptive technology" – such as an advance in hyperpolarization methods or high-temperature superconductors – could substantially change the conditions to favor greater development of MRS in clinical oncology.

References

1. Kreis R. Issues of spectral quality in clinical 1H-magnetic resonance spectroscopy and a gallery of artifacts. NMR Biomed 2004;17:361–381. doi: 10.1002/nbm.891.
2. Bottomley PA. The trouble with spectroscopy papers. Radiology 1991;181:344–350. doi: 10.1148/radiology.181.2.1924769.
3. Lin AP, Tran TT, Ross BD. Impact of evidence-based medicine on magnetic resonance spectroscopy. NMR Biomed 2006;19:476–483. doi: 10.1002/nbm.1058.
4. Lin AP, Clementi V, Tran, T, Ross BD. Reimbursement for Magnetic Resonance Spectroscopy. Proc Intl Soc Magn Reson Med 2009;17:2509.
5. Barker PB. Clinical MR spectroscopy: techniques and applications. Cambridge: Cambridge University Press; 2010.
6. Oz G, et al. Clinical Proton MR Spectroscopy in Central Nervous System Disorders. Radiology 2014, *in press*
7. Kurhanewicz J, Vigneron DB. Advances in MR spectroscopy of the prostate. Magn Reson Imaging Clin N Am 2008;16:697–710, ix–x. doi: 10.1016/j.mric.2008.07.005.
8. Mazaheri Y, Shukla-Dave A, Muellner A, Hricak H. MRI of the prostate: clinical relevance and emerging applications. J Magn Reson Imaging 2011;33:258–274. doi: 10.1002/jmri.22420.
9. Weinreb JC, Blume JD, Coakley FV, et al. Prostate cancer: sextant localization at MR imaging and MR spectroscopic imaging before prostatectomy--results of ACRIN prospective multi-institutional clinicopathologic study. Radiology 2009;251:122–133. doi: 10.1148/radiol.2511080409.
10. Bolan PJ. Magnetic resonance spectroscopy of the breast: current status. Magn Reson Imaging Clin N Am 2013;21:625–639. doi: 10.1016/j.mric.2013.04.008.
11. Begley JK, Redpath TW, Bolan PJ, Gilbert FJ. In vivo proton magnetic resonance spectroscopy of breast cancer: a review of the literature. Breast Cancer Research 2012;14:207. doi: 10.1186/bcr3132.
12. Baltzer PAT, Dietzel M. Breast Lesions: Diagnosis by Using Proton MR Spectroscopy at 1.5 and 3.0 T—Systematic Review and Meta-Analysis. Radiology [Internet] 2013. doi: 10.1148/radiol.13121856.
13. Tozaki M, Fukuma E. 1H MR spectroscopy and diffusion-weighted imaging of the breast: are they useful tools for characterizing breast lesions before biopsy? AJR Am J Roentgenol 2009;193:840–849. doi: 10.2214/AJR.08.2128.
14. Baek H-M. Diagnostic value of breast proton magnetic resonance spectroscopy at 1.5T in different histopathological types. ScientificWorldJournal 2012;2012:508295. doi: 10.1100/2012/508295.
15. Bathen TF, Heldahl MG, Sitter B, et al. In vivo MRS of locally advanced breast cancer: characteristics related to negative or positive choline detection and early monitoring of treatment response. MAGMA 2011;24:347–357. doi: 10.1007/s10334-011-0280-9.
16. Hylton NM, Blume JD, Bernreuter WK, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY TRIAL. Radiology 2012;263:663–672. doi: 10.1148/radiol.12110748.