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PERSPECTIVE

Lost in translation: lessons learned from the "demise" of MRSI of the prostate

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Abstract
At times, technologies fail for reasons other than an inability to deliver on their promises. The iconic Blackberry, for example, was once coined "Research in Motion", sold tens of millions of units, and then "disappeared" from the market because it did not accompany the new trends in design. Promising technologies may also "disappear" in the medical field. What follows is the tale of the rise and fall of proton magnetic resonance spectroscopic imaging (^{1}H MRSI) of the prostate.

Keywords Diagnostic test · Translation · MRI

From bench to bedside: studies of clinical efficacy

About 30 years ago, the first results showing the potential of ^{1}H MRSI to distinguish benign tissue from prostate cancer were published [1–3]. These studies utilized cell lines, tissue, and animal models, but soon the technique was translated to research in patients [4, 5].

Since then, hundreds of studies that evaluated ^{1}H MRSI were published. Until recently, the vast majority of prostate cancer ^{1}H MRSI studies employed PRESS type sequences, which are prone to suboptimal slice selection with chemical shift displacement errors causing unpredictable lipid signal contamination into the spectral region of interest (2–4 ppm), a particularly significant problem as the prostate is surrounded by a large pool of lipids. Yet, results from experienced centers, often with dedicated teams of specialists, have shown that ^{1}H MRSI increases specificity and improves the diagnosis and characterization of prostate cancer [6–8]. Such results, however, may have been overoptimistic because of bias introduced by quality control of spectral data, commonly done by MR spectroscopists. Lagemaat et al., for instance, concluded that ^{1}H MRSI of the prostate was a reproducible method, but only after excluding 35% of the voxels because of bad quality [9].

ACRIN 6659 casts doubt on the community

In 2009, the American College of Radiology Imaging Network (ACRIN) 6659 Clinical Trial determined that ^{1}H MRSI had no incremental value over T2-weighted imaging (T2WI) to discriminate sextants with and without prostate cancer [10]. Secondary analysis suggested that ^{1}H MRSI was more sensitive when tumors were large, while Gleason score (GS) had no impact on the results. Yet, these are not surprising. Virtually, all diagnostic tests are more likely to be positive when the target disease is more advanced. This was probably also true for T2WI, but not reported. The lack of difference in sensitivity after stratification of GS can be explained by selection bias. Patients with large and small tumors were as likely to have a GS of 7 or more because they were all scheduled to undergo prostatectomy. Overdiagnosis and overtreatment of prostate cancer was already a recognized problem when ACRIN 6659 was published. While high-grade cancers would usually be treated with surgery and radiation, many men with small GS 3 + 3 and some GS 7 tumors would opt for active surveillance.

Often overlooked, though, is the fact that before enrollment, two patients were excluded because of poor ^{1}H MRSI quality and an additional 27 studies (24.5%) were considered poor or non-diagnostic on centralized review. This clearly reflects the complexity of ^{1}H MRSI acquisition and limited

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robustness and reliability of PRESS-type sequences, and to a great extent explains its suboptimal diagnostic accuracy.

MRSI's challenger: DWI

The use of diffusion-weighted imaging (DWI) to detect prostate cancer was brought under the spotlight in the early 2000's [11, 12]. And by the time ACRIN 6659 was published, it had gained much greater acceptance among radiologists than ^{1}H MRSI. DWI did not require the use of an endorectal coil, it was easier to acquire, and much simpler to interpret. The chasm between the two techniques was exacerbated by the publication of Prostate Imaging Reporting and Data System (PI-RADS), which first considered ^{1}H MRSI an optional technique [13] and later excluded it from the guidelines [14]. Thereafter ^{1}H MRSI was relegated to a second plan.

One of the last bastions

The University of California San Francisco (UCSF), Department of Radiology and Biomedical Imaging is one of the places of birth of ^{1}H MRSI, and one of the last centers to use it routinely.

For many years, a highly skilled team of researchers was responsible for the acquisition of all prostate magnetic resonance imaging (MRI) scans, including ^{1}H MRSI, which was an integral part of the protocol. The acquisition of ^{1}H MRSI data was very complex and required attention to details, starting with the selection of the volume that will be investigated and placement of very selective saturation bands, followed by accurate shimming to optimize water and lipid suppression. ^{1}H MRSI required the use of an endorectal coil to overcome low signal, and because of marked sensitivity to susceptibility artifact, the use of perfluorocarbon (PFC) to inflate its balloon.

After the acquisition was finished, extensive post-processing was needed to combine the data from different coil elements, build the spectra array, and determine its spatial distribution. Post-processing also included frequency and phase corrections, baseline corrections, and estimation of metabolite peaks. These processes were done semi-automatically and require careful manual adjustments by the spectroscopists.

Members of the research team also determined the quality of the spectra and the likelihood of each spectrum represented cancer, using a 5-point scale based on the signal-to-noise ratio and metabolite peak area ratios.

Following the development of PI-RADS, the urological community fully embraced MRI, in particular to guide transrectal ultrasound biopsies [15, 16]. As the number of patients referred to our institution increased, the research team was no longer able to provide the necessary support to maintain an efficient workflow without jeopardizing their other priorities.

A plan was devised, training provided, and over a period of several months the acquisition of images was transferred to the clinical technologists and post-processing to the Department's Quantitative Image Processing Center. Interpretation was now the sole responsibility of radiologists.

Translation to practice: issues arise

Soon after the prostate MRI program was transferred to the clinical program of the Department, it became apparent that obtaining high-quality ^{1}H MRSI would be difficult.

The purchase, manipulation, storage, and disposal of PFC, a substance that was intended for industrial use, was challenging. Unable to devise a feasible system that ensured the steady supply and safe use of the product, we opted for utilizing air to fill the e-coil's balloon. This inevitably led to an increased chance of susceptibility artifact and degraded images.

Suboptimal positioning of the endorectal coil and protocol mistakes became more prevalent as a much greater number of technologists of varied experiences and interests began acquiring these images. Moreover, the new automated post-processing system could not achieve the same level of fine adjustments that were once routine.

Interpretation was also a problematic, and not only because the scoring of ^{1}H MRSI was no longer provided. An internal survey of 23 faculty members and graduating clinical fellows showed that the quality of the ^{1}H MRSI spectra was considered adequate for interpretation in only 30% of times, and relevant for management in a quarter of those cases. The latter likely reflects the most common current indication of MRI at our institution, TRUS-MRI fusion biopsy, rather than tumor characterization. Further, three respondents told they ignored ^{1}H MRSI data all together. The frustration with the inconsistency and overall low quality of ^{1}H MRSI led to the decision to no longer acquire it for clinical cases. Nevertheless, ^{1}H MRSI continues to be acquired as part of ongoing research projects.

Conclusion

^{1}H MRSI does have clinical value when it is acquired, processed, and, sometimes, interpreted by a team of dedicated research experts; however, this expertise is not easily translated to the community–as seen even in a major academic center–and, therefore, good results are not achievable at the vast majority of imaging centers.

Will clinical radiologists ever incorporate ^{1}H MRSI of the prostate to their protocols? Unlikely in its present form. As the Blackberry, ^{1}H MRSI failed to follow the trend: MR sequences are expected to be fast, easy to acquire and reproduce, and simple to interpret. Yet, work continues to be done to improve MR spectroscopy. Researchers and MR manufacturers are currently developing completely automatic ^{1}H MRSI protocols of the prostate that will be acquired by a technician alone [17]. PRESS sequences have been improved [18] and new ^{1}H MRSI sequences with better slice-selective pulses are now available and have been shown to be more robust than the ^{1}H MRSI obtained using the conventional PRESS sequences [19]. Additionally, it has been shown that these new sequences can successfully be used without an endorectal coil, which has several processing advantages, facilitating clinical applicability [20]. In addition, although PI-RADS is quickly becoming the standard of interpretation, the system suffers from some limitations [21] and additional or alternative more quantitative approaches seem to be needed. A more robust and practical MRSI technique could be one of such techniques, as it adds a type of information that is different from the other MRI sequences typically utilized in prostate cancer.

We should learn from this example and remember the basic characteristics of good diagnostic tests. Perhaps upcoming tools will then have a better fate than the initial ^{1}H MRSI methods that were applied to the prostate.

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