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REVIEWS

The Role of *in vivo* Proton Magnetic Resonance Spectroscopy (MRS) in the Evaluation of Breast and Prostate Cancers

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Abstract | *In vivo* proton (^{1}H) magnetic resonance spectroscopy (MRS) has evolved as a non-invasive technique for the investigation of cancer biochemistry and metabolism. As an adjunct to magnetic resonance imaging, MRS plays a promising role in increasing the specificity of cancer diagnosis and assessment of treatment response in breast and prostate cancers. Various breast MRS studies have documented water-to-fat ratio (W-F) and a peak at 3.2 ppm corresponding to various choline (Cho) containing compounds as promising biomarkers for the diagnosis of breast cancer. Recent breast MRS studies have also documented the determination of the absolute concentration of tCho metabolite, and cut-off values were determined for the discrimination of malignant, benign and normal breast tissues. MRS parameters like W-F ratio and the concentration of tCho have also been evaluated as useful biomarkers for monitoring therapeutic response of breast cancer patients. Prostate cancer (PCa) is the most common malignancy affecting men. The measurements of relative levels of citrate (Cit), creatine (Cr), Cho, and polyamines (PA) using ^{1}H MRS have established lower Cit and high Cho levels as characteristics of PCa. These parameters have also been used to monitor the therapeutic response of PCa patients. In this review, we present briefly the current status and the future potential of various ^{1}H *in vivo* MRS methods in breast and prostate cancer research, and their potential in relation to diagnosis, monitoring of therapeutic response and metabolism.

1 Introduction

In recent years magnetic resonance imaging (MRI) has evolved as an indispensible diagnostic tool, primarily due to its capability to non-invasively generate high-resolution anatomical images based on intrinsic soft tissue contrast.[1–3] It provides essential information on the tumor extent and the pathology. However, it does not provide information on the underlying biochemical processes that accompany tumor activity. *In vivo* MR spectroscopy (MRS) has emerged as an adjunct methodology to MRI that provides information on the alterations of metabolic pathways during the disease processes by detection and quantification of metabolites present in tissues.[4–6] Specific information on metabolites and their relative levels basically provide the biochemical status of tissues from a particular region/organ. Such information may help to gain knowledge on developing biomarkers for the differentiation of the normal, benign and pathological state of tissues. The advantage of *in vivo* MRS is its non-invasive nature, because of which it can also be used repetitively to monitor the response of tumors to various therapeutic modalities and also evaluate the efficacy of drugs.[6–8] In general, one can perform *in vivo* MRS on nuclei such as hydrogen (^{1}H), phosphorus (^{31}P), carbon (^{13}C), lithium (^{7}Li), sodium (^{23}Na), fluorine (^{19}F) etc. But among these

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nuclei, ^{1}H and ^{31}P are widely used owing to their high natural abundance in human tissues.

Women worldwide, suffer from breast cancer, and is a major cause of cancer related death.[9] In recent years, routine MRI investigation along with dynamic contrast enhanced (DCE-MRI) has gained increasing importance in breast cancer diagnosis. The various areas of its applications include breast cancer management like detection of multi-focal lesions, preoperative cancer staging, indeterminate mammographic findings in dense breasts, detection of recurrent cancer as well as in monitoring the tumor response to therapy.[10–15] *In vivo* proton (^{1}H) MRS has been reported to distinguish cancer from benign and normal breast tissues, through use of water-to-fat (W-F) ratio and the observation of the composite choline (tCho) signal, which is shown to increase the specificity of diagnosis.[16–21]

Prostate cancer (PCa) is a common malignancy in elderly men and remains the second leading cause of cancer related death among men.[9] Various MR methods including MRI and MRS are used for obtaining anatomical, functional and biochemical information on PCa. *In vivo* ^{1}H MR spectrum acquired from the cancerous region showed decreased citrate (Cit) and increased Cho compared to the normal region of the prostate. The Cit and Cho levels observed by MRS are usually expressed as ratios of integral of the resonance peak of metabolites, e.g. Cit/Cho, [Cit/(Cho + Cr)] or [(Cho + Cr)/Cit].[22,23]

The objective of this review is to briefly describe the potential of *in vivo* ^{1}H MRS in breast and prostate cancers and its use in monitoring tumor response to therapy. In addition, we briefly describe the potential role of pre-biopsy MR investigations of prostate cancer to avoid unnecessary biopsies.

2 *In vivo* Localized MR Spectroscopy

Generally, an *in vivo* MR spectrum is obtained from a particular region of interest (ROI) for which localization of the ROI is important. To achieve localization of a particular ROI and to acquire the *in vivo* MR spectrum with optimal sensitivity, initially surface coils were used. Coils were positioned close to the surface of the organ of interest; spatial selectivity was achieved by varying the radio-frequency pulse length. By this method, only rough localization can be achieved, and lesions deep inside the organ are not accessible. Further, contamination from normal portion of tissue cannot be avoided as localization of tumor region alone is not possible with a surface coil MRS.

In the present day, most localization methods are image guided methods and use proton images in three orthogonal planes to guide the placement of the ROI. With these methods MR spectra can be acquired exclusively from localized area of the tissues. Localized MRS is acquired either from a single voxel (SV) or from multiple small voxels [referred as chemical shift imaging (CSI) or magnetic resonance spectroscopic imaging (MRSI)]. MRSI method can also be used to generate metabolite images in which the pixel intensity is proportional to the relative concentrations of the metabolites, thus providing visual assessment of the spatial variation of metabolite concentrations.

Before acquiring the *in vivo* ^{1}H MR spectrum, the patient is positioned in a suitable coil (like breast coil for breast MRS and endorectal coil for prostate MRS) to obtain maximum signal reception, and routine MR images in three orthogonal planes are obtained. In addition, fat saturated high-resolution images are acquired to identify the full extent of malignant tumors. DCE-MRI is also used in most circumstances for proper positioning of a voxel of an appropriate size for obtaining the MR spectrum, which usually depends on the tumor size. For SV localization, the generally-used pulse sequences are stimulated echo acquisition mode (STEAM),[24] point resolved spectroscopy (PRESS)[25] and for multi-voxel, CSI and MRSI.[26,27]

One of the major problems in ^{1}H MRS investigation is the detection of resonances from metabolites with low concentrations in the presence of a large water signal. In order to suppress the water resonance, chemical shift selective radio-frequency pulses that excite a limited narrow band (~ 50 to 60 Hz) of frequencies corresponding to the water signal are used.[28] Another major drawback is the overlap of the dominant lipid peaks with other metabolites as in the case of breast and prostate MRS. In such cases, pulse sequences to suppress simultaneously both the water and lipid signals are used to improve the detection of metabolites that are of low concentration.[29] In general, both un-suppressed and water, or water and lipid suppressed MR spectra are acquired using an appropriate echo time from the ROI.

3 Breast MRS

The first breast ^{1}H MRS study was reported by Sijens et al., in which the authors used a surface coil for acquisition of ^{1}H MR spectrum from a breast cancer patient and reported that tumor tissues contain high water content.[30] Since then, breast MRS technology has evolved, owing to developments in breast coil design, design of radio-frequency pulse sequences that suppress both water and lipid and MR hardware. A number of research groups have explored the potential of *in vivo* ^{1}H

MRS in differentiating malignant breast lesions from benign lesions.[16–21] Two important biomarkers that are calculated through breast MRS are water-to-fat ratio (W-F) and tCho. The potential of these parameters have been reported in the diagnosis and monitoring of therapeutic response to breast cancer patients. The observation of a distinct peak at 3.2 ppm due to trimethyl groups of choline containing compounds in the *in vivo* localized ^{1}H MR spectrum of breast cancer patients has given a hope to find a non-invasive biomarker for breast cancer diagnosis. This peak was designated as tCho and the presence of this peak was studied in breast cancer and benign lesions. Despite many years of the development of breast MRS, it is still challenging to obtain a good quality spectrum. Majority of breast MR studies till date have been performed using a 1.5 T MRI scanner; however, few studies at higher fields of 3T and 4T have also been reported.[31–36]

3.1 *Role of water-fat ratio (W-F) in the diagnosis of breast cancer*

The W-F ratio is determined by acquisition of proton MR spectrum of breast tissue without water and fat (lipid) suppression. Figure 1A shows the MR image of the breast of a volunteer while 1B shows a typical ^{1}H MR *in vivo* spectrum obtained without water and fat suppression. The spectrum is dominated by a lipid resonance at 1.33 ppm (methylene $[-(CH2)_n]$ protons) while the water peak was seen at 4.7 ppm. The water-to-fat (W-F) ratio can be calculated from the respective peak areas in the un-suppressed spectra.[16,18,37,38] Figure 2A shows the T2 weighted proton MR image of the tumor of a patient suffering from locally advanced breast cancer (LABC; infiltrating duct carcinoma), while Figure 2B shows the ^{1}H MR spectrum without water and lipid suppression. The water+lipid suppressed spectrum obtained from the same voxel is shown in Figure 2C. The ^{1}H MR spectrum of the normal breast tissue is characterized with the predominance of fat resonances, while the water signal is less. While tumor spectrum showed opposite characteristics with the predominance of water peak and low contributions from protons of lipids (Fig. 2B). Thomas et al. reported the evaluation of W-F ratio using 2D spectral peak volumes from *in vivo* localized 2D correlated spectroscopy, and suggested an association between tumor lipid content with its development and progression.[39] However, comparison of the W-F ratio between benign and malignant breast lesions showed overlap in their values indicating limited diagnostic ability of W-F ratio in breast cancer diagnosis.

3.2 *Role of tCho in the diagnosis of breast cancer*

Figure 3 shows the water + lipid suppressed proton MR spectra obtained from a LABC patient, patient with benign lesion, and normal breast tissue of a volunteer. As described earlier, the principal feature of the *in vivo* ^{1}H MR spectrum (water suppressed) of malignant breast lesion is an intense peak due to tCho at 3.2 ppm (see Fig. 3B). The tCho signal has contributions

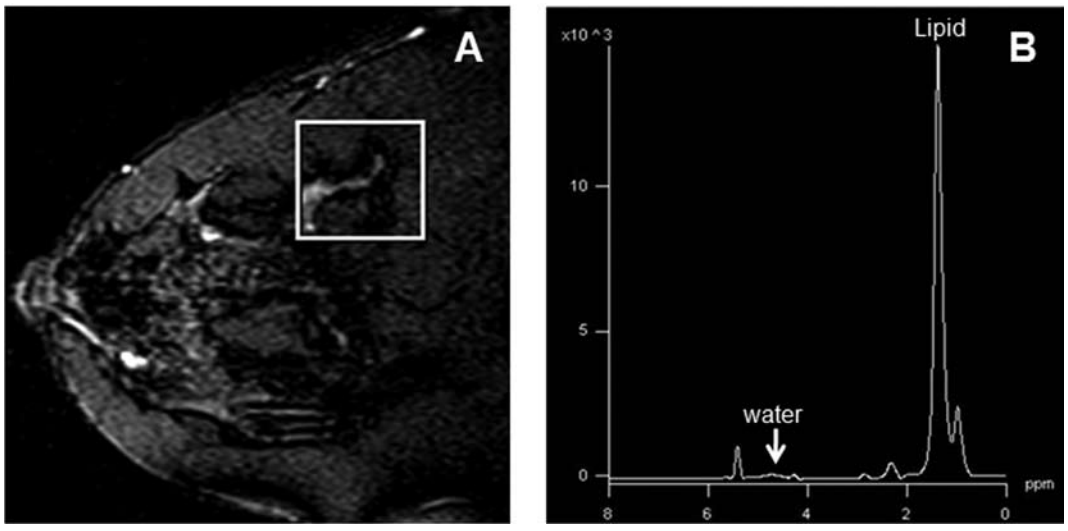

Figure 1: (A) MR image of a normal volunteer showing the voxel position from which the SV ^{1}H MR in vivo spectrum (B) was obtained from the normal breast tissue of a volunteer without water and fat (lipid) suppression (Reproduced with permission from John Wiley & Sons from Ref. 57).

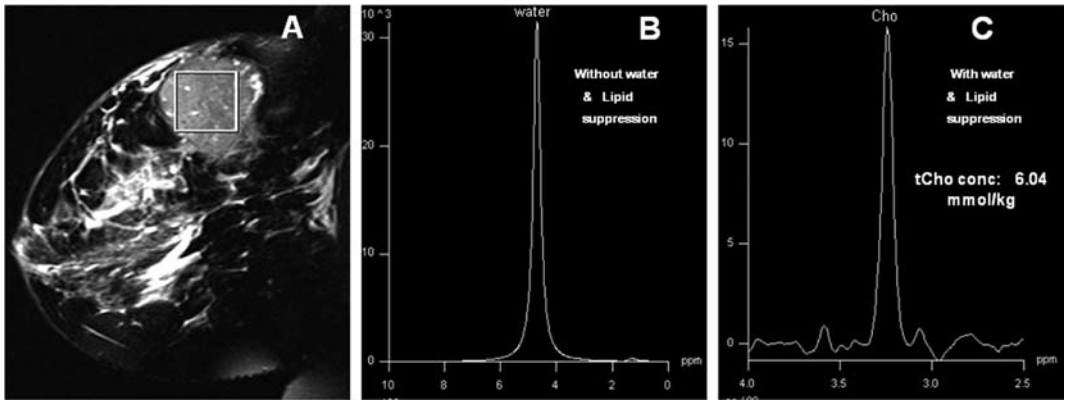

Figure 2: (A) MR image of a locally advanced breast cancer patient showing the voxel position from which the single voxel ^{1}H MR in vivo spectrum obtained without water and fat (lipid) suppression (B), while (C) shows that obtained with the suppression of water + lipid resonances (Reproduced with permission from John Wiley & Sons from Ref. 57).

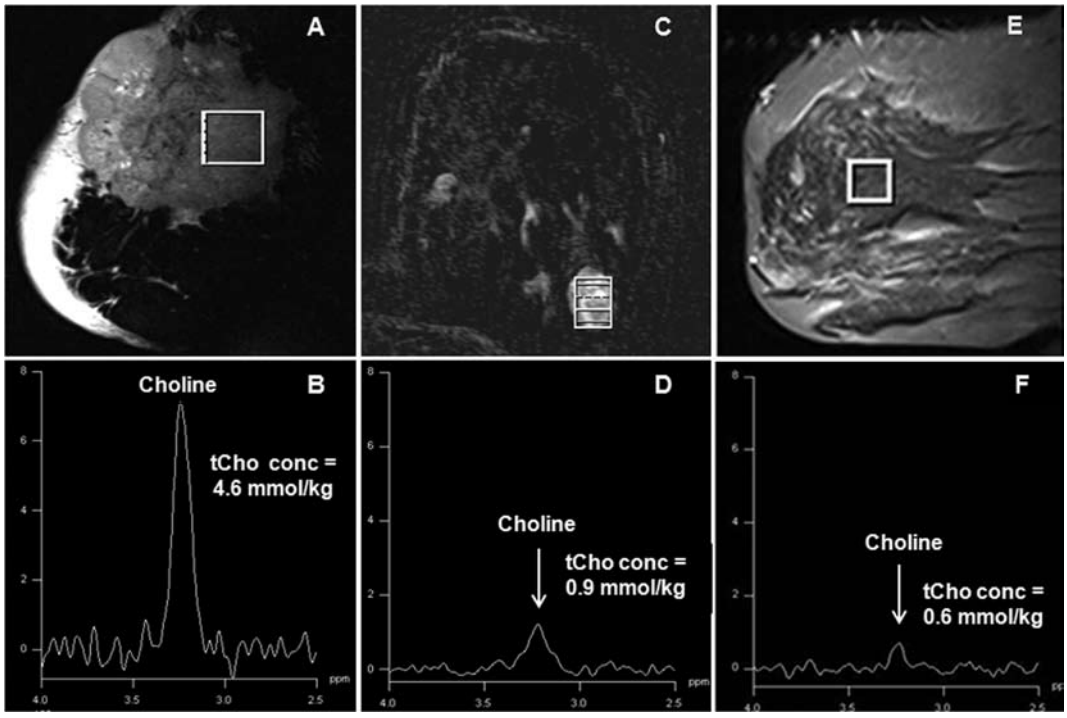

Figure 3: T_2-weighted sagittal MR image (A) showing the voxel location from a malignant tumor and (B) shows the corresponding proton MR spectrum; contrast enhanced axial MR image (C) showing the voxel location from a benign tumor and (D) the corresponding spectrum acquired from the same voxel; T_2-weighted sagittal MR image (E) showing the voxel location from a normal breast tissue of a volunteer and (F) the corresponding proton MR spectrum acquired (Reproduced with permission from John Wiley & Sons from Ref. 53).

from N-methyl groups of many Cho containing compounds such as phosphocholine, glycerophosphocholine, and free choline, but major component is phosphocholine in breast cancer tissue.[21] Several studies have established that tCho is specific to malignancy and can serve as a biomarker to differentiate malignant from benign breast lesions.[16–20,40,41] The increased level of tCho may be due to being a part of membrane synthesis, required for proliferation of tumor cells for tumor growth. Both biosynthesis and catabolism of phosphocholine regulated by choline kinase

and specific phospholipase respectively, has been shown to increase in breast tumors.[42]

A meta-analysis of the data of five studies that reported ^{1}H MRS of malignant and benign breast lesions[21] showed that the combined sensitivity and specificity of MRS was 83% and 85%, respectively. However, in younger patients (≤ 40 years of age), the sensitivity was 100% and the specificity was 89%–100% for MRS.[18–20] Later, with the inclusion of more MRS data, Bartella et al. reported increased sensitivity and specificity as 87% with a positive predictive value of 90%.[43] In 2013, Begley et al. reviewed the sensitivity and specificity obtained in various MRS studies on breast cancer.[44]

Multi-voxel MRS (MRSI) that reported the differentiation of breast cancer from benign lesions have also been reported.[45,46] The advantages that MRSI has over the SV spectroscopy (SVS) include the ability to assess multiple lesions and tissues simultaneously, as well as to distinguish the lesion borders and infiltration into the surrounding tissues.[47]

The tCho signal was observed in some benign and normal breast tissues as well, thus necessitating the need for quantitative estimation of tCho. Initially, many researchers used the semi-quantitative method by measuring the signal-to-noise ratio (SNR) of tCho resonance (ChoSNR)[48] and tCho integral.[49] ChoSNR is measured using the peak intensity (height) of the Cho resonance and noise intensity in an off-resonance region of the spectrum. For diagnosis of malignancy with 90% sensitivity and 89% specificity, a threshold ChoSNR value of ≥1.9 was reported; however, a sensitivity of 97% was obtained on exclusion of lesions smaller than 1 cm.[48] A cut-off ChoSNR value as ≥2 for malignancy was reported by Bartella et al.[50] Baek et al. reported a mean ChoSNR of 5.9 ± 3.4 (range 2.1–17.5) for malignant and 2.8 ± 0.8 (range, 1.8–4.3) for the benign lesions using CSI. They used a cut-off ChoSNR value of >3.2 to differentiate malignant from benign lesions that resulted in 81% sensitivity, 78% specificity and 81% accuracy.[51]

The method of quantification of absolute concentration of tCho involves the use of external or internal water referencing. By the use of external reference method, the concentration of tCho in malignant tumors was reported to be in the range of 0.7–2.1 mM.[18] In 55 patients with breast lesions, Meisamy et al. quantified the concentration of tCho using SVS.[35] They showed that the MRS data has higher sensitivity, specificity, accuracy, and inter-observer agreement when MR imaging features like morphology and contrast enhancement was combined. Baik et al. reported a wide range of concentration of tCho (0.76 to 21.2 mmol/kg) using the water peak as an internal reference.[52] The advantages of internal reference method is that there is no need for correction for partial volume effect and separate calibration as required in the external reference method.

Recently we, in our laboratory, calculated the concentration of tCho in 120 LABC patients (stage IIB, IIIA, IIIB and IIIC), 31 early breast cancer (stage IIA) patients, 38 patients with benign lesions and 37 controls using *in vivo* ^{1}H MRS at 1.5 T.[53] Our data indicated statistically significantly higher tCho concentration and lower tumor volume in early breast cancer patients compared to LABC patients. tCho cut-off values were also obtained for the differentiation of malignant from benign breast tissues (2.54 mmol/kg), malignant versus normal (1.45 mmol/kg), and benign versus normal breast tissues (0.82 mmol/kg).[53]

3.3 *tCho in lactating and normal breast tissues*

The observation of tCho is not unique to malignant breast tissue but seen in normal breast tissue of lactating women.[40,41,54] Stanwell et al. reported a post-processing method for improved spectral resolution for tCho observation. It was documented that the peak in normal volunteers has major contribution from glycerophosphocholine instead of phosphocholine.[54] Recently we reported the potential of diffusion weighted MRI and *in vivo* ^{1}H MRS in the differentiation of normal breast tissue of healthy lactating women volunteers (n = 12) and LABC patients (n = 12).[55] tCho was observed in all breast cancer patients and in 10/12 lactating women. In 10/12 lactating women, an additional peak at 3.8 ppm corresponding to lactose was seen. The calculated concentration of tCho was similar in both the malignant breast tissue of patients (3.51 ± 1.72 mmol/kg) and in normal breast tissue of lactating women (3.52 ± 1.70 mmol/kg). However, the apparent diffusion coefficient values calculated from diffusion MRI showed significantly higher values in the normal breast tissue of lactating women ($1.62 \pm 0.22 \times 10^{-3}$ mm^2/s) compared to the malignant breast tissue of patients ($1.01 \pm 0.10 \times 10^{-3}$ mm^2/s). Thus, our study suggested that observation of lactose peak with higher apparent diffusion coefficient in the breast tissue of healthy lactating women volunteers may help in differentiation of normal breast tissue with lactation compared to malignant tissue.[55]

3.4 *Association of tCho with molecular markers*

Breast cancer is a heterogeneous disease comprising of distinct biological subtypes and is influenced by estrogen receptor, progesterone receptor and human epidermal growth receptors (HER2) status of patients. Tse et al. documented relation between tCho and expression of HER2/Neu.[56] Our group investigated the association of estrogen receptor, progesterone receptor and HER2 status of breast cancer patients with tCho concentration and tumor volume using *in vivo* ^{1}H MRS and MRI.[53] Estrogen receptor negative patients showed significantly larger tumor volumes, indicating higher angiogenesis with aggressive tumor behavior. Non-triple negative and triple positive patients had a significantly higher tCho concentration compared to triple negative patients ($p < 0.05$), pointing towards complex molecular mechanism of cell proliferation and the molecular heterogeneity of breast lesions.

3.5 *Role of in-vivo breast MRS in the evaluation of therapeutic response*

To monitor the effect of neoadjuvant chemotherapy (NACT) in LABC patients, Jagannathan et al.[16,17,38,57] reported the potential use of W-F ratio (see Figure 4). They showed that the reduction of W-F ratio following NACT is associated with the reduction of the primary tumor size indicating its use as a non-invasive indicator of favorable clinical outcome of therapy. Further, in another study they observed that the presence of tCho before treatment that showed reduction/absence after treatment indicating that tCho may also serve as a useful indicator of tumor response to therapy.[41] Within 24 hours of administering chemotherapy, changes in tCho was reported by Meisamy et al.[34] These changes were found to be correlated positively with the lesion size changes, thus showing the potential of tCho as a predictor of therapeutic response. Recently, our group reported that the tCho concentration is a better predictor of early response of breast cancer patients than tumor volume.[58] Sequential MRI and *in vivo* SV ^{1}H MRS in 30 breast cancer patients was carried out prior to and during various stages of NACT. As early as after I NACT, the pre-therapy concentration of tCho showed significant reduction in responders compared to non-responders. Further reduction in tCho was seen after II and III NACT in responders, while the tumor volume showed significant decrease only after II NACT.

The potential of ChoSNR, tumor volume and diameter in the assessment of tumor response in 30 LABC patients undergoing NACT has also been reported using sequential MRSI and conventional MRI (see Figures 5 and 6).[59] The pre-therapy ChoSNR in 14 responders was 7.8 ± 5.1. Ten patients out of these 14 responders showed

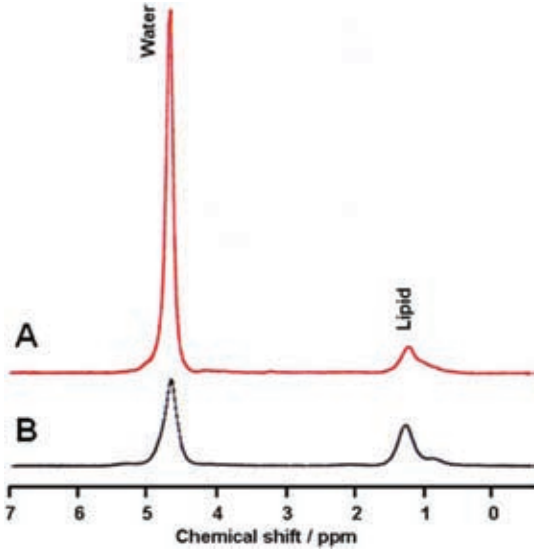

Figure 4: Proton MR spectra from an 8 ml voxel positioned in the tumor region of a patient suffering from locally advanced breast cancer: (A) pre-therapy and (B) post-therapy (Reproduced with permission from John Wiley & Sons from Ref. 38).

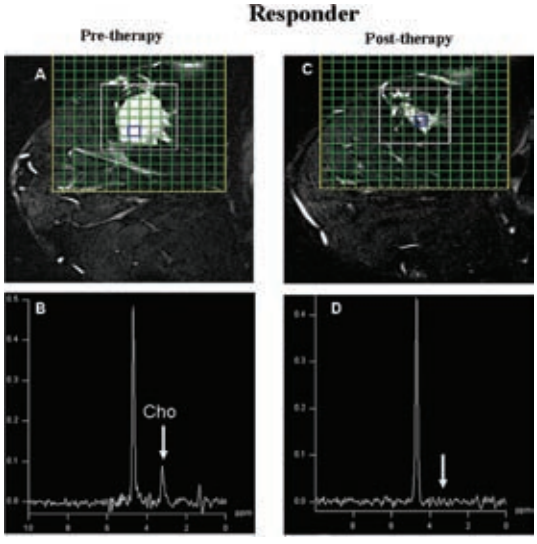

Figure 5: (A) Pre-therapy T_2-weighted sagittal fat suppressed image of a locally advanced breast cancer patient who is a responder with the MRSI grid. (B) Proton MR spectrum obtained from a voxel shown in (A) with the tCho signal. (C) Post-therapy MR image of the same patient after III NACT. (D) Spectrum obtained from a voxel highlighted in (C) that showed no tCho (Reproduced with permission from John Wiley & Sons from Ref. 59).

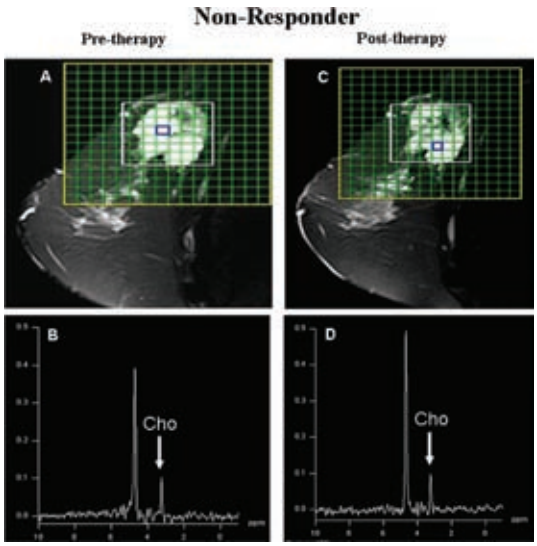

Figure 6: (A) Pre-therapy T_2-weighted sagittal fat suppressed image of a locally advanced breast cancer patient who is a non-responder with the MRSI grid. (B) Spectrum obtained from a voxel highlighted in (A) showing the tCho signal. (C) Post-therapy T_2-weighted sagittal fat suppressed image of the same patient after III NACT. (D) Spectrum obtained from a voxel highlighted in (C) showing tCho signal (Reproduced with permission from John Wiley & Sons from Ref. 59).

no Cho after III NACT, while in the remaining four patients the ChoSNR reduced to 3.6 ± 1.1, which was statistically significant. All the non-responders showed no statistically significant change in ChoSNR. The sensitivity to detect responders from non-responders using ChoSNR was 85.7% with 91% specificity, while 100% sensitivity was observed for volume and diameter but with reduced specificity of 73% for volume and 81.8% for diameter. However, when all the three parameters were combined, 100% sensitivity, 82% specificity with 87.5% positive predictive value (PPV) and 100% negative predictive value (NPV) was achieved, indicating the use of mutli-parametric approach to evaluate the tumor response to therapy.[59]

4 Prostate MRS

The application of *in vivo* MRS to human prostate started with the advent of endorectal coil, and many studies have been reported.[60–64] Sillerud et al. were the first to document the detection of Cit using *in vivo* ^{13}C MRS of human prostate.[65] Later, Narayan et al. reported ^{31}P MRS of canine prostate using transrectal probe.[66] This application later led to the use of transrectal probe for *in vivo* prostate MRS in humans.[67–69] These studies demonstrated the feasibility of MRS to differentiate cancer from benign prostate hyperplasia (BPH) and normal regions based on increased Cho and decreased Cit levels.

4.1 *Characteristics of ^{1}H MRS of prostate*

Figure 7 shows the T_2-weighted axial MR images of (A) prostate of a volunteer, and (B) of a patient showing the tumor (arrows). The tumor in PZ is seen as a hypointense area in Figure 7B. The *in vivo* ^{1}H MR spectrum of the normal prostate consists of three dominant resonances arising from metabolites such as Cho, Cr and Cit resonating at 3.2, 3.0 and 2.6 ppm, respectively (see Figure 8A). Resonance peak at 3.1 ppm due to polyamines (PA) (mainly spermine) was also reported.[70,71] The ^{1}H MR spectrum obtained from a patient suffering from BPH is shown in Figure 8B. Significant decrease in Cit peak with increased Cho can be seen in the spectrum acquired from cancerous region of the peripheral zone (PZ) of the prostate (see Figure 8C). The Cho resonance at 3.2 ppm arises from the tetramethylamine group $-N(CH_3)_3$ present in compounds such as Cho, phosphocholine and glycerophosphocholine, as discussed earlier. The high proliferation rate of malignant cells requires an increased membrane biosynthesis. Since the Cho containing compounds are components of cell membrane, an increased Cho signal is observed in malignant prostate tissues. High levels of polyamines (PA) levels are also seen in normal prostate and their levels decrease in PCa.[70,72] This additional information has been shown to improve the accuracy to distinguish PCa.[70]

The changes in various prostate metabolites such as Cit and Cho levels are expressed by ratios of metabolites like Cit/Cho, [Cit/(Cho + Cr)], [(Cho + Cr)/Cit] or [(Cho + Cr + PA)/Cit]. The (Cho + Cr)/Cit ratio was found to be a specific marker for PCa, with 98% of the ratios falling above 3 standard deviations of the mean healthy PZ value.[22,23] A scoring method for identifying cancer of the prostate was proposed by Jung et al. and it consist of score of 1–5 based on mean normal (Cho + Cr)/Cit.[73]

4.2 *Detection and localization of PCa*

As disused earlier, metabolites such as Cit and PA and their ratios to Cho and Cr are generally used to improve the specificity of MRI in identifying PCa. In 53 patients, with biopsy-proven PCa, better localization of cancer to a prostatic sextant was reported using combined MRI and MRSI compared to MRI alone.[74] Another study also reported that the localization accuracy of MRI and MRSI was similar to sextant biopsy.[75] Similarly, Hasumi

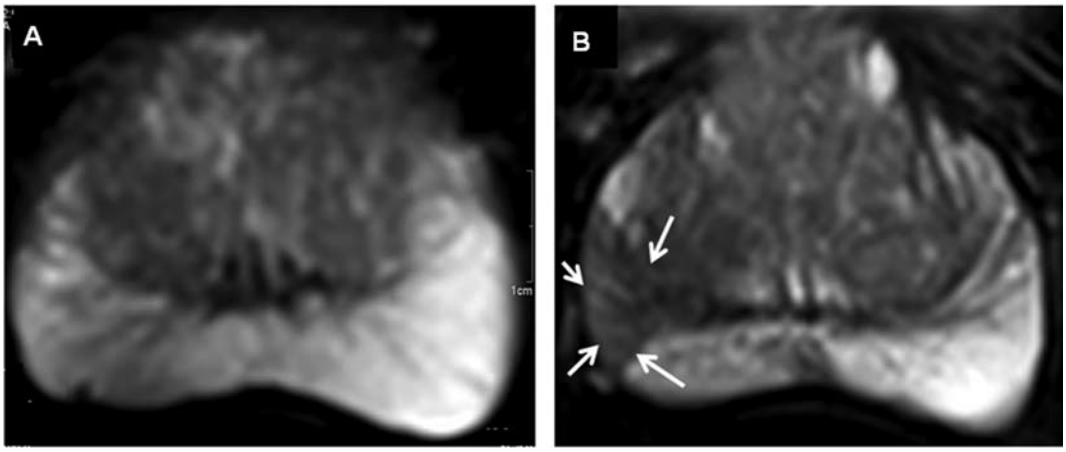

Figure 7: T_2-weighted axial MR images of (A) prostate of a volunteer, and (B) of a patient showing the tumor (arrows) (Reproduced with permission from John Wiley & Sons from Ref. 63).

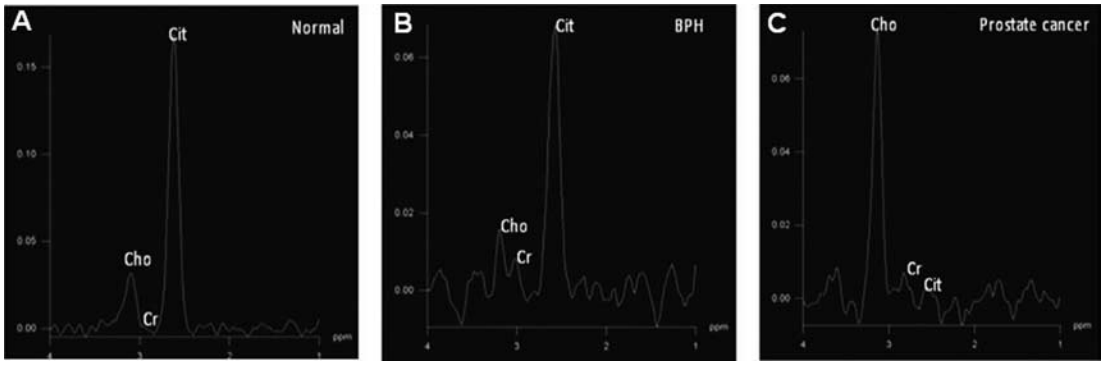

Figure 8: Representative proton MRSI spectrum obtained from normal peripheral zone (A), BPH (B) and cancer tissue (C). Abbreviations used: Cho, Choline; Cr, Creatine; Cit, Citrate (Reproduced with permission from John Wiley & Sons from Ref. 63).

et al. reported an accuracy of 81% for the combined MRI and MRS for cancer detection compared to 71.4% for MRI alone.[76] Later, several studies reported better diagnostic performance of MRI and MRS in the detection of PCa in patients with elevated prostate specific antigen (PSA).[77,78] These studies showed that combination of MRI and MRS yields better diagnostic results than either method alone.

Klijn et al. reported that pattern recognition (qualitative) and numerical assessment (quantitative) approach to MRS for cancer detection in the PZ yielded similar diagnostic results.[79] Testa et al., in their study, showed that MRSI has a higher sensitivity compared to positron emission tomography/computed tomography in localizing PCa.[80] However, other studies have shown the limitation of combined MRI and MRSI in the detection and localization of small tumors in prostate.[81,82] The addition of MRI and MRSI information to Transrectal ultrasound guided (TRUS) biopsy makes it more accurate, however, with the false positive findings due to prostatitis as a limitation of MRSI.[83] Yuen et al. reported a sensitivity of 82.1%, a specificity of 100%, and an accuracy of 79.2%, for combined MRI and MRSI for the detection of PCa in men with prior negative TRUS-guided biopsy.[84] In a prospective study, the accuracy of TRUS-guided biopsies by using MRI/MRSI in patients was evaluated with persistently high PSA and earlier negative TRUS guided biopsy.[85] Prostate MRS has been shown to have a high NPV. This may allow avoiding subsequent biopsy in patients with negative MRSI findings.

4.3 *Pre-biopsy applications of MR in PCa*

Pre-biopsy MRI and MRSI may provide the areas suspicious of malignancy and thus help in accurate targeted biopsy of the prostate as it improves the diagnostic yield, and reduces the number of biopsies.[63,86] Several studies recently focused on

the potential of pre-biopsy MR examination in identifying whether a patient should undergo biopsy and also the yield of biopsies.[63,87,88]

Further, it has been reported that the addition of pre-biopsy MRSI and diffusion MRI to conventional prostate MRI allows a significant improvement in the sensitivity and the specificity of PCa diagnosis.[89] Kumar et al. reported that the combined use of metabolite ratio obtained through MRSI and the apparent diffusion coefficient from DWI yielded 100% sensitivity and NPV with a specificity of 33% and 64% PPV in predicting the presence of cancer in comparison to TRUS-guided biopsy.[87]

A combination of MRI, MRS and free-to-total PSA ratio was shown to be more accurate in predicting PCa than the models using MRI/MRS/PSA separately.[90] Villeirs et al. reported that combined MRI and MRSI had a significantly higher sensitivity for high grade tumors than for lower grade tumors.[91] A study from our laboratory showed a detection rate of 25% with MRSI directed TRUS-guided biopsy, while the detection rate was 9% in another group of 120 patients without MRSI guidance.[87]

The use of MRSI to target needle biopsies under TRUS guidance for the detection of prostate malignancy in patients with previous negative TRUS biopsies have also been reported.[83–85,92–96] A few studies reported the combined use of DCE-MRI and MRS/I for a precise biopsy for the detection of PCa,[97,98] and their study concluded that the combination of MRSI and DCE-MRI showed the potential to guide biopsy to cancer foci in patients with previously negative TRUS biopsy. Recently, data from our group suggested that patients who are deemed as malignancy-positive in the PZ by MRSI may be subjected to prostate biopsy to confirm the diagnosis of cancer in a study that included 123 men with elevated PSA or an abnormal digital rectal examination (DRE).[99]

Prediction of the absence of PCa is another promising role of MRSI in men with raised PSA. This may help reducing the number of patients undergoing biopsies. The high NPV may be used to predict the absence of PCa instead of invasive biopsy.[100] To test the hypothesis that MRSI might be able to identify patients with noncancerous PSA elevation and help avoid unnecessary biopsies, MR investigations were carried out before biopsy in patients with PSA between 4–10 ng mL^{-1}. Thirty six out of one hundred fifty five men who showed no malignant voxels on MRSI were followed for at least 18 months. None of these 36 men had cancer on their initial TRUS guided biopsies. Interestingly, 4 patients required repeat biopsy and one with persistently elevated PSA was diagnosed with PCa after 29 months of initial MRSI. The authors suggested that prostate biopsy can be deferred in patients with an increased serum PSA between 4 to 10 ng mL^{-1} if their MRSI does not show any malignant voxel.[100]

4.4 *Treatment planning and therapeutic response/follow-up*

The metabolic information obtained from MRSI also has great potential for improving the ability of MR in treatment planning and to identify PCa recurrence after therapy. A novel brachytherapy treatment planning that registers MRSI to intraoperative-obtained ultrasound images that were subsequently used to escalate the dose to intraprostatic tumors has been reported.[101] For localized PCa, MRSI guided brachytherapy has also been reported.[102] In another study, the addition of MRS to localize the lesion that allows optimization of dosage in regions suspicious of cancer, was reported.[103]

The clinical potential of MRSI in the follow-up of the response to cryosurgery has demonstrated its reliability in the assessment of the presence of spatial extent of recurrent local disease after therapy.[23] The superiority of MRSI over TRUS and MRI in differentiating among PCa, BPH and necrosis has been reported when local recurrence after cryosurgery is suspected.[104] For the detection of recurrence after radiation therapy, Pucar et al. reported higher sensitivities of MRI (68%) and MRS (77%), in contrast to DRE (16%) and TRUS-guided biopsy (48%), when step-section pathology was used as reference.[105] To identify the viable tumor after radiotherapy, MRS combined with multivariate methods was used.[106] For visualizing the locally recurrent PCa after external beam radiation therapy, MRSI provides greater level of confidence compared to the combination of PSA and biopsy.[107,108]

Higher accuracy was seen when MRSI with DCE-MRI was combined compared to each method alone in the depiction of local recurrence of cancer in patients with biochemical progression after radical prostatectomy.[109] No additional value of MRS over MRI in detecting residual or local recurrent cancer has been reported.[110]

Combination of MRSI and DCE-MRI at 3T with fluorine-18 (18F) fluorodeoxyglucose positron emission tomography/computed tomography showed detection of local PCa recurrence in patients with biochemical progression after radical retropubic prostatectomy.[111] This study reported higher sensitivity and specificity of combined MRSI and DCE-MRI compared to positron emission tomography/computed tomography to identify local cancer recurrence. Efficacy of neoadjuvant hormone therapy was also assessed by

monitoring metabolic changes during hormone therapy.[112]

5 Summary & Future Directions

Over the last two decades researchers have been evaluating the role of various MR methodologies beyond conventional MRI, like *in vivo* MRS in detection, localization and staging of cancer, which is still a formidable challenge. At present, both *in vivo* MRS and MRI are complementary tools to other well known radiological diagnostic methods like ultrasound, CT, etc. Breast ^{1}H MRS studies reported till date showed tCho as a promising biomarker that can provide clinically useful information for diagnosis and assessment of tumor response to therapy. In a similar way, metabolites like Cit, Cho and Cr and their relative levels are used as biomarkers for the detection of PCa for monitoring the tumor response to therapy. However, the detection of small lesions by MR spectroscopy still remains a challenge in spite of the availability of high field scanners. In future, the sensitivity and specificity of *in vivo* MRS needs to be improved before *in vivo* MRS can be incorporated into clinical practice. However, the available *in vivo* MRS data from various centers across the globe on variety of cancers indicate that any improvement in SNR that will effectively enhance the detection of *in vivo* metabolites may increase the sensitivity and improve the diagnostic potential of MRS. Design of special radio-frequency pulse sequences with effective simultaneous suppression of water and lipid signals and the use of respiratory-gating whenever required to improve motion related artifacts, will further optimize the detection of *in vivo* metabolites. In addition, advances in the design of MR coils and the use of metabolic imaging will also allow exploration of tumor heterogeneity and characterization.

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