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Current Role and Future Perspectives of Magnetic Resonance Spectroscopy in Radiation Oncology for Prostate Cancer

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Abstract

Prostatic neoplasms are not uniformly distributed within the prostate volume. With recent developments in three-dimensional intensity-modulated and image-guided radiation therapy, it is possible to treat different volumes within the prostate to different thresholds of doses. This approach has the potential to adapt the dose to the biologic aggressiveness of various clusters of tumor cells within the gland. The definition of tumor burden volume in prostate cancer can be facilitated by the use of magnetic resonance spectroscopy (MRS). The increasing sensitivity and specificity of MRS to the prostate is causing new interest in its potential role in the definition of target subvolumes at higher risk of failure following radical radiotherapy. Prostate MRS might also play a role as a noninvasive predictive factor for tumor response and treatment outcome. We review the use of MRS in radiation therapy for prostate cancer by evaluating its accuracy in the classification of aggressive cancer regions and target definition; its current role in the radiotherapy planning process, with special interest in technical issues behind the successful inclusion of MRS in clinical use; and available early experiences as a prognostic tool.

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Introduction

Further to the development of three-dimensional (3D) conformal, intensity-modulated, image-guided, adaptive radiation therapy, major changes have occurred in the last three decades in the treatment planning of nonmetastatic prostate cancer. These techniques have significantly improved treatment precision, allowing for greater sparing of critical organ and delivery of escalated doses of radiation to the target volume.

It is now feasible to treat different volumes within the prostate with different thresholds of doses, with the potential to adapt the dose delivered to each subtarget area to the biologic aggressiveness of the various clusters of tumor population present in the gland.

A variety of magnetic resonance imaging (MRI) techniques is used nowadays in the field of cancer research, including dynamic contrast-enhanced (DCE) MRI, functional MRI, and diffusion-weighted MRI [1–6]. In the clinical practice of radiation therapy, MRI is routinely added to conventional computed tomography (CT) planning to improve target volume definition. Unfortunately, although standard MRI scans are able to provide extremely detailed anatomic imaging, their findings do not always correlate with tumor biology. Magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopy imaging (MRSI) have been successfully used in other regions (i.e., brain, head, and neck) to measure biochemical changes within the target volume, detect metabolic markers of different tumor phenotypes [7], and characterize tumor microenvironments in terms of blood volume and vessel permeability. The sensitivity and specificity of MRS-MRSI techniques for prostate studies increased significantly in the last few years, causing new interest for their potential role as a tool for the definition of target subvolumes at higher risk of failure following radical radiotherapy. Similarly to other tumor sites, prostate MRS-MRSI might also play a role as a noninvasive predictive factor of tumor response and treatment outcome.

The aim of this paper is to provide a comprehensive review of the use of MRS-MRSI in radiation therapy for prostate cancer by evaluating: their accuracy in terms of target definition and classification of aggressive cancer regions; their current role in the radiotherapy treatment planning process, with special interest in technical issues behind the successful clinical use of MRS data; and available early experiences as a diagnostic tool for follow-up after radiotherapy.

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Search Criteria

To provide a comprehensive review of the use of MRS-MRSI in radiation oncology for prostate cancer, we conducted an electronic search for relevant studies in databases such as PubMed, Medline, and EMBASE. During this search, a list of keywords relevant to the subject of review was used. Results were limited to articles published in English peer-reviewed journals between 1980 and 2007. Further studies were located by a search in literature references identified by the first search of the review.

MRS

MRS employs nuclear magnetic resonance techniques to investigate the metabolism of chemicals in the living body. Different chemicals containing the same nucleus exhibit characteristic chemical shifts in resonance frequency, allowing the chemical form of the element to be identified. Thus, MRS provides a noninvasive window on the metabolism of the organ under investigation.

A significant number of metabolites found in normal and pathological prostates contain either ^{1}H or ^{31}P. ^{31}P spectroscopy provides information on metabolites involved in providing energy for cellular processes. Researchers demonstrated that malignant prostate cancers are characterized by significantly decreased levels of phosphocreatine and increased levels of phosphomonoesters, compared to healthy prostates [8–11].

However, there have been no published recent studies on ^{31}P likely due to a shift in researchers' interest toward proton MRS (^{1}H MRS) since the development of efficient water and fat-suppression techniques.

As a result, the majority of investigations on prostate cancer with MRS employed ^{1}H MRS. Molecules that can be studied with ^{1}H MRS include choline, citrate, lactate, and creatine, as well as water and lipids, which are usually suppressed. In the prostate, an elevated level of choline may be an indicator of active tumor, as choline is essential for cellular membrane composition and repair. Areas that are significantly infiltrated by prostate adenocarcinoma have a higher choline/citrate ratio compared with normal prostatic tissues and benign hypertrophy [12,13]. Creatine helps in supplying energy to muscle cells; because of its close proximity to the choline peak, it is often added to the choline peak when the choline/citrate ratio is calculated.

All the articles further reviewed in this manuscript refer to ^{1}H MRS. In addition, MRS and spectroscopic imaging are referred to in the literature by a number of names and abbreviations, including MRS, MRSI, and chemical shift imaging (CSI). In this article, for consistency, we chose to refer to all spectroscopic variants as MRS.

MRS in Radiotherapy Treatment Planning

A peculiar characteristic of prostate adenocarcinoma is its multifocality and the synchronous presence of different clusters of aggressiveness within the tumor volume.

Several analyses of clinical trials suggest that an increased radiation dose to the prostate is associated with a reduced rate of biochemical failure and may, therefore, increase local control rates and decrease the risk for distant metastasis and overall mortality rate [14–18]. This observation is important for the management of intermediate-risk and high-risk prostate cancer patients; however, an increased radiation dose may be associated with an increased risk of treatment morbidity [19].

Traditionally, the whole prostate gland had been treated with a homogenous high-dose level, with dose escalation carried out for the whole gland. It is possible, however, to adopt an approach whereby the whole prostate is treated with a homogenous dose while the tumor burden area, as detected by 3D-MRS, is treated to a higher dose. The higher dose should be derived according to tumor control probability (TCP) and aimed at maintaining the dose to surrounding organs.

So far, this has been realized using either prostate brachytherapy or intensity-modulated radiation therapy (IMRT) to produce inhomogeneous gradients of dose within the gland and to administer a boost to one or more so-called dominant intraprostatic lesions (DILs).

Coregistration of MRI/MRS with CT/Ultrasound

To be used in radiation therapy planning, MRS images must be accurately matched and coregistered with images providing the anatomic information of the patient, such as CT and MR. Such coregistration should be capable of taking into account deformations, especially if organs are deformable as it is in the case of the prostate. Variations to be taken into account include interfraction and intrafraction movements, as well as prostate displacement and deformation, which are especially relevant if an endorectal (ER) coil is used for MRS examination. The standard deviation of prostate movement over the course of radiation therapy, as reviewed by Langen and Jones [20], reported ranges in the anterior–posterior direction from 1.5 to 4.5 mm, in the superior–inferior direction from 1.7 to 3.9 mm, and in the left–right direction from 0.7 to 1.9 mm. The maximum prostate movement over one fraction in one of the studies was found to be 13.86, 9.88, and 1.40 mm in the anterior–posterior, superior–inferior, and left–right directions, respectively [21].

The presence of an ER coil, although required for optimal MRS of the prostate with high resolution [22], adds additional displacement, which is a potential problem for the radiotherapy treatment planning of the prostate. In addition, T_2-weighted images of the prostate obtained with the ER coil provide much higher soft-tissue contrast of the prostate than normally provided by routine pelvic scans that do not employ an ER coil [23]. However, the coil deforms the prostate during MR/MRS investigation, changing its geometry from the treatment geometry. There have been a number of studies investigating the issue of the coregistration of MRS images distorted by an ER coil with MR/CT, and there are several approaches to overcoming this problem at present. One of the methods proposed was based on the assumption that the relative position of points within the prostate is maintained with respect to the axial contours of the prostate [24,25]. A second method involved the visual transfer of the location of dominant lesions [26,27], whereas other methods took into account either control points selected from the

contour of the prostate as an input to a transformation algorithm [28,29] or all points contained in the narrow band around the delineated prostate [29]. The idea of registration by mutual information, involving the correlation of intensity levels (gray scale) between pixels in two images, was also implemented [30]. Other registration techniques include biomechanical modeling of soft tissues [31] and the use of intraprostatic fiducial gold markers as reference points [32].

With one exception [31], differences in density and elasticity parameters within prostatic tissues were not taken into account in the abovementioned studies dealing with problems imposed by ER coil–related prostate deformation. The authors argued that the voxel size of MRS is generally very coarse (currently ~5 mm) compared to anatomic images and, therefore, increased registration accuracy by more advanced methods may not be necessary for prostate mapping purpose. However, one can expect advances in MRS leading to decreased voxel size and more precise tumor burden localization.

One way of overcoming the problem of the registration of coil-deformed and nondeformed prostate volumes is by performing MRS without the ER coil. A two-dimensional MRS study using external surface coils for the evaluation of prostate cancer provided comparable detection accuracy to ER surface coil CSI [33]. In addition, 3D-MRS of the prostate was found to be feasible using a spine array surface coil at 1.5 T. However, spectral quality and signal-to-noise ratio are clearly inferior to 3D-MRSI examinations with ER coils [34]. Our experience at Townsville Cancer Center (Queensland, Australia) confirms that a combination of multiple external coil MRS is feasible with diagnostic signal-to-noise ratio.

Other solutions can be the use of an ER balloon during radiation therapy, the shape of which is comparable to the MRS coil. The registration of prostatic volume at different rectal-filling levels is also a way of assessing the internal margin, accounting for expected physiological movement and variations in the geometry of clinical target volume (CTV) or gross tumor volume during the administration of radiation therapy.

Target Definition with MRS

An ideal imaging technique for target volume localization should be highly sensitive to and specific for cancer detection, be able to provide enough information for precise tumor delineation (including extensions outside the organ's anatomic boundaries), and allow the prediction of tumor response to radiation.

In a number of studies investigating the sensitivity and specificity of MRS for locating prostate adenocarcinoma, MRS sensitivity was found to be within the range 38.5% to 77%, and specificity was found to be between 38.5% and 78% [22,35,36]. Combined MRI/MRS had increased sensitivity, up to 100% [37]. Differences between studies can be explained by varying methodologies, difficulties in ensuring the correspondence of transrectal ultrasound biopsy spatial accuracies to suspicious areas on MRI and MRS, differences in MRS coverage of the target, and limitations of the scanning and postprocessing software used.

The sensitivity of MRS appears to improve with higher Gleason score, with detection rate being greatest for tumors with a Gleason score of $\geq 4 + 3 = 7$ [38].

The value of MRS for the localization of cancer nodules within the prostate volume is supported by studies of MRS use to direct prostate biopsy. For patients with previous negative biopsies but other signs of prostate cancer, such as elevated prostate-specific antigen (PSA) and positive digital rectal examination, it has been shown that the use of MRI/MRS combination may reduce the rate of false-negative biopsies and hence decrease the need for more extensive biopsy protocols and/or repeated biopsy procedures [39]. For sextant localization of prostate cancer, MRI and MRS are found to be more sensitive but less specific than biopsy, with sensitivities of 67% for MRI, 76% for MRS, and 50% for biopsy, and with specificities of 69% for MRI, 68% for MRS, and 82% for biopsy [40]. In one study, the authors found that two of seven patients would have had cancers missed if transrectal ultrasound biopsy had not been directed at abnormal areas detected by combined MRI and MRSI [22].

Coakley et al. [41] compared MRI, 3D-MRS, and a combination of both with respect to their ability to assess tumor volume. Not all three measurements could be performed for each tumor nodule because some nodules were not detected with all three methods. For all techniques, systematic overestimation of tumor volume occurred, and all techniques were more accurate for higher tumor volumes. Tumor volume measurements with all methods were positively correlated with histopathological tumor volume for nodules > 0.5 cm^3, but only measurements with MRS and a combination of MRI and MRS demonstrated statistical significance. It could be concluded that the addition of MRS to MRI increases the overall accuracy of prostate cancer tumor volume measurement, although measurement variability limits consistent quantitative tumor volume estimation, particularly for small tumors. In a study by Hom et al. [42], overestimation of tumor volume was observed once again when a true-positive lesion is defined with MRI and MRS by size alone. Given the reported limitation of MRI and MRS to assess tumor volume, the authors concluded that the assumption that a technically successful dose escalation in spectroscopically suspicious locations implies improved clinical outcome must be viewed with caution [43].

Results support the use of 3D-MRS as a predictor of extracapsular extension (ECE). A combination of volumetric data from MRS and anatomic display of MRI significantly improves the evaluation of ECE. Patients with the least extensive tumor demonstrated by MRS were found to have only a 6% risk of ECE, whereas patients with the most extensive tumor (more than four cancer voxels per section) had an 80% risk of ECE [44].

In terms of tumor burden delineation, the classification of MRS voxels as described by Kurhanewicz et al. [12] is often used. A voxel is classified as normal, suspicious for cancer, or very suspicious for cancer. Furthermore, a voxel may contain nondiagnostic levels of metabolites or an artifact that obscures the metabolite frequency range. Voxels are considered suspicious for cancer if (choline + creatine)/

citrate is at least 2 SD above the average ratio for the normal peripheral zone. Voxels are considered very suspicious for cancer if (choline + creatine)/citrate is > 3 SD above the average ratio.

The aggressiveness of prostate cancer, which in most cases correlates with the Gleason score from biopsy, is a key predictor of treatment outcome [45–47]. The (choline + creatine)/citrate ratio in the lesion from MRS examination was found to correlate with the Gleason grade, with elevation of choline and reduction of citrate indicating increased cancer aggressiveness [38]. Although there was an overlap between the metabolites ratio at various Gleason score levels [38], this finding provides an important rationale for adding MRI/MRS to the pretreatment evaluation of prostate cancer patients.

MRS-Guided Brachytherapy

Brachytherapy is one of the techniques capable of delivering intentionally inhomogeneous dose distribution to the target. There exist a number of studies investigating the feasibility of including MRS data in brachytherapy planning.

Zaider et al. [24] employed a biologically based treatment planning optimization module for brachytherapy to calculate TCP according to an expression developed previously [48] and to study dose escalation in MRS-defined tumor lesions within the prostate. MRS was registered to ultrasound images, and this information was incorporated into the treatment planning system. The prescription dose was 144 Gy using ^{125}I seeds; the dose to intraprostatic lesion was set to be at a minimum of 120% of the prescription dose with no upper limit. They have shown that it is theoretically possible to achieve tumor dose escalation in MRS-identified intraprostatic tumor deposits without concomitant delivery of escalated doses to the urethra (dose bounds of 100–120% of the prescription dose). As can be expected, the magnitude of TCP increase appeared to be greater when the tumor was well localized.

DiBiase et al. [26] created standard 3D brachytherapy plans that prescribed 145 Gy, using ^{125}I, to the planning target volume, so that 100% of the prostate received the prescribed dose. MRS-defined boost volumes were then manually planned, using ^{125}I as well. In 14 of 15 patients planned with MRS, data were successfully incorporated into their treatment plan and used to increase the radiation dose prescription to 130% in MRS-defined volumes. In one patient, MRS revealed significant multifocal disease (four separate cancer foci) that made focal boosts impractical. Postimplant dosimetry confirmed a median V_{100} of 95% (range, 89–98%) in the 15 evaluated patients for the prescription dose of 145 Gy to the target volume. The median BTV_{100} for the abnormal citrate region was 90% (range, 80–100%). Urethral and rectal dose–volume histograms were within normal limits. Morbidity was comparable with that for conventionally treated patients. Although this series was small and had short follow-up, MRS-guided implants are feasible and warrant further investigation as a means to improve the therapeutic ratio in prostate treatment.

Pouliot et al. [27] conducted another brachytherapy planning study to escalate dose to MRS-defined lesions. Treatment planning was performed for 10 patients, of which 8 had two DILs in the prostate and 2 had a single lesion. The dose to the DIL could be escalated to a minimum of 120% while the entire prostate is treated simultaneously, without increasing the dose to surrounding normal tissues. Higher boost levels between 150% and 170% were deemed feasible, but at the cost of slightly larger doses delivered to the rectum and urethra.

MRS-Guided IMRT

Another technique that is capable of delivering an inhomogeneous dose distribution is IMRT. IMRT was initially proposed for the irradiation of tumors with close proximity to sensitive organs, allowing an increase in dose to target while sparing organs at risk [49]. However, combined with inverse planning algorithms, it can simultaneously deliver different prescribed dose levels to intraprostatic lesions and to the remainder of the prostate volume.

Pickett et al. [50] demonstrated that the combined use of static field IMRT and MRI/MRS allowed a treatment plan design that would deliver higher doses to tumor-bearing regions of the gland without exceeding the tolerance of surrounding normal tissues. In this study, treatment plans involved one region of the prostate (DIL) being treated with a dose of 90 Gy while the whole prostate is treated with > 70 Gy. MRI/MRS was performed with the rectum dilated, and CTV was generated by adding prostate volumes contoured on CT and MR studies as an attempt to consider all likely positions of the prostate during treatment. The spectroscopic threshold for DIL was placed at 3 SD above the levels expected for normal prostatic peripheral zone tissues. The transfer of the dominant lesion from the MRI/MRS study to CT was performed by aligning bony pelvic and femoral anatomy. The authors achieved acceptable dose distributions when the dominant lesion was encompassed by a 90-Gy isodose without margins. Prostate movement was tracked during treatment delivery using gold seeds viewed with online portal imaging. Static field IMRT provided 25% more dose to the dominant lesion than traditional 3D conformal radiotherapy techniques. Based on dose–volume histograms, the authors concluded that there appeared to be an increase in the projected probability of tumor control and a decrease in the projected complication probability.

The same group evaluated the feasibility of dose escalation to parts of the prostate using three methods: forward and inversely planned segmental multileaf collimator (SMLC), intensity-modulated radiotherapy, and sequential tomotherapy (ST) [51]. CTV was defined as prostate volume on CT. Planning target volume (PTV) was obtained by expanding the CTV by 5 mm in all directions without overlapping other defined organs. Regions of prostate for dose escalation were two MRS-identified DILs: one at the left base and the other at the right apex of the prostate. The transfer of lesions from MRI/MRS to CT images was performed by visual approximation. They were planned to be treated with 90 Gy while the prostate gland was treated to a dose of 75.6 Gy. Planning

dose–volume thresholds for the rectal wall and bladder were estimated to cause a Radiation Therapy Oncology Group (RTOG) grade 2 complication rate of < 10%. Once again, prostate movement was monitored with gold seeds implanted in the prostate and was tracked with an electronic portal image device. It was concluded that the dose escalation to MRS-defined DILs within chosen dose constrains was feasible with all three methods; however, whether the treatment scheme will prolong patient survival remains to be determined. ST provided the best dose conformity and the highest dose (100 Gy compared with 97.8 Gy for the inverse SMLC plan and 93.2 Gy for the forward SMLC plan). Dose inhomogeneity inside the PTV was similar for all plans, whereas forward SMLC provided a more homogenous dose distribution in DILs. Inverse planning techniques were better at protecting the rectal wall, with inverse SMLC proving to be slightly better [51].

Another study of a boost dose to a selected region of prostate was conducted by van Lin et al. [52]. Radiotherapy treatment plans for five patients were prepared in this study. For each patient, a single DIL volume was defined by combined DCE-MRI and MRS. For each patient, four gold markers were implanted in the prostate and used during the coregistration of CT and MR image sets. CTV was defined as the prostate volume on MR images and transferred to CT images. DIL volume was transferred to CT images using the fusion window tools of a commercial treatment planning system. The dose prescribed to the PTV (prostate volume plus 7 mm of isotropic margin) was 70 Gy, whereas the DIL volume plus a 5-mm isotropic margin was treated up to a total dose of 90 Gy. For each patient, a second IMRT plan was also realized with a prescribed dose of 78 Gy to the prostate volume plus 7 mm of margin, without the boost dose. Plans were compared in terms of TCP for prostate and DIL, as well as normal tissue complication probability for the rectal wall with serious rectal toxicity as end point. The results have indicated that DIL IMRT may improve the therapeutic ratio by decreasing the normal tissue complication probability with an unchanged high TCP. The complication probability of the rectal wall was decreased by 1% to 3% to a mean of 4% in four of five patients [52].

These studies show that radiotherapy planning using MRS-defined regions for boost dose is technically feasible with IMRT. The choice of method for volume transfer between MR and CT images is still an open issue, whether the transfer is conducted by visual approximation, by the use of rectal balloon during both CT and MR examinations, or by other means. In addition, the boost dose to which DILs should be irradiated has not been adequately investigated. However, it can be expected that adding a margin to the dominant lesion to define the volume for boost dose should improve lesion coverage.

It needs to be stressed that IMRT delivery differs significantly from brachytherapy techniques. In high-dose brachytherapy, the target volume is immobilized with needles; in low-dose brachytherapy, radioactive seeds are implanted into the prostate volume and move together with it. Therefore, organ motion does not influence treatment outcome and does not need to be considered in treatment planning or brachytherapy quality assurance processes. Oppositely, in IMRT techniques, internal organ motion and the manner by which it is accounted for are important factors influencing the precision of dose delivery. It is paramount for successful IMRT delivery that the daily spatial location of the target volume is known—or, at the very least, that its distribution can be predicted. To improve the precision of IMRT delivery, the process of adaptive radiotherapy was introduced and is being further developed [53–55]. It uses target image feedback and either treatment plan or patient position adjustments to account for day-to-day variations in target position. Adaptive radiotherapy has the potential to allow a precise and safe delivery of MRS-guided IMRT plans with dose escalation to intraprostatic dominant lesion.

MRS in Follow-Up Treatment

The most common method used to confirm the resolution of prostate cancer after definitive radiotherapy is the serum PSA test. However, bouncing PSA values are common after external beam radiation therapy [56]. It can take up to 4 years for PSA results to reach a nadir after external radiotherapy [57]. Even when a nadir is achieved, it is often difficult to interpret [58,59], especially in patients undergoing androgen deprivation therapy because of the direct effect on PSA production. In addition, the use of MRI in detecting recurrence after therapy is not well established, partly because the exact site of local, regional, or distant recurrence in patients with rising PSA is, in most cases, uncertain, which in turn makes the targeting of an imaging site difficult [43].

The ability of MRI to depict residual/recurrent disease after radiotherapy is limited because of posttreatment changes, including prostatic shrinkage, development of diffuse low T_2-weighted signal intensity in the gland, and indistinctness of normal zonal anatomy [60]. In addition, even if the tumor is detected, MRI does not have the ability to distinguish active tumor from treated tumor. MRS, which detects abnormal metabolism rather than abnormal anatomy, has shown considerable promise in the local evaluation of prostate cancer after treatment.

MRS can diagnose metabolic atrophy, which is indicative of successful treatment because the growth of normal or abnormal cells cannot occur without metabolism. Thus, MRS has the potential to be an earlier indicator for the resolution of local disease compared to the PSA nadir. If supported by longer follow-up, the time to metabolic atrophy may be used as an adjunct to PSA determination for assessing local control after both permanent prostate seed implantation and external beam radiotherapy [61,62]. Benign PSA blips were not associated with an increase in metabolic activity, suggesting that these blips are secondary to the death of epithelial cells leaking into the bloodstream [62]. This study also suggests that, when used in conjunction with PSA determination and biopsy, MRS may provide a greater level of confidence when assessing local control.

Pitfalls of MRS

In a study by Kaji et al. [13], the addition of MRS to MRI resulted in a significant increase in the accuracy (52–75%)

and specificity (26–66%) of tumor detection. However, postbiopsy hemorrhage may hamper tumor detection in the prostate, leading to either underestimation or overestimation of tumor presence and local extent. Regions of extensive hemorrhage can result in either loss of all prostatic metabolites or overcalling of cancer due to a larger decrease in citrate rather than choline. MRS can accurately identify tissues underlying hemorrhage approximately 62% of the time. In addition, MRS spectral degradation was found to be inversely related to time from biopsy, with mean percentages of degraded peripheral zone voxels of 18.5% within 8 weeks after biopsy and 7% after 8 weeks [63]. Therefore, MRS should be delayed for at least 4 to 8 weeks after prostate biopsy [63–65].

Hormone therapy, one of the treatment options for prostate cancer, also influences the results of MRS by changing the metabolism of the prostate. In a study by Mueller-Lisse et al. [66], it has been shown that there was a significant time-dependent loss of prostatic metabolites during hormone deprivation therapy, leading to complete loss of metabolites after a longer time of therapy. In a group of patients undergoing short-term androgen deprivation therapy (1–6 weeks), the metabolic pattern of both the normal prostate and prostate cancer was similar to that of untreated patients. In 25% of patients receiving long-term hormonal therapy (> 34 weeks), there was complete loss of metabolites on MRS; in 69% of these patients, loss of detectable citrate was observed. In the absence of citrate in the spectra, residual prostate cancer could be detected by elevated choline levels (choline/creatine ratio > 1.5). In some of the cases, when creatine was also reduced to noise level, the presence of cancer could be still detected by the choline peak in the proton spectrum, with a signal-to-noise ratio of > 5. This observation was also confirmed by imaging and biopsy diagnosis of cancer. At each point of hormonal therapy, a significant difference between the metabolic spectra of healthy prostate tissue and the metabolic spectra of malignant prostate tissue was seen [66]. However, it was concluded that within 4 months of androgen deprivation therapy, combined MRI and 3D-MRS had the same accuracy in localizing prostate cancer as in nontreated patients [67].

The production, storage, and secretion of prostatic citrate are hormone-dependent [68]. Results suggesting an association between serum PSA levels and citrate detection in the prostate after androgen deprivation therapy have also been reported [69]. After hormonal therapy, patients with detectable citrate on MRS had PSA levels significantly higher than those of patients without detectable citrate on MRS [69].

For these reasons, the use of citrate as a reference for detecting the increase in choline levels is questionable. A patient with elevated choline level and high citrate level may have the same metabolite ratio as a patient with much lower choline level and low citrate level.

As well as the influence of postbiopsy changes and hormonal therapy, there are a number of pitfalls associated with MRS. MRS is technically demanding and needs specialized software and a high level of expertise, both in performing MRS and in evaluating results. The quality of spectra (signal-to-noise ratio) varies from site to site, depending on equipment and signal acquisition techniques. There is an interplay between MRS resolution and signal-to-noise ratio; for acceptable signal-to-noise ratio, MRS resolution often has to be crude. Consequently, poor spatial resolution causes difficulties in the interpretation of signal from voxels that overlap different tissue regions (e.g., voxels on the edge of prostate and muscle or fat). Additionally, there are no established protocols for MRS signal processing; hence, the process is operator-dependent. For each 3D prostate MRS, > 4000 single spectra can be produced, making manual evaluation an extremely time-consuming and complex task.

Finally, DICOM 3 and DICOM RT conformance statements (digital imaging communication protocols for diagnostic imaging and radiotherapy) are not fully implemented for MRS. As a consequence, image and data transfers between postprocessing workstations suffer from lack of mutual standards between manufacturers.

Summary and Future Challenges

Biologic imaging, including MRS, has the potential for changing radiation therapy by precise tumor localization. The region of high (choline + creatine)/citrate ratio on prostate MRS is most commonly considered as the biologic target volume for which an additional dose can be delivered. As such, the ratio of metabolites becomes a functional determinant of cancer location within the prostate. Future studies should further clarify the role of each detectable metabolite. Ideally, with improved MRS acquisition, creatine should not be added to choline as there is no indication of its relation with tumor aggressiveness.

The use of MRS to distinguish between normal and cancerous areas has great potential in enhancing the therapeutic ratio of brachytherapy and IMRT. Studies conducted to date show that delivering a boost dose to DILs within the prostate gland is feasible using both techniques, with a corresponding decrease in normal tissue complication probability. Further work is required to analyze the exact level of dose escalation needed. Ideally, biologic imaging methods could be used to determine the level and location of boost dose on a patient-specific basis.

There is considerable evidence from the work presented in this review that supports the value of MRS in prostate cancer treatment. To date, however, trials have been small and somewhat restricted in scope, and there is a need to undertake larger clinical trials covering a greater range of grade, number, and location of intraprostatic lesion to better define the full usefulness of MRS in prostate treatment. This work should also provide a better understanding of when and how to best incorporate MRS such that it leads to improved treatment outcome.

Biologic and technical pitfalls of MRS need to be addressed before its introduction into routine clinical practice.

Interoperator differences in MRS evaluation should be decreased either by the introduction of new protocols for spectral processing or by the automation of this process.

Indeed, developments in spectral processing methodology and the use of innovative signal processing methods such as signal entropy analysis [70] can aid in both consistency of results and improvement in metabolite detection sensitivity and specificity.

Improved analysis may also be gained from coanalysis with tissue segmentation information and statistical methods that include comparisons with normal metabolite concentrations, which vary as a function of location and subject parameters, thus gaining more information without necessarily increasing the signal-to-noise ratio.

An automated pattern recognition of the spectra is a promising approach to overcoming the difficulties associated with manual evaluation [71]. An expert system trained on a set of reference data showed potential for being less sensitive to high noise levels, automatically identifying unusable spectra and decreasing overall spectra evaluation time.

Additionally, progress in signal acquisition technology and hardware can lead to improved signal-to-noise ratio, allowing for smaller voxel dimensions with a corresponding increase in spatial resolution and more precise metabolite maps of cancer activity within the target volume. The installation base of 3-T MRI scanners is constantly growing. A higher static field strength is desirable especially for spectroscopy in terms of providing improved signal-to-noise ratios, higher resolution, and shorter scan times, and of improving the utilization of external coils instead of ER coils [72]. It is not clear which of these potential advantages will be the most important in upcoming clinical 3T protocols. Adaptive radiotherapy for prostate cancer IMRT, although not widely available yet, will eventually be used in studies evaluating the clinical benefit of MRS-supported IMRT treatments.

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