Medical Policy

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Title: Magnetic Resonance Spectroscopy

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DESCRIPTION

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to measure the concentrations of different chemical components within tissues. The technique is based on the same physical principles as magnetic resonance imaging (MRI) and the detection of energy exchange between external magnetic fields and specific nuclei within atoms.

Background

With MRI, this energy exchange, measured as a radiofrequency signal, is then translated into the familiar anatomic image by assigning different gray values according to the strength of the emitted signal. The principal difference between MRI and MRS is that in MRI, the emitted radiofrequency is based on the spatial position of nuclei, while MRS detects the chemical composition of the scanned tissue. The information produced by

MRS is displayed graphically as a spectrum with peaks consistent with the various chemicals detected. MRS may be performed as an adjunct to MRI. An MRI image is first generated, and then MRS spectra are developed at the site of interest, termed the voxel. While an MRI provides an anatomic image of the brain, MRS provides a functional image related to underlying dynamic physiology. MRS can be performed with existing MRI equipment, modified with additional software and hardware.

MRS has been studied most extensively in a variety of brain pathologies. In the brain, both 1-H (i.e., proton) and 31-P are present in concentrations high enough to detect and thus have been used extensively to study brain chemistry. For example, proton MRS of the healthy brain reveals 5 principal spectra:

- Arising from N-acetyl groups, especially N-acetylaspartate (NAA) [NAA intensity is thought to be a marker of neuronal integrity and is the most important proton signal in studying central nervous system (CNS) pathology. Decreases in the NAA signal are associated with neuronal loss.]
- Arising from choline-containing compounds (Cho), such as membrane phospholipids (e.g., phosphocholine and glycerophosphocholine). Choline levels increase in acute demyelinating disease. Brain tumors may also have high signals from Cho.
- Arising from creatine and phosphocreatine [In the brain, creatine is a relatively constant element of cellular energetic metabolism and thus is sometimes used as an internal standard.]
- Arising from lipid
- Arising from lactate [Normally this spectrum is barely visible, but lactate may increase to detectable levels when anaerobic metabolism is present. Lactate may accumulate in necrotic areas, in inflammatory infiltrates, and in brain tumors.]

Different patterns of the above spectra and others, such as myoinositol and glutamate/glutamine, in the healthy and diseased brain are the basis of clinical applications of MRS. The MRS findings characteristically associated with non-necrotic brain tumors include elevated Cho levels and reduced NAA levels. The International Network for Pattern Recognition using Magnetic Resonance (available online at: http://azizu.uab.es/INTERPRET/index.html) has developed a user-friendly computer program for spectral classification and a database of 300 tumor spectra with histologically validated diagnoses to aid radiologists in MRS diagnosis.(1)

All the findings reported in this policy refer to proton MRS, unless otherwise indicated.

One of the limitations of MRS is that it provides the metabolic composition of a given voxel, which may include more than one type of tissue. For some applications, the voxels are relatively large (e.g., greater than 1 cm^3), although they may be somewhat smaller using a (3 Tesla) 3T MRI machine versus a 1.5T magnet. The 3T technique creates greater inhomogeneities, however, which require better shimming techniques.(2) There are 2 types of MRS data acquisition: single voxel or simultaneous multivoxel, also called chemical shift imaging. Reliable results are more difficult to obtain from some areas, e.g.,

close to the brain surface or in children with smaller brains because of the lipid signal from the skull. Some techniques are used to deal with these issues; various MRS techniques continue to be explored as well. A combination of MRS is often used with other MRI techniques, including diffusion-tensor imaging, susceptibility-weighted imaging, etc., and possibly other types of imaging such as positron emission tomography (PET).

Peripheral applications of MRS include the study of myocardial ischemia, peripheral vascular disease, and skeletal muscle. Applications in non-CNS (central nervous system) oncologic evaluation have also been explored. Nomograms for prostate cancer are being developed that incorporate MRI and MRS results.(3)

Multiple software packages for performing proton MRS have received clearance by the U.S. Food and Drug Administration (FDA) through the 510(k) process since 1993.

POLICY

Magnetic resonance spectroscopy is considered **experimental / investigational**.

RATIONALE

Validation of a new imaging technique involves the following steps:

1. Demonstration of its technical feasibility, including assessment of its reproducibility and precision.
2. An understanding of normal and abnormal values as studied in different clinical situations. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a reference standard must be known.
3. The clinical utility of an imaging study is related to how the results of that study can be used to benefit patient management. The clinical utility of both true-positive and true- negative tests must be assessed. Relevant outcomes of a negative test (i.e., suspected pathology is not present) may be avoidance of more invasive diagnostic tests or avoidance of ineffective therapy. Relevant outcomes of a positive test (i.e., suspected pathology is present) may also include avoidance of a more invasive test plus the institution of specific, effective therapy. Use of the imaging study should result in net health benefit.

The published data indicate that the second and third criteria have not been met for magnetic resonance spectroscopy (MRS). MRS has been investigated in a wide variety of clinical situations; key potential applications are discussed below.

There are a variety of potential indications for MRS, both for cancer and non-cancer conditions. The clinical utility of MRS will be evaluated separately for each of these indications.

Brain Tumors

A TEC Assessment was completed in 2003 evaluating MRS for evaluation of suspected brain tumors. The 2003 TEC Assessment(4) used the following study selection criteria to identify studies for inclusion in the MRS assessment:

1. Sample sizes of 10 or more subjects;
2. A method to confirm the MRS diagnosis;
3. Specified criteria for a positive test; and
4. Available data to calculate diagnostic performance.

The Assessment identified 7 studies including a total of 271 subjects. MRS would be judged to produce a beneficial effect on a health outcome if MRS correctly determined the presence or absence of a tumor and avoided the need for a brain biopsy. The Assessment concluded that MRS did not meet TEC criteria for evaluation of suspected brain tumors.(4)

One study of 12 children treated with radiation for a brain tumor had a magnetic resonance imaging (MRI) scan suggestive of either progressive/recurrent tumor or delayed cerebral necrosis.(5) MRS identified 5 of 7 recurrent tumors, for a sensitivity of 71%. MRS identified 4 of 5 cases (80%) of delayed necrosis, and a fifth case was considered inconclusive.

Five studies that evaluated a heterogeneous group of patients, some with known prior tumor, some with unknown new masses, showed variable diagnostic test characteristics for MRS with sensitivities ranging from 79% to 100% and specificity ranging from 74% to 100%.(6-11) The positive predictive value ranged from 92% to 100%, while the negative predictive value ranged from 60% to 100%. The wide range reported for diagnostic performance in these studies may reflect heterogeneous groups of patients, differences in MRS protocols, or both.

One study evaluated 51 patients with intracranial cystic lesions.(11) MRS properly assigned the correct diagnosis in 47 of 51 patients (92%). However, MRS interpretation was based on investigator judgment, rather than on formal criteria.

The 2003 TEC Assessment concluded that the overall body of evidence did not provide strong and consistent evidence regarding the diagnostic test characteristics or clinical utility of MRS for any condition. Studies of diagnostic performance often included a heterogeneous mix of patients who had clinically important differences and did not clearly delineate how MRS information would be used to guide patient management. Furthermore, differences in MRS technique and methods of analysis across studies made it difficult to synthesize findings from different studies.

A systematic literature review on MRS for the characterization of brain tumors was performed in 2006. This review evaluated whether MRS could differentiate malignant from non-malignant lesions; high-grade tumors from low-grade tumors; and metastatic from primary brain tumors. The review concluded that the evidence on MRS for characterizing brain tumors is promising but that additional high-quality studies are needed.(12) Many of the articles reviewed were flawed, in some cases because of research design and in other cases because key information needed to evaluate the study was not reported (e.g., how many days elapsed between the imaging test and the biopsy, which served as the reference standard).

Other research has attempted to determine whether MRS can differentiate the type of brain tumor. In 2012, Vicente et al reported on a multi-center study to evaluate the ability of single voxel, proton MRS to differentiate 78 histologically confirmed pediatric brain tumors (29 medulloblastomas, 11 ependymomas, and 38 pilocytic astrocytomas).(13) Significant metabolic differences in tumor types were identified by MRS when results from short and long echo times were combined, suggesting that MRS may provide non-invasive diagnostic information.

In 2012, Wilson et al evaluated MRS as a prognostic tool. This study reported on single voxel, proton MRS using short echo times to predict survival of patients with pediatric brain tumors in 115 patients followed for a median of 35 months.(14) Metabolic changes were identified that predicted survival. Poor survival was associated with lipids and scyllo-inositol while glutamine and N-acetylaspartate (NAA) were associated with improved survival ($p<0.05$).

Studies on the use of MRS to categorize newly diagnosed brain tumors(15); to distinguish between tumors and abscesses or other infectious processes(16); or to diagnose mitochondrial diseases(17) identify the MRS patterns associated with each type of lesion but, once again, do not include the necessary validation study or they report MRS findings that overlap across the categories of interest. Many are also retrospective.(16, 18) Preliminary studies done in Asia with a 3T MRI machine for detecting tumor versus radiation injury reported diagnostic quality MRS studies in 26/28 (93%) cases, and the sensitivity and specificity for those 26 patients based on cutoffs identified in the study were 94.1% and 100%, respectively.(15); see also(19). Validation studies using the same cutoffs in larger samples are needed.(15)

A 2009 review on MRS in radiation injury concludes the following:

MR spectroscopy is presently one of the noninvasive radiologic methods used to distinguish recurrent tumor and radiation injury in patients previously treated with radiation for neoplasm. Still, despite a considerable volume of research in the field, no consensus exists in the community regarding ratio calculations, the accuracy of MR spectroscopy to identify radiation necrosis, and the accuracy of MR spectroscopy in differentiating radiation necrosis from tumor recurrence or the true value of the method in clinical decision making.(20); for another review, see(21).

In a 2011 study, Amin et al compared MRS to single-photon emission computed tomography (SPECT) in the identification of residual or recurrent glioma versus radiation necrosis in 24 patients treated with surgery and radiotherapy.(22) MRS and SPECT results differed in 9 cases of recurrence and were more accurate with SPECT. Specificity and positive predictive value were 100% in both MRS and SPECT; however, sensitivity was 61.1% versus 88.8% and negative predictive value was 46.2% versus 75%, respectively. The use of a single voxel rather than multiple voxels is noted as a limitation in interpreting the MRS results in this study.

Section Summary

Although a number of studies have examined the use of MRS to differentiate between brain tumor recurrence and radiation necrosis, the cumulative evidence remains weak. The studies tend to have small sample sizes(23, 24); they provide incomplete histopathologic data to serve as the reference standard(25); they find that combined imaging modalities, such as MRS and perfusion MRI or diffusion-weighted MRI, outperform MRS by itself(19, 26); or they identify the patterns of interest and the cutoff values for making a diagnosis without providing validation studies.(18, 27) In some cases, a mixed reference standard is used, with histopathologic findings for lesions that are excised, undergo biopsy, or are reviewed at autopsy and longer follow-up for patients not undergoing surgery.(18, 19) Although having a mixed reference standard is not optimal, it may be the only feasible option in patients with brain tumors, some of which are located in parts of the brain not amenable to surgery. Some studies report mostly on primary brain tumors,(15, 19) while others focus mostly on metastases of cancers located in other parts of the body.(23, 25)

Dementia

Research continues on using MRS to identify dementia, especially in its early stages. Tumati et al conducted a systematic review and meta-analysis of 29 studies on MRS for mild cognitive impairment (MCI).(28) Included in the analysis were a total of 607 MCI patients and 862 healthy controls. Patterns in metabolite concentration, including NAA, creatine (Cr), and choline (Cho) and myoinositolin, in various regions of the brain were identified and associated with MCI. For example, levels of creatine were found to be significantly lower in the hippocampus and paratrigonal white matter. NAA was found to be most associated with MCI, but other markers including myoinositolin, Cho, and Cr may also contribute to MCI. A

community-based study was conducted to evaluate whether MRS could distinguish between patients with normal cognition (group 1), dementia (group 2), or MCI (group 3), in a population with a low Mini-Mental State Examination (MMSE) score.(29) From an initial population of 215 with low MMSE scores, MRS results were obtained for 56 patients. Comparing MRS to clinical diagnoses, the results were mixed for MRS, with statistically significant differences in metabolic patterns between patients with dementia (group 2) and patients without dementia (group 1 and group 3) but not between patients with MCI and those with normal cognition (group 1 vs group 3). In a 2012 study, Shiino et al compared proton MRS in 99 patients with Alzheimer's disease (AD), 31 patients with subcortical ischemic vascular dementia (SIVD), and 45 elderly controls.(30) Differences in metabolic patterns were seen in both AD and SVID patients. Especially notable were increases in myoinositol concentration in the hippocampus identified in AD but not in SIVD (0.95 area under the receiver operating characteristic [ROC] curve).

Section Summary

Although a number of studies have examined the use of MRS for identifying and monitoring cognitive impairment and dementia, the cumulative evidence is insufficient to determine any role for MRS outside of the research setting. There are no clear criteria for diagnosing cognitive impairment or dementia with MRS and insufficient data on diagnostic comparators. Additionally, the impact of MRS imaging on clinical management and health outcomes is unknown.

Breast Cancer

MRS is being investigated to improve the specificity of MRI of the breast, which has a high false-positive rate. In 2013, Baltzer et al conducted a systematic review and meta-analysis of 19 studies on MRS for detecting benign versus malignant breast lesions.(31) The combined total number of patients in the studies reviewed was 1183 and included 452 benign and 773 malignant lesions. In the pooled estimates, sensitivity of MRS was 73% (556 of 761; 95% confidence interval [CI], 64% to 82%) and specificity was 88% (386 of 439; 95% CI, 85% to 91%). The area under the ROC curve for MRS detecting breast cancers versus benign lesions was 0.88. There was significant heterogeneity between studies and evidence of publication bias, limiting interpretation of findings.

Bartella et al conducted a preliminary study using MRS to evaluate suspicious lesions 1 cm or larger identified on MRI.(32) They found that the addition of MRS increased the specificity of MRI in the specific population examined to 88% (23/26) and could have prevented unnecessary biopsies; the sensitivity was 100% (31/31). As the authors note, these findings need to be confirmed in larger studies and with a more diverse set of lesions. In particular, their sample only included one ductal carcinoma in situ (DCIS), and other studies have suggested that the choline peak they used to indicate a positive MRS result may be less likely to occur with DCIS.

Liver Disease

MRS has been evaluated as a noninvasive alternative to liver biopsy in the diagnosis of hepatic steatosis. It has been compared to other noninvasive imaging procedures such as computed tomography (CT), dual-gradient echo magnetic resonance imaging (DGE-MRI), and ultrasonography (US); liver biopsy was the reference standard and a 3T MRI machine was used. In a prospective study of 161 consecutive potential living liver donors, DGE-MRI was reported to be the most accurate test for diagnosing hepatic steatosis. While DGE-MRI and MRS were similar for hepatic steatosis 5% or greater, DGE-MRI outperformed MRS for hepatic steatosis 30% or greater (especially regarding specificity) and on quantitative estimates.(33); see also(34). In a systematic review of imaging liver fat in children, Awai et al reviewed 5 MRI studies and found

varying methodologies for measuring liver fat by MRI or MRS. Therefore, the available evidence was not sufficient to evaluate the utility of MRI or MRS for assessment of hepatic steatosis in children.(35)

Prostate Cancer

The utility of MRS has also been investigated for identifying whether prostate cancer is confined to the organ, which has implications for prognosis and treatment. In a 2013 Health Technology Assessment, Mowatt et al systematically reviewed 51 studies to evaluate image-guided prostate biopsy with MRS and other enhanced MRI techniques (ie, dynamic contrast-enhanced MRI and diffusion-weighted MRI) compared to T2-MRI and transrectal ultrasound (TRUS) in patients with suspicion of prostate cancer due to elevated prostate-specific antigen (PSA) levels, despite a previous negative biopsy.(36) MRS had the highest sensitivity in the meta-analysis of individual tests (92%; 95% CI, 86% to 95%), with an estimated specificity of 76% (95% CI, 61% to 87%). TRUS-guided biopsy had the highest specificity (81%; 95% CI, 77% to 85%).

Wang et al found that the addition of MRI findings, both endorectal MRI and MRS, improved the accuracy of the staging nomograms traditionally used to predict the likelihood of organ-confined prostate cancer.(37) Although the study was not ideally designed to assess the incremental value of MRS over MRI alone, it found that the area under the ROC curve was larger when MRS was included, but the difference was not statistically significant.

The results of the American College of Radiology Imaging Network (ACRIN) study 6659 were published in April 2009.(38) This prospective, multicenter study compared the use of MRI with and without MRS to identify the extent of prostate cancer by sextant prior to prostatectomy in 134 patients. The results from centralized histopathologic evaluation of prostate specimens served as the reference standard; MRI and MRS images were independently reviewed by 8 readers. With complete data on 110 patients, no difference was found in the area under the ROC curve for MRI alone versus MRI and MRS combined. That is, the use of MRS provided no incremental value in identifying the extent of prostate cancer.

In a meta-analysis of 7 studies (of 140 screened) on using MRS to diagnose prostate cancer, the pooled weighted sensitivity was 0.82 (95% confidence interval [CI]: 0.73–0.89); specificity, 0.68 (95% CI: 0.58–0.76); and the area under the curve, 83.40. (35) All of these results are based on a cutoff for identifying “definitive” tumor of 0.85 for the ratio of (choline plus creatine) to citrate.

A single-institution randomized, controlled trial (RCT) published in 2010 compared conducting a second randomly selected biopsy (group A) to a biopsy selected partly based on MRS and dynamic contrast-enhanced (DCE) MRI results (group B).(40) The participants were selected from 215 consecutive men with an elevated prostate-specific-antigen (PSA) (between 4 and 10 ng/mL), an initial negative biopsy result, and a negative digital rectal examination; 180 patients participated in the study. Cancer was detected in 24.4% of group A patients and 45.5% of group B participants. Fifty patients from group A with 2 negative biopsy results agreed to undergo biopsy a third time using MRS and DCE MRI results; 26 more cancers were found. Overall, 61.6% of the cancers detected had Gleason scores 7 (4+3) or more. The cancers detected after using MRS and dynamic contrast-enhanced MRI imaging also lined up with the suspicious areas detected on imaging. The sensitivity and specificity of MRS were 92.3% and 88.2%, respectively; adding dynamic, contrast-enhanced MRI increased the sensitivity to 92.6%, and the specificity to 88.8%. Limitations of the study include that it was conducted at a single center, analysis was confined to the peripheral zone of the prostate gland, and more samples were drawn from group B patients than from group A patients (12.17 vs. 10 cores, respectively). Furthermore, given the concerns about potential overtreatment among patients with early stage prostate cancer, the benefits of detecting these

additional cancers need to be evaluated by examining clinical outcomes for these patients. Similar issues arise in Policy 7.01.121 on saturation biopsy of the prostate.

In a similar report from this institution by these authors, 150 patients with a negative prostate biopsy, despite PSA elevations, were randomized to MRS or MRS plus DCE-MRI to locate prostate cancer foci for a second targeted biopsy.(41) See also(42). The addition of DCE-MRI to MRS yielded increased sensitivity and specificity over MRS alone (93.7% and 90.7% versus 82.8% and 91.8%, respectively). Pedrona et al also reported on the combined use of MRS and DCE-MRI for prostate cancer in 106 patients in a prospective cohort study.(43) The authors reported combined MRS and DCE-MRI results yielded unacceptably low positive predictive value of 19%. Negative predictive value was 91%. Sensitivity was 71% and specificity was 48%. The authors indicated the combined MRS and DCE-MRI may be useful in avoiding biopsy since the negative predictive value was 91%; however, further study is needed.

Section Summary

Although a number of studies have examined the use of MRS for localizing prostate cancer for biopsy and for monitoring of patients with prostate cancer, the cumulative evidence remains uncertain. Data comparing the diagnostic accuracy of MRS to alternative imaging strategies is limited. Additionally, the impact of MRS imaging compared to other imaging strategies on clinical management and health outcomes is unknown and further study is needed.

Gauging Treatment Response

The possibility of using MRS to track treatment response and failure has been explored. A small (n=16), preliminary study of tamoxifen treatment for recurrent gliomas found MRS patterns differed between responders and nonresponders.(44) Serial MRS demonstrated that metabolic spectra stabilized after initiation of therapy among responders and then changed in advance of clinical or radiologic treatment failure. In other words, MRS might help predict imminent treatment failure. However, there are relatively few studies with small sample sizes assessing this possible use of MRS. In addition, a number of other types of imaging are being evaluated for the same use, including dynamic, contrast-enhanced MRI, diffusion-weighted MRI, and 18-fluorodeoxyglucose position emission tomography (FDG-PET). Additional studies are needed, including studies comparing modalities or evaluating multimodalities.(45, 46)

Other Indications

MRS has also been evaluated for other uses, such as tracking disease changes among patients with multiple sclerosis,(47, 48) systemic lupus erythematosus,(49) assessing carotid plaque morphology,(50) as biomarkers of traumatic brain injury(51, 52) predicting long-term neurodevelopmental outcome after neonatal encephalopathy,(51); see also(54, 55) and other applications in children.(56, 57) Additional evidence on these applications is needed. MRS has also been studied in a variety of psychiatric disorders in the research setting, but no studies on the clinical use of MRS for the treatment of psychiatric disorders were found.(58,59)

Ongoing Clinical Trials

Physician Specialty Society and Academic Medical Center Input

In 2008, in response to requests, input was received from 3 physician specialty societies and 1 academic medical center while this policy was under review. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The input received from these reviewers disagreed with the conclusions in the policy statement. In particular, information provided was in support of MRS in

differentiating radiation necrosis from recurrent tumor and in the differential diagnosis of certain CNS tumors from non-tumors.

SUMMARY

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to measure the concentrations of different chemical components within tissues. The available studies do not provide strong and consistent evidence regarding the diagnostic test characteristics of MRS. Studies do not clearly delineate how MRS information would be used to guide patient management. Thus, it is not possible to determine whether MRS provides relevant clinical information that will safely influence diagnostic thinking and therapeutic choice. The scientific evidence at this time does not permit conclusions concerning the net effect of this technology on health outcomes. Therefore, the use of MRS is considered investigational.

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network's (NCCN) clinical practice guidelines on central nervous system tumors identifies MRS, along with MR perfusion or brain PET, as a modality that can be considered to rule out radiation necrosis, as compared to recurrence of brain tumors.(60) The authors also state that MRS may be helpful in grading tumors or assessing response and that the most abnormal area on MRS would be the best target for biopsy. The limitations include tumors near vessels, air spaces, or bone; the extra time required in an MRI machine; and the limitations occurring with any MRI, such as the exclusion of patients with implantable devices. The NCCN guidelines on prostate cancer mention MRS as a possible element of "more aggressive workup for local recurrence (e.g., repeat biopsy, MR spectroscopy, endorectal MRI)," which is one possible element of salvage therapy for patients after radical prostatectomy with rising PSA or positive digital rectal examination after radical prostatectomy with a negative biopsy and studies negative for metastases.(61) The NCCN guideline on breast cancer does not mention MRS.

The American College of Radiology updated its practice guideline on MRS of the CNS in 2008.(62) Most of the guideline is devoted to the actual performance of MRS, but it also lists 22 possible indications for MRS when MRI or CT are inadequate for answering specific clinical questions.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

76390	Magnetic resonance spectroscopy

DIAGNOSES

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

06-16-2009	Added policy to bcbsks.com web site.
02-24-2012	Description updated.
	Rationale updated.
	References updated.
03-26-2013	Updated Description section.
	Updated Rationale section.
	Updated Reference section.
09-17-2014	Updated Rationale section.
	Updated Reference section.

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