Regence

Medical Policy Manual Radiology, Policy No. 27

Magnetic Resonance Spectroscopy

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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.

MEDICAL POLICY CRITERIA

Magnetic resonance spectroscopy (MRS) is considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease, Laboratory, Policy No. 47

BACKGROUND

With magnetic resonance imaging (MRI), an energy exchange measured as a radiofrequency signal, is translated into the familiar anatomic image by assigning different grey values according to the strength of the emitted signal. The principal difference between MRI and

magnetic resonance spectroscopy (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, at the level of the voxel (three-dimensional volume X pixel). The voxel of interest (VOI) is typically a cube or rectangular prism with a dimensional pixel with a volume of 1 to 8 cm^3. 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 which is provided on all new MRI scanners. Imaging time in the scanner is increased by 15 to 30 minutes.

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. Proton MRS of the brain reveals principal spectra arising from N-acetyl groups, especially n-acetylaspartate (NAA); choline-containing phospholipids (Cho) such as membrane phospholipids (e.g., phosphocholine and glycerophosphocholine); creatinine and phosphocreatinine; myo-Inositol (ml); lipid; and lactate. NAA is an amino acid that is generated by mitochondria and is present almost exclusively in neurons and axons in the adult central nervous system (CNS). NAA intensity is thought to be a marker of neuronal integrity and is the most important proton signal in studying CNS pathology. Decreases in the NAA signal are associated with neuronal loss, damage to neuronal structures, and/or reduced neural metabolism. An increase in Cho is considered a marker of pathological proliferation/degradation of cell membranes and demyelination. Choline levels increase in acute demyelinating disease, but an increase in Cho levels is most commonly associated with neoplasms. Cho levels can also be affected by diet and medication. In the brain, creatinine is a relatively constant element of cellular energetic metabolism and thus is sometimes used as an internal standard. Myo-Inositol is a polyalcohol that is present at high concentration in glial cells. An increase in the ratio of ml to NAA suggests gliosis and regional neuronal damage. The presence of lipids is indicative of a severe pathological process in which membrane lipids are liberated. Lactate may increase a normally barely visible spectrum 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, in both 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. Peripheral applications of MRS include the study of myocardial ischemia, peripheral vascular disease and skeletal muscle. Applications in non-CNS oncologic evaluation have also been explored.

REGULATORY STATUS

Since 1993, multiple software packages for performing proton MRS have received clearance by the Food and Drug Administration (FDA) through the 510(k) process. Single voxel MRS is available on all modern MR scanners. FDA product code: LNH.

EVIDENCE SUMMARY

Validation of a new imaging technique involves the following steps:

1. Demonstration of its technical feasibility, including assessment of its reproducibility and precision. For comparison among studies, a common standardized protocol is necessary.

2. Establishment 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 gold standard must be known.

3. Assessment of the clinical utility of both positive and negative tests. The clinical utility of an imaging study is related to how the results of that study can be used to benefit patient management. 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 outcome is present) may also include avoidance of a more invasive test plus the institution of specific, effective therapy.

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

CANCER

The primary health outcomes associated with evaluation of suspected malignancy may include avoidance of invasive biopsy procedures. Other measures are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life may be another primary outcome, particularly among patients living with refractory disease.

Brain Tumors

Magnetic resonance imaging (MRI) is a sensitive tool for identifying space occupying CNS lesions, but it is relatively nonspecific in distinguishing between benign and malignant lesions. Magnetic resonance spectroscopy (MRS) can provide a chemical profile of the lesions that may help in this determination. To understand the impact of the addition of MRS to the diagnostic evaluation of brain tumors, well-designed randomized controlled trials (RCTs) that compare changes in treatment planning and the resulting health outcomes from patients evaluated with MRI alone to those evaluated with MRI and MRS (where MRS is proposed for adjunctive use) are needed.

Systematic Reviews

Li published a meta-analysis to evaluate the use of MRS combined with diffusion-weighted imaging (DWI) to differentiate between recurrent glioma and radiation-induced brain injury.[1] The apparent diffuse coefficient (ADC) is the measure of diffusion of water molecules used to quantify DWI. The meta-analysis included eleven studies with a total of 320 patients with glioma. No publication bias was detected using the Egger's test and Deeks funnel plots, but bias related to patient selection was high (>50%). Relative ADC (rADC) was lower in the recurrent glioma group than the radiation injury group (SMD = -1.29, 95% CI (-1.87, -0.71), $p<0.001$). The choline (Cho)/creatinine (Cr) ratio was significantly higher in the recurrent glioma group compared to the radiation injury group (WMD=0.65, 95% CI (0.40, 0.90), $p<0.001$). The Cho/N-acetyl-aspartate (NAA) ratio was also significantly higher in the recurrent

glioma group than in the radiation injury group (WMD=0.80, 95% CI 0.39, 1.21), p<0.001). Heterogeneity in the meta-analysis was high (ADC, I^2 = 79.4%; Cho/Cr, I^2=73.0%; Cho/NAA, I^2=83.1%). The authors conclude that the combination of MRS and DWI is effective in diagnosing recurrent glioma if the Cho/Cr and Cho/NAA ratios are increased and ADC is decreased, and radiation injury can be diagnosed if the ratios and ADC present differently. However, comparisons to other methods of diagnosis were not presented, and the authors note that additional research is needed to determine the clinical applicability of DWI with MRS in the differentiation of recurrent glioma and radiation-induced brain injury.

A systematic review conducted by Bhandari (2021) evaluated the diagnostic accuracy of 2-hydroxyglutarate (2HG) MRS for determination of IDH status in differentiating low-grade glioma (WHO grade II or III) from glioblastoma (WHO grade IV).[2] The review included nine studies of individuals with low-grade glioma (n=181) or glioblastoma (n=77) undergoing preoperative 2HG MRS using histopathological diagnosis as a reference standard. Pooled sensitivity and specificity was 93% (95% CI 58% to 99%; I2=82%) and 84% (95% CI 51% to 96%; I2=60%) for low-grade glioma; for glioblastoma, sensitivity was 84% (95% CI 25% to 99%; I2=0%) and specificity was 97% (95% CI 43% to 100%; I2=23%). There was no statistical difference between tumor type sensitivities (p=.58) or specificities (p=.06). Positive and negative predictive values were 87% and 73% for low-grade glioma and 50% and 97% for glioblastoma. Study quality was assessed using the QUADAS-2 tool and studies were generally judged to be of low risk of bias and applicability concerns, although 2 studies were found to have high risk of patient selection bias. The included studies also used different MRS techniques and cut-off values, potentially affecting pooled measures of diagnostic accuracy.

A systematic review with meta-analysis was conducted by Suh (2018) to assess 2-hydroxyglutarate (2HG) MRS as an alternative to biopsy with immunohistochemistry and/or genomic sequencing analysis for confirmation of isocitrate dehydrogenase (IDH) mutant glioma.[3] Fourteen original articles with 460 patients were included. Eight of 14 studies were regarded as having an unclear risk of bias in patient selection because of non-consecutive enrollment and 13 of the 14 studies were regarded as having an unclear risk of bias in the index test, as it was unclear whether 2HG MRS was performed blinded to the reference standard. The pooled sensitivity and specificity for the diagnostic performance of 2HG MRS for prediction of IDH mutant glioma were 95% (95% CI, 85-98%) and 91% (95% CI, 83-96%), respectively. Limitations noted include that only six of the 14 studies were prospective in design, most studies had a small sample size, and there was considerable heterogeneity in MRS sequence design limiting the robustness of grouped data analysis. Although the systematic review found 2HG MRS for prediction of gliomas with IDH mutations associated with high sensitivity and specificity, results were not stratified according to glioma grade. IDH mutations are found in about 80% of low-grade gliomas, but only about 5% of glioblastomas.

Zhang (2016) conducted a meta-analysis to evaluate whether MRS could differentiate recurrent glioma from radiation necrosis.[4] A total of 455 patients from 18 studies were included in the analysis. Pooled results indicated that the sensitivity and specificity for Cho/Cr ration were 0.83 (95% CI 0.77 to 0.89) and 0.83 (95% CI 0.74 to 0.90), respectively. The area under the curve (AUC) under the summary receiver operating characteristic curve (SROC) was 0.90. The pooled sensitivity and specificity for Cho/NAA ratio were 0.88 (95% CI 0.81 to 0.93) and 0.86 (95% CI 0.76, to 0.93). The AUC under the SROC was 0.92. The largest prospective study included in the review (Amin, 2012) is described in the nonrandomized study section. Authors concluded these results suggest MRS, when combined with other imaging techniques, provides moderate diagnostic performance in differentiating glioma recurrence from radiation

necrosis; however, these findings are limited by a lack of comparison with current methods for detecting recurrence.

Wang (2015) evaluated the diagnostic performance of MRS for preoperative grading of gliomas, differentiating high-grade gliomas (HGGs) from low-grade gliomas (LGGs).[5] A meta-analysis included thirty articles with 1228 total patients, and resulted in pooled sensitivity/specificity of Cho/Cr, Cho/NAA and NAA/Cr ratios of 0.75/0.60, 0.80/0.76 and 0.74/0.70, respectively. There was no significant difference in the area under the curve between the Cho/Cr and Cho/NAA groups; the Cho/NAA ratio showed higher sensitivity and specificity than Cho/Cr ratio and NAA/Cr ratio. The authors concluded that MRS had moderate diagnostic performance in distinguishing HGGs from LGGs though suggested MRS as combination technique to aid in improving diagnostic accuracy.

Fouke (2015) conducted a systematic review and developed evidence based practice guidelines for the management of low grade glioma (LGG) from their findings.[6] The authors made recommendations applicable to newly diagnosed lesions with a suspected or histopathologically proven LGG. Studies identified regarding MRS diagnostic specificity were all of Class III evidence, that is, data is provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios. Though the authors state the clinical role of MRS and nuclear medicine methods are yet to be defined, they state there are multiple Class III evidence support use of such techniques to attain additional diagnostic specificity. For follow-up of a suspected or biopsy proven LGG, a Level III recommendation was made regarding MRS, stating that MRS may be helpful in identification of progression for oligodendrogliomas and mixed gliomas. A Level III recommendation has the same ranking as Class III evidence in terms of strength and quality.

Wang (2014) reported a meta-analysis of 24 studies (615 cases and 408 controls) on the diagnostic performance of MRS for detection or grading of brain tumors.[7] Twenty-two studies assessed gliomas, and two studies assessed ependymomas and primitive neuroectodermal tumors. Seven studies evaluated recurrence, nine studies evaluated the grade of tumor, five studied evaluated the detection of tumors, one evaluated residual tumor, and two evaluated tumor metastases. Meta-analysis found the overall sensitivity and specificity of MRS to be 80.1% and 78.5%, respectively. The area under the receiver operating characteristics (ROC) curve was 0.78.

A systematic literature review published in 2006 on MRS for the characterization of brain tumors concluded the following:[8]

> “A number of large diagnostic performance studies have demonstrated that 1H-MR spectroscopy can accurately distinguish between high- and low-grade astrocytomas. This work now needs to be extended to demonstrate: (1) diagnostic thresholds selected a priori, rather than post hoc, can achieve similar diagnostic accuracy, (2) the incremental diagnostic yield of 1H-MR spectroscopy compared with anatomic MR imaging, and (3) that any improvement in tumor grading by 1H-MR spectroscopy leads to a reduction in biopsy rates or changes in therapy.”

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 authors concluded that the evidence on MRS for characterizing brain tumors is promising, but that additional comparative diagnostic studies (MRI with and without MRS), along with RCTs of

primary health outcomes are needed before any conclusions can be made about utility of MRS in diagnosing brain tumors.

Nonrandomized Studies

Manias (2019) prospectively evaluated children with brain lesions aged 16 and under (n=51) between December 2015 and 2017 via MRI and single-voxel MRS, blinded to histopathology.[9] MRS spectra were obtained in 47/51 eligible patients (52 tumors), however, only 72% of tumors were considered analyzable via MRS. Proportions of correct diagnoses and interrater agreement at each stage were assessed. The diagnostic accuracy of the principal MRI diagnosis was 69%, improving to 77% with MRS. Together, MRI and MRS resulted in a significant increase in additionally correct diagnoses compared to MRI alone ($p = 0.035$) and a significant increase in interrater agreement ($p = 0.046$). Patients were managed without conclusive histopathology in 25% of cases. This study was conducted at an institution with a robust imaging research program, and additional data are needed to validate these outcomes in a range of clinical settings.

Hellstrom (2018) evaluated whether MRS adds to the diagnostic value of MRI in differentiating low-grade tumors, high-grade tumors, and non-neoplastic lesions through the retrospective analysis of data on 208 lesions from 186 patients.[10] Diagnoses were grouped into three categories of non-neoplastic disease (n=70), low-grade tumor (n=43), and high-grade tumor (n=95). The clinical value of MRS was considered very beneficial if it provided the correct category or location when MRI did not, beneficial if it ruled out suspected diseases or was more specific than MRI, inconsequential if it provided the same level of information, or misleading if it provided less or incorrect information. For MRI, the category was correct in 130 cases (62%), indeterminate in 39 cases (19%), and incorrect in 39 cases (19%). Supplemented with MRS, 134 cases (64%) were correct, 23 cases (11%) indeterminate, and 51 (25%) incorrect, which were not statistically significantly different from MRI alone ($p = 0.055$). Additional data from MRS was found to be very beneficial, beneficial, inconsequential, or misleading in 3%, 12%, 68%, and 17% of cases, respectively. The authors concluded that, in most cases, supplementary MRS did not add to the diagnostic value of MRI.

Andronesi (2018) reported on an open-label phase I clinical trial investigating the utility of 2HG MRS to assess the pharmacodynamics of an investigational mutant IDH1 inhibitor drug (IDH305, Novartis Pharmaceuticals) in glioma patients.[11] Eight patients were enrolled, and data from five patients was available for tumor 2HG level analysis at baseline and following one week of treatment with IDH305. Tumor 2HG levels were found to decrease during mutant IDH1 inhibition, with statistically significant decreases in the ratios of 2HG to healthy creatinine (2HG/hCr), tumor creatinine (2HG/tCr), and glutamine plus glutamate (2HG/Glx). However, further study is required to validate whether these results can identify treatment response as patient clinical outcomes were not reported in the present study. Furthermore, the authors acknowledge that recent preclinical data has failed to show an effect on tumor growth with mutant IDH1 inhibitors. Importantly, mutant IDH1 patients have significantly longer survival compared to patients with wild-type IDH1, therefore the value of mutant IDH1 treatment and response monitoring is currently unclear.

Manias (2018) reported on a multicenter U.K. study that retrospectively evaluated MRS for the noninvasive diagnosis of brain tumors.[12] This study analyzed 64 consecutive children who had MRI, MRS, and histopathology. The clinical information was reviewed by a tumor board, which included pediatric oncologists, pediatric radiologists specializing in neuroradiology,

clinical oncologists, neurosurgeons, and histopathologists, who arrived at consensus diagnosis and treatment planning. The reference standard was the diagnosis by the tumor board, verified through clinical course. MRI alone was correct in 38 (59%) of 64 patients. The addition of MRS increased diagnostic accuracy to 47 (73%) out of 64, with 17 cases incorrectly diagnosed by MRI plus MRS. A subsequent study by Manias (2018) assessed the diagnostic accuracy of MRS in children (n=26) with pilocytic astrocytoma, ependymoma, and medulloblastoma, reporting modest correct classification rates of 60%, 50%, and 80%, respectively.[13]

A study by Naveed (2018) evaluated the use of MR techniques (MRS, apparent diffusion coefficient, and dynamic susceptibility contrast imaging) for the grading of oligodendroglial tumors in the brain.[14] Dynamic susceptibility contrast images were processed to generate cerebral blood volume maps and permeability. A combination product of these two variables yielded an AUC of 0.74 (95% CI 0.41 to 0.90) for distinguishing grade II (n=23) from grade III (n=17) tumors. MRS, relative cerebral blood volume, and apparent diffusion coefficient did not meet statistical significance for distinguishing these groups.

Abdelaziz (2016) published a study that compared the diagnostic yields of MRS for 27 patients with known deeply seated intra-axial brain lesions.[15] All patients had an MRI and MRS prior to stereotactic biopsy. MRS accurately identified neoplastic and nonneoplastic lesions in 25 of the 27 patients. MRS glioma staging matched that of the histopathologic biopsy in 10 of 12 patients. The authors concluded MRS is a useful procedure that can assist in the management of brain lesions.

A study of combined MRI and MRS to diagnose the type of pediatric brain tumor was reported in 2015 from multicenter Children's Hospitals in the U.S.[16] MRI/MRS imaging was performed in 120 pediatric patients as part of the usual pre-surgical workup, followed by biopsy or resection. Pediatric brain tumors are histologically more diverse that adult brain tumors and include tumor types such as embryonal tumors, germ cell tumors, polocytic astrocytoma, and ependymomas. For the first 60 patients (from 2001 to 2004), MRS was performed but was considered experimental and was not used for diagnosis. For the next 60 patients (2005 to 2008), radiologists utilized information from both MRI and MRS. The percentage of correct diagnoses was reported for the first 60 patients using only MRI (63% correct), when re-diagnosed with blinded MRI at the time of the study (71% correct, not significantly different from the first MRI reading) and compared with blinded diagnosis using both MRI/MRS (87% correct, $p<0.05$). For the second group of 60 patients who were diagnosed using MRI/MRS, the type of tumor was correctly identified in 87% of patients ($p<0.005$ compared to initial diagnosis with MRI alone). Together, the results indicate an increase (from 71% to 87% correct) in the diagnosis of tumor type when MRS is combined with MRI.

Vicente (2013) 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).[17] 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.

Wilson (2013) evaluated MRS as a prognostic tool and reported their findings. Single voxel, proton MRS using short echo times was evaluated for predicting survival of patients with pediatric brain tumors (n=115) followed for a median of 35 months.[18] Metabolic changes were identified that predicted survival. Poor survival was associated with lipids and scyllo-inositol while glutamine and N-acetyl aspartate were associated with improved survival ($p<0.05$).

Ha (2013) evaluated the clinical feasibility of (31)P MRS for making the differential diagnosis of brain tumors.[19] The study included 28 patients with brain tumorous lesions (22 cases of brain tumor and six cases of abscess) and 11 normal volunteers. Authors concluded the brain tumor group showed increased PME/PDE ratio compared with that in the normal control group. Authors suggested that clinically applicable (31)P MRS, and the pH, PME/PDE, PDE/Pi, PME/PCr, and PDE/PCr ratios were helpful for differentiating among the different types of brain tumors.

Amin (2012) reported comparison of MRS with 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.[20] MRS and SPECT results differed in nine 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.

At least one study (Chernov, 2009) has investigated the use of MRS-guided stereotactic brain biopsy of parenchymal brain lesions.[21] Diagnostic accuracy of the MRS-guided technique was not advantageous over MRI-guided biopsy. MRS has also been proposed to distinguish between tumors and abscesses or other infectious processes.[22] Other noncomparative nonrandomized studies[23-25] and case series exist in the literature.[26] However, due to the lack of comparison with a gold standard, or lack of evaluation of primary health outcomes following testing with MRS, interpretation of these findings is limited.

Breast Tumor

Systematic Reviews

Baltzer (2013) conducted a systematic review and meta-analysis of 19 studies on MRS for detecting benign versus malignant breast lesions.[27] The combined total number of patients in the studies reviewed was 1,183 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%, 82%) and specificity was 88% (386 of 439, 95% CI 85%, 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.

Nonrandomized Studies

Bayoumi (2019) conducted a prospective study evaluating the additive role of MRS and MRI in the confirmation of pathological complete response after neoadjuvant chemotherapy of breast cancer in 47 patients.[28] Patients were evaluated via MRI and MRS at baseline and following treatment with four cycles of anthracycline-based chemotherapy administered at three-week intervals. Pathological response to neoadjuvant chemotherapy was confirmed via histopathological evaluation following surgical excision. A choline (Cho) peak at 3.2 ppm was considered positive. The mean tumor size before and after treatment was 4.21 ± 0.99 cm and 0.9 ± 0.44 cm, respectively, with corresponding mean Cho signal-to-noise ratios of 9.53 ± 1.7 ppm and 2.53 ± 1.3 ppm. MRI detected a complete response in 22/47 patients, corresponding to a sensitivity of 83.3%, specificity of 65.7%, positive predictive value (PPV) of 45.5%, negative predictive value (NPV) of 92%, and a diagnostic accuracy of 70.2%. In contrast, combined MRI and MRS demonstrated a sensitivity of 75%, specificity of 97.1%, PPV of 75%,

NPV of 91.9%, and an improved diagnostic accuracy of 91.5%. The cut-off for differentiating between complete response and residual disease was 1.95 ppm with a corresponding diagnostic accuracy of 85.11%. Patient characteristics and eligibility criteria were not specified.

A study by Thakur (2019) reported a correlation between MRS analysis of lipid resonances and the presence of malignant vs. benign breast lesions.[29] However, the test performance characteristics were not reported.

Sun (2017) published a study evaluating the feasibility and efficacy of diffusion-weighted imaging (DWI)-guided MRS for 258 patients with suspicious breast lesions greater than one centimeter.[30] DWI-guided MRS, using readout-segmented echo-planar imaging was performed. The MRS results correlated with the histological biopsies. The authors concluded MRS is a feasible and accurate diagnostic tool for breast lesions.

Cho (2016) published a study comparing how pathological response to neoadjuvant chemotherapy for 35 breast cancer patients can be predicted using single-voxel proton magnetic resonance spectroscopy ([1]H-MRS) versus (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET)[31] MRS and FDG-PET were performed before and after the first NAC treatment. The authors concluded MRS is comparable to FDG-PET in predicting response to NAC by detecting tumor cellular changes.

Bartella (2006) conducted a preliminary study on the use of MRS to evaluate suspicious lesions 1 cm or larger identified on MR imaging.[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. Although this study adds to the body of literature on MRS in breast tumors, interpretation of these results is limited by lack of comparative, blinded testing and the failure to control for potential bias in favor of MRS. Additional study of diagnostic accuracy and clinical utility is required to evaluate the effectiveness of MRS in breast tumors.

Prostate Tumor

The utility of MRS has also been investigated for identifying whether prostate cancer is confined to the prostate, which has implications for prognosis and treatment.

Systematic Reviews and Technology Assessments

Cai (2019) published the results of a SR with meta-analysis conducted to assess the value of MRS in the diagnosis of suspected prostate cancer (PC).[33] A total of 19 studies with patient-level analysis of PC were included. All studies were determined to have used an acceptable reference standard independent of the index test and interpretation of the reference standard was concealed from the results of the physical examinations in all studies. The pooled sensitivity, specificity, diagnostic odds ratio, and area under the summary receiver-operating characteristic curves were 0.86, 0.78, 22, and 0.89, respectively. Summary negative likelihood ratio and positive likelihood ratio for MRS diagnosis of PC were determined to neither confirm nor exclude the diagnosis of cancer. The authors noted lack of formal validity testing procedures and a lack of quality assessment criteria as limitations and concluded that large-scale studies will be required to validate the clinical use of MRS as a diagnostic tool for PC.

Chen (2016) reported results of a meta-analysis evaluating 1.5-T and 3-T magnetic resonance spectroscopy imaging in the diagnosis of prostate cancer.[34] Seventeen articles were included in the analyses; pooled sensitivities, specificities, positive likelihood ratios, negative likelihood ratios, and 95% confidence intervals were calculated, and summary receiver-operating characteristic curves were used to assess the results. Area under the curve values of 1.5-T magnetic resonance spectroscopy imaging with the use of an endorectal coil, 1.5-T magnetic resonance spectroscopy imaging without the use of an endorectal coil, and 3.0-T magnetic resonance spectroscopy imaging without the use of an endorectal coil were 0.90 ± 0.03, 0.75 ± 0.03, and 0.93 ± 0.02, respectively.

Mowatt (2013) published a health technology assessment, which systematically reviewed 51 studies to evaluate image-guided prostate biopsy with MRS and other enhanced MRI techniques (i.e., 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.[35] 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%).

Randomized Controlled Trials

A single-institution RCT published by Sciarra (2010) compared conducting a second randomly selected biopsy (group A) to a biopsy selected partly based on MRS and dynamic contrast-enhanced MRI results (group B).[36] 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 two negative biopsy results agreed to undergo biopsy a third time using MRS and dynamic contrast-enhanced MRI results; 26 more cancers were found. Overall, 61.6% of the cancers detected had Gleason scores 7 (4+3) or higher. 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 MRI were 84.6% and 82.3%, respectively; adding MRS 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 were not evaluated by examining clinical outcomes for these patients.

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.[37] 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). However, treatment decisions were not based on results of differential testing; therefore, the impact of testing on health outcomes (e.g., clinical utility) was not addressed in this study and awaits future clinical research.

Nonrandomized Studies

Lahoti (2017), in a study from India, prospectively evaluated the diagnostic accuracy of ultrasonography, MRI, and a combination of MRI plus MRS in 66 patients with a strong clinical suspicion of prostate pathologies.[38] All patients underwent ultrasonography, MRI, and MRS, followed by biopsy. Diagnostic accuracy for MRI plus MRS was the highest (sensitivity 97.6%, specificity 92%), followed by MRI alone (sensitivity 95.1%, specificity 84%) and ultrasound (sensitivity 78%, specificity 88%). Of 41 patients with malignant lesions, MRI identified 39 as malignant and MRI plus MRS identified 40 as malignant. Of 25 patients with benign lesions, MRI identified 21 as benign and MRI plus MRS identified 23 as benign.

A study by Pedrona (2011) evaluated the combined use of MRS and MRI for prostate cancer in 106 patients in a prospective cohort study.[39] The authors reported combined MRS and 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%.

Results from this study, like several others identified,[40, 41] are limited by lack of comparator group (without which it is not possible to isolate the contribution of MRS to the diagnosis). Studies which include long-term follow-up on primary health outcomes, along with randomization to comparative diagnostic groups, are needed to evaluate the clinical utility of MRS in prostate cancer.

Other Cancer Indications

MRS has been evaluated for use in other types of cancer, including for differentiating borderline from malignant epithelial ovarian tumors,[42] and differential diagnosis in lymphoma,[43] but these have generally been preliminary or pilot studies.

Treatment Response

The possibility of using MRS to track treatment response and failure has been explored. As in the evidence required for determination of treatment benefit in detection of malignant tumors (see breast and prostate above), RCTs measuring clinical outcomes are required.

The evidence on MRS for evaluating treatment response consists of non-comparative observational studies in recurrent gliomas, including a small (n=16), preliminary study of tamoxifen treatment for recurrent gliomas by Sankar and colleagues in 2008.[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.

Section Summary

Several systematic reviews have evaluated the performance of MRS for diagnosis and evaluation of various cancers. Most studies included in the meta-analyses were small, retrospective, and used various ratios of MRS spectra. Although a number of studies have examined the use of MRS for localizing cancer for biopsy and for monitoring patients with cancer, the clinical utility of results from MRS testing has not been evaluated. Overall, additional RCTs are necessary to fully evaluate the benefit MRS may have for patient management.

NON-CANCER CONDITIONS

Dementia

MRS has been proposed for use in the identification of dementia, especially in its early stages. Primary outcomes associated with treatment of dementia include: improvement in behavioral, emotional or neurological function (as measured by a validated clinical instrument). Identification of improvement in such outcomes associated with diagnosis by MRS is best achieved by conducting RCTs of appropriate size and duration. However, to date, evidence identified on the use of MRS for diagnosis of dementia consists entirely of non-randomized studies, an example of which is detailed below.

Systematic Reviews

Song (2021) published the results of a meta-analysis targeting the identification of patterns of brain metabolic alterations in mild cognitive impairment (MCI) and Alzheimer's disease (AD).[45] Data from a total of 79 studies were included in the analysis, which focused on regional differences in spectroscopy measures. The authors found decreased N-acetyl aspartate (NAA) and creatine (Cr) but increased myo-inositol (mI) levels in both MCI and AD, and decreased glutathione in MCI. No evaluation of the impact of MRS metrics on health outcomes was evaluated.

Piersson (2020) conducted a systematic review of 24 studies to evaluate the relationship between neurochemical changes quantified by MRS metabolite levels and validated AD biomarkers.[46] Decreased levels of NAA, NAA/creatine (NAA/Cr), and NAA/myo-inositol (NAA/mI), and increased mI, mI/Cr, choline/Cr (Cho/Cr), and mI/NAA were detected in the posterior cingulate cortex and precuneus. Increased mI and decreased NAA/Cr was associated with increased tau levels. NAA and glutathione levels are reduced in APOE ε4 carriers. The authors conclude that large, longitudinal studies are necessary to elucidate the effect of APOE ε4 on brain metabolites. No evaluation of the impact of MRS metrics on health outcomes was evaluated.

Zhang (2014) identified 30 studies since 2007 on low field (<1.5T) MRS and 27 studies on high field (>3.0T) MRS that compared results from patients with Alzheimer’s disease (AD), MCI, and healthy controls. While metabolite changes are heterogeneous across brain regions, most of these studies focused on detecting changes in individual metabolites or their ratios.[47] The review concluded that to effectively characterize AD-associated neurochemical changes, future approaches should interactively analyze multiple quantifiable metabolites from different brain regions.

Tumati (2013) conducted a systematic review and meta-analysis of 29 studies on MRS for mild cognitive impairment (MCI).[48] Included in the analysis were a total of 607 MCI patients and 862 healthy controls. Patterns in metabolite concentration, including N-acetyl aspartate (NAA), creatine (Cr), choline (Cho) and myoinositolin (mI), 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 mI, Cho, and Cr may also contribute to MCI.

Liver Disease

MRS has been evaluated as a noninvasive alternative to liver biopsy in the diagnosis of hepatic steatosis and/or nonalcoholic fatty liver disease. To understand the contribution of

MRS in this setting, prospective RCTs are needed to evaluate long-term health outcomes, such as development of liver fibrosis, risk of mortality, or quality of life.

A randomized trial by Noureddin (2013) investigated the utility of MRI-estimated proton-density-fat-fraction (PDFF) to assess quantitative changes in liver fat by a three-way comparison between MRI-estimated PDFF and MRS-measured PDFF with liver histology-determined steatosis grade at two-time points in patients with nonalcoholic-fatty-liver-disease (NAFLD).[49] Fifty biopsy-proven NAFLD patients who participated underwent paired evaluation with liver biopsy, MRI-estimated and MRS-measured PDFF of the liver at baseline and 24 weeks. Authors concluded MRI-estimated PDFF correlates well with MRS-measured-PDFF and is more sensitive than histology-determined steatosis grade in quantifying increase or decrease in liver fat content. This RCT includes a small sample size and limited follow-up.

Several non-randomized studies, have evaluated the diagnostic accuracy of MRS compared with other noninvasive imaging procedures (e.g., computed tomography, dual-gradient echo magnetic resonance imaging, and ultrasonography), and/or invasive biopsy as the reference standard.[50-53]

Mitochondrial Disorders

MRS is proposed as an adjunctive diagnostic test in patients with primary mitochondrial cytopathies with CNS involvement. The principle health outcomes associated with improved diagnosis and treatment planning in this population may include increases in quality of life or activities of daily living. Other outcomes important for study include risk of adverse events (including hospitalization) and secondary or intermediate health outcomes may consist of changes in muscle strength or endurance or biochemical markers of disease.[54]

The evidence available on the use of MRS as an adjunctive diagnostic tool in patients with suspected mitochondrial disorders consists of non-comparative observational studies. For example, Bianchi and colleagues reported on the use of MRI and MRS in the evaluation of mitochondrial disease in 15 patients.[55] Both tests were performed on all patients and statistical analysis was used to estimate the correlation between results on MRS and clinical findings (of brain abnormalities). However, this study and others like it failed to report sensitivity, specificity and positive and negative predictive values compared with existing genetic, biochemical, and pathologic tests. In addition, there are no published studies demonstrating the clinical utility of MRS in evaluating mitochondrial disorders, i.e., how test results impact patient management.

Multiple Sclerosis

Solanky (2020) published a cross-sectional analysis of 119 patients with secondary-progressive MS recruited from the MS-Secondary Progressive Multi-Arm Randomization Trial (MS-SMART).[56] The relationship between neurometabolites and various clinical disability measures was examined via Spearman rank correlations. Significant associations were further analyzed via multiple regression models adjusted for age, sex, disease duration, T2 lesion load, normalized brain volume and history of recent relapse occurrence. Significant associations in normal-appearing white matter were found for tNAA and Nine-Hole Peg Test (9HPT) (r=0.23; 95% CI, 0.06 to 0.40), tNAA and Paced Auditory Serial Addition Test (PASAT) (r = 0.21; 95% CI, 0.03 to 0.38), tNAA/tCr and PASAT (r=0.19; 95% CI, 0.01 to 0.36), and mIns/tCr and PASAT (r=-0.23; 95% CI, -0.39 to -0.05). No significant associations were found

for any neurometabolite levels and the Expanded Disability Status Scale (EDSS) or Timed 25-Foot Walk (T25FW) tests following multiple regression analysis.

Sun (2017) published a study of on 17 patients with relapsing-remitting MS comparing them to 21 healthy participants as a control to determine if MRS versus MRI can identify metabolite abnormalities in normal appearing white matter (NAWM) of the brain,[57] Significant changes in certain metabolite rations were found in MS patients. The study had methodological limitations including but not limited to small sample size and only examined one type of MS.

Llufriu (2014) published a study of MRS in a preliminary data set of 59 patients with MS and 43 healthy controls, and a confirmatory independent data set of 220 patients.[58] The change in brain volume and measures of disability were obtained annually. The ml:NAA ratio in normal-appearing white matter was found to be a predictor of brain-volume change over 4 years (p=0.02) and of clinical disability (e.g., a decrease in the Multiple Sclerosis Functional Composite evolution scale of -0.23 points annually, p=0.01). Effect sizes in this study were low, indicating that the measure is not sufficiently reliable to predict the future disease course in individual patients. Future studies are needed that include larger cohorts with progressive MS, serial measurements of outcomes, and complementary measures of disease activity.[59]

Bellmann-Strobl (2008) evaluated the correlation between MRI-based lesion load assessment with clinical disability in seventeen untreated patients with early relapsing remitting multiple sclerosis (RRMS).[60] Seventeen control patients were matched on sex and age. Their aim was to evaluate the suitability of MRS and MTI in monitoring neuroinflammatory parenchymal brain damage in correlation with conventional MRI as well as clinical disability scores at the time of initial diagnosis (cross-sectional study aim), and throughout the disease course after initiating interferon β (IFN β) treatment in patients with RRMS (longitudinal study aim). Clinical scores of disability were correlated, with longitudinal measurement and follow-up available for six patients. RRMS patients were treated with IFN β-1a 22 µg and monitored monthly for one year, with a follow-up after 24 months. The authors concluded their results suggested advanced MR techniques (MTI and MRS) performed better than MRI for detection of early parenchymal damage as well as reflecting patients' status in RRMS. Larger cohorts, in longer term studies are necessary to evaluate therapeutic efficacy and significance of these initial findings.

Other Indications

The Congress of Neurological Surgeons (2016) published a systematic review that reviewed 122 articles pertaining to preoperative imaging for pituitary adenomas.[61] MRS was one diagnostic technique considered. One hundred and twenty-two articles were analyzed. There was insufficient evidence to make a recommendation for the use of MRS.

The use of MRS has been studied in other indications, such as diagnosis of radiation necrosis,[62-70] stroke progression immediately after acute stroke,[71] fetal lung maturity,[72] placental metabolite detection,[73] lipid tissue detection in atherosclerotic coronary or carotid plaques,[74, 75] epilepsy,[76, 77] systemic lupus erythematosus,[78] essential tremor,[79] pathologies of the spinal cord,[80] neurological impairment in patients with cervical spondylosis,[81] traumatic brain injury,[82, 83] predicting long-term neurodevelopmental outcomes in hypoxic-ischemic encephalopathy,[84] and in a variety of psychiatric disorders in the research setting.[85-96] MRS has also been utilized in research studies for measurement of study outcomes.[54]

Section Summary

Although a number of studies have examined the use of MRS for identifying and monitoring various indications, the cumulative evidence is insufficient to determine the clinical role for MRS outside of the research setting. Due to limitations such as the lack of a consensus MRS diagnostic protocol, lack of head-to-head comparisons with gold standard diagnostic tests, results from these studies require replication in larger studies with adequate representation of the target population before any conclusions regarding diagnostic accuracy can be established. Additionally, studies of clinical utility are required to demonstrate that any increases in diagnostic accuracy provided by MRS are accompanied by improvements in net health outcomes.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

The National Comprehensive Cancer Network (NCCN) guidelines on central nervous system cancers (v.1.2023) regarding adult glioma, high grade with recurrence advise, “Consider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/ MRI, or re-image to follow changes that may be due to progression versus radionecrosis.”[97]

The NCCN guidelines for prostate cancer (v.3.2023) state in the Goals of Imaging, “Imaging is performed for the detection and characterization of disease, to select treatment or guide change in management. Imaging techniques can evaluate anatomic or functional parameters:

- Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
- Functional imaging techniques include radionuclide bone scan, PET/CT, and advanced MRI techniques, such as spectroscopy and diffusion-weighted imaging (DWI).[98]

The NCCN clinical guidelines on breast cancer (v.12023) do not mention MRS.[99]

THE AMERICAN ASSOSICATION OF NEUROLOGICAL SURGEONS

The American Association of Neurologic Surgeons (2015) published a guideline on the role of imaging for adults with diffuse low-grade glioma.[6] The guideline states “Multiple series offer Class III evidence to support the potential for magnetic resonance spectroscopy (MRS) and nuclear medicine methods including positron emission tomography and single-photon emission computed tomography imaging to offer additional diagnostic specificity although these are less well defined and their roles in clinical practice are still being defined.”

AMERICAN COLLEGE OF RADIOLOGY AND AMERICAN SOCIETY OF NEURORADIOLOGY

The American College of Radiology (ACR) and American Society of Neuroradiology (ASNR) practice guideline (revised 2019) on MRS of the central nervous system lists 25 possible indications for MRS imaging, when conventional imaging by MRI or CT is inadequate for answering specific clinical questions.[100] However, these guidelines are not evidence-based and were developed through consensus.

The ACR Appropriateness Criteria® (AC) MRS of the head without IV contrast is considered "usually not appropriate" in dementia (including cognitive decline and suspected Alzheimer disease), head trauma in adults and children, movement disorders, and neurodegenerative diseases.[101, 102]

Prostate Cancer

The 2017 ACR guideline regarding the pretreatment detection, staging and surveillance of prostate cancer state that “MRS cannot yet be considered to provide significant advantages in local staging before treatment.”[103]

THE CONGRESS OF NEUROLOGICAL SURGEONS

The Congress of Neurological Surgeons (2016) published a guideline on preoperative imaging assessment for patients with suspected nonfunctioning pituitary adenomas (NFPA). They concluded there is insufficient evidence for a recommendation MRS as a diagnostic tool to assess NFPA.

SUMMARY

There is not enough research to show that magnetic resonance spectroscopy (MRS) improves health outcomes for people with any indication. No clinical guidelines based on research recommend MRS for all indications. Therefore, the use of MRS is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	0609T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); acquisition of single voxel data, per disc, on biomarkers (ie, lactic acid, carbohydrate, alanine, laal, propionic acid, proteoglycan, and collagen) in at least 3 discs
	0610T	;transmission of biomarker data for software analysis
	0611T	;postprocessing for algorithmic analysis of biomarker data for determination of relative chemical differences between discs
	0612T	;interpretation and report
	76390	Magnetic resonance spectroscopy
HCPCS	None	

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