MAGNETIC RESONANCE SPECTROSCOPY FOR BRAIN TUMORS

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Abstract

Magnetic Resonance Spectroscopy For Brain Tumors

Introduction

Diagnosing and treating space-occupying tumors of the brain presents special challenges due to the similarities of tumors to other pathologic entities on conventional imaging, the similarities of individual tumor cell types on conventional imaging, the inaccessibility of these lesions, and their proximity to complex brain structures. A non-invasive technique that could provide information about the chemical and histologic composition of brain tissue could greatly aid diagnosis and treatment of brain tumors by helping to avoid unnecessary biopsies, by helping to guide biopsies, and by providing additional information for improving treatment. The Centers for Medicare & Medicaid Services (CMS) requested a technology assessment by the Agency for Healthcare Research and Quality (AHRQ) to assess the value of Magnetic Resonance Spectroscopy (MRS) for diagnostic evaluation, surgical planning, and patient management of space-occupying brain tumors. The Tufts-New England Medical Center Evidence-based Practice Center was asked to conduct an assessment of this technology.

Methods

An OVID search of the MEDLINE® database was conducted on November 6, 2002. Filters and limitations were used to eliminate inappropriate publications, with inclusion and exclusion criteria developed to identify articles to be reviewed. The search used applicable MeSH headings and textwords with appropriate Boolean operators. After filtering irrelevant publication types (such as publications not containing original clinical data), the search resulted in 959 citations for download and screening. Hand screening of the abstracts resulted in accepting 137 citations for complete article retrieval. All abstracts were reviewed to identify full articles that met the criteria. In addition, abstracts from the following relevant professional society proceedings for the years 2001 and 2002 were reviewed and included in the analyses: American Society of Neuroradiology (ASNR), Radiological Society of North America (RSNA), and the International Society for Magnetic Resonance in Medicine (ISMRM).

Results

Ninety-six articles met our inclusion criteria for evaluation, and 85 of these only provided information about technical feasibility. Eleven of the

articles provided information beyond the level of technical feasibility. Eight articles evaluated the test performance of MRS in various settings. Three articles addressed the impact of MRS on diagnostic thinking and therapeutic decision making. No article was found that addressed improvement of patient outcome.

Cho/Cr (choline/creatine) is the only metabolite ratio that has been found to be useful in differentiating neoplasm and non-neoplasm and supported by several studies. Among all the full articles examined in this technology assessment only one provided the most complete reporting of the metabolite signal intensities and ratios for each type of tumor found in their study population. However, no single metabolite or ratio, other than perhaps a very high Cho/Cr ratio to diagnose peripheral neuroectodermal tumors (PNET), by itself could differentiate among different neoplasms, among different tumor grades, or between neoplastic and non-neoplastic lesions.

The only study that addressed the incremental gain in the proportion of diagnostic tissue obtained demonstrated that MRS added to conventional MRI improved the number of correct diagnoses and reduced the number of incorrect or equivocal diagnoses.

Three studies addressed the potential impact of MRS results on diagnostic thinking or therapeutic decision making. Conclusions that can be drawn from these studies are severely limited due to the fact that the two prospective studies had only 15 and 17 patients, respectively, and the only large study was a retrospective analysis of medical records to identify potential opportunities of MRS to influence diagnostic thinking. No study explicitly evaluated the impact of voxel position on the accuracy of MRS. No study commented on the potential impact of operator error in placement of the voxel.

Conclusion

Human studies conducted on the use of MRS for brain tumors demonstrate that this non-invasive method is technically feasible and suggest potential benefits for some of the proposed indications. However, there is a paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision making. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized. In summary, while there are a large number of studies that confirm MRS' technical feasibility, there are very few published studies to evaluate its diagnostic accuracy and whether it can positively affect diagnostic thinking and therapeutic choice. Those studies that do

address these areas often have significant design flaws including inadequate sample size, retrospective design and other limitations that could bias the results.

1. INTRODUCTION

1.1 Background

Diagnosing and treating space-occupying tumors of the brain presents special challenges due to the similarities of tumors to other pathologic entities on conventional imaging, the similarities of individual tumor cell types on conventional imaging, the inaccessibility of these lesions and their proximity to complex brain structures. Standard imaging diagnostic procedures include computerized tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) imaging. Following is a summary of invasive and non-invasive means of diagnosing brain tumors:

Tech-nique	Degree of Invasiveness	Description
Biopsy	Invasive	Extraction of tissue for histopathological diagnosis. The reference standard.
CT	Noninvasive Uses ionizing radiation	Computed 2-dimensional map of the attenuation voxels of tissue using externally generated x-rays delivered in a circular fashion.
MRI	Noninvasive No ionizing radiation	Spatial localization of tissue properties that relate to alignment of protons in strong magnetic fields.
SPECT	Noninvasive Uses radio-isotopes	Spatially localizes emitted photons (gamma rays) after administration of radioactive agent.
PET	Noninvasive Uses radio-	Spatially localizes emitted positrons after administration of radioactive agent.

Tech-nique	Degree of Invasiveness	Description
	isotopes	
MRS	Noninvasive No ionizing radiation	Spatial localization of tissue chemical properties that relate to alignment of protons in strong magnetic fields. Proton (hydrogen) MRS uses the frequency response of hydrogen, while other versions examine the frequency response of other elements (phosphorus and sodium).

Confirming the preliminary diagnosis requires tissue biopsy to assess the histologic composition of the brain tissue in question. A non-invasive technique that could provide information about the chemical and histologic composition of brain tissue could greatly aid diagnosis and treatment of brain tumors by helping to avoid unnecessary biopsies, by helping to guide biopsies, and by providing additional information for improving treatment.

Magnetic Resonance Spectroscopy is a technique related to magnetic resonance imaging (MRI). Both techniques rely on the tendencies of some proportion of protons to align with or against a strong magnetic field. MRI refers to localizing the total tissue signal produced by a small, localized collection of tissue (voxel). The tissue signal is produced by the rates of magnetic alignment (or decay) of the protons in two planes as well as the overall proton density. T1 relaxation refers to alignment with the magnetic field, and T2 relaxation refers to alignment perpendicular to the

magnetic field). This phenomenon is produced by stimulating the blocks of tissue with a broad-spectrum signal that disrupts the magnetic alignment. The signal is eventually produced, after electromagnetic manipulation, as the protons re-align themselves to their original configurations.

MRS, on the other hand, relies on a very different phenomenon of proton alignment with the magnet that is based on frequency. The ability of the alignment of protons to be disrupted is frequency dependent. The exact frequency that disrupts the alignment depends on the chemical structures containing the protons. In MRS, tissue blocks (or voxels) are stimulated with very narrow bandwidth frequencies, and a graph is made of the signal strength vs. the frequency of stimulation. This produces characteristic peaks related to the amount of certain chemical compounds present in the tissue. MRS, therefore, has the potential to provide information about specific metabolites in brain tissue that can indicate the presence of tumor, necrotic tissue, and other pathologic entities. It should be noted that MRS has been evaluated as a diagnostic tool for a variety of diagnostic applications including not only CNS tumors but other non-CNS conditions. In this report, we exclusively examine MRS for brain tumors.

Finally, the majority of brain tumor studies focus on proton (hydrogen) MRS, but other elements (i.e. phosphorus and sodium) are used. This

report deals with proton hydrogen MRS (to be referred herein simply as "MRS").

1.2 Requests by the Centers for Medicare and Medicaid Services

The Centers for Medicare & Medicaid Services (CMS) requested a technology assessment by the Agency for Healthcare Research and Quality (AHRQ) to assess the value of MRS for diagnostic evaluation, surgical planning, and patient management of space-occupying brain tumors. Also requested was a review of factors that may affect the performance of MRS. The Tufts-New England Medical Center Evidence-based Practice Center was asked to conduct an assessment of this technology. For patients presenting with signs or symptoms of a space-occupying brain lesion, the key questions to be addressed were:

1. For what metabolic profiles does the yield of MRS provide equivalent, complementary, or more accurate diagnostic information for (i) initial diagnosis, (ii) recurrence, or (iii) assessing therapy than
   - Brain biopsy
   - Conventional anatomic imaging studies
   - MRS + conventional anatomic imaging studies vs. brain biopsy
2. Does the use of MRS lead to an improved net health outcome by

- Avoiding unnecessary biopsy
- Obtaining appropriate biopsy, from appropriate location
- Directing biopsy to an appropriate location
- Receiving appropriate treatment
- Avoiding an inappropriate treatment

3. Are voxel positions and operator error important factors in obtaining diagnostic images? If so, how do they impact MRS accuracy?

1.3 Analytic Framework

To address these issues we developed an analytic framework describing each of the potential uses of MRS. Potential uses of MRS are described for patients newly diagnosed with a space-occupying brain mass as well as for patients with a previously diagnosed brain tumor undergoing treatment. The potential uses include diagnostic evaluation and prognostication, patient management and planning for surgery, and potential outcome measures for evaluating performance. Factors that might affect performance are also included in the framework, which is presented in Appendix A.

1.3.1 Diagnostic evaluation

Experimentation with in-situ Magnetic Resonance Spectroscopy (MRS) for tumor assessment has been ongoing since 1985 (Maris et al., 1985). It was initially hoped that MRS would provide definitive spectrographic signatures of tumor histologic types. Clinical MRS research has led to multiple specific applications of MRS for both diagnostic work-ups and treatment follow-up of CNS tumor. Combined with findings from conventional anatomic MRI, MRS may have the potential to improve the diagnosis and management of brain tumors.

Primary diagnostic categories where some authors have suggested that MRS may present important diagnostic information are:

Distinguishing single metastatic lesions from primary tumors of the CNS, such as astrocytomas

This distinction is important, because single brain metastatic lesions would trigger a whole-body diagnostic workup for the source of the tumor, whereas primary brain tumors would be staged and treated as such. The treatment regimens for different metastatic types of tumors vary greatly. In virtually all cases, metastatic lesions are treated with regimens

considerably different than primary brain tumors, so establishing the exact nature of the neoplasm is exceedingly important in treatment planning.

In distinguishing abscesses from CNS tumors

Diagnosing an abscess quickly is critical. The clinical presentation of tumors and CNS abscesses in the Medicare population overlap significantly. Mistaking an abscess for a tumor can lead to a significant delay in diagnosis that can be catastrophic, because diagnosing a tumor may involve a relatively long workup. Rapid intervention in the case of an abscess can result in minimizing neurologic damage, leaving the patient in a high-functioning state.

Tumor grade

In primary CNS tumors, MRS may provide a more accurate means of determining tumor grade, and hence prognosis, than conventional anatomic MRI imaging with the contrast agent, gadolinium. Currently, tumor grade is estimated by its potential to enhance with gadolinium. The specificity of this diagnostic means is only moderate. Establishing the grade is important in determining treatment protocol. Low-grade tumors are often simply watched, whereas high-grade tumors are often de-bulked,

irradiated and sometimes treated with chemotherapy. If a technique produces sufficient specificity for tumor grade, a biopsy could be foregone in many instances. MRS may have an advantage over biopsy in reducing sampling error as well.

In distinguishing peripheral neuroectodermal tumors (PNET) from astrocytic lesions in adults

The ability to distinguish these tumors reliably could speed treatment of PNETs. These are typically very aggressive tumors that may sometimes respond to chemotherapy more readily than astrocytic tumors. Similarly, it is important to distinguish “bright spots” on conventional T2-weighted MRI imaging, associated with neurofibromatosis type 1 (NF1), from astroglial tumors occurring in this same patient population. Neurofibroma bright spots are hamartomas that typically do not expand in size. Follow-up exams are usually not necessary. The astrocytomas associated with NF1 are low grade, and typically do not progress to high-grade tumors. Nonetheless, they can grow in size and are typically followed with imaging studies.

Biopsies

MRS has also been recently investigated for use in biopsies. Biopsy guidance is an area where MRS may reduce sampling error associated with determination of tumor grade (and prognosis) in primary CNS tumors. Accurate determination of tumor grade is important in determining prognosis and adjuvant therapy.

1.3.3 Patient management and planning for surgery

The management of CNS tumors depends on tumor type and multiplicity. In primary astrocytomas of the CNS, treatment depends on grade. Low-grade tumors (WHO classification grades 1-2) are usually observed, with follow-up, if small, and do not represent an immediate neurological crisis. In cases of neurologic crisis, tumors are either excised or debulked. In high-grade astrocytomas, tumors are debulked surgically, followed by whole-brain radiation.

Single metastatic brain lesions have conventionally been excised when in accessible locations. Excision is often accompanied by chemotherapy. Multiple lesions have conventionally been treated with whole brain radiation and chemotherapy. Gamma knife therapy (focused stereotactical radiation) has become an important and increasingly used

alternative means of treating both single and multiple metastatic lesions. Its use in single lesions depends on the primary tumor's sensitivity to radiation.

In patients treated for CNS tumors, MRS may provide important diagnostic criteria for:

Determining tumor recurrence

Tumor recurrence changes the prognosis of patients. Because recurring brain tumors are associated with a shortened life span, prognosis is important for patients to plan the final stages of their lives. Prognosis can, in some cases, be improved by additional focused radiation. This treatment, either alone or with additional chemotherapy, is usually not administered until there is definite evidence of tumor recurrence.

Distinguishing radiation necrosis from tumor recurrence

The rate of tumor recurrence has prognostic value, as well as therapeutic implications. However, the presence of mixed recurrent tumor and radiation necrosis is common. Radiation necrosis would contraindicate additional radiation. While the effects are significant, they are not usually related to eventual mortality. Investigators have suggested that MRS could

distinguish recurrent tumor from radiation necrosis under some circumstances.

Determining tumor response to therapy

Establishing that tumors are responding to the designated treatment is imperative, in determining if treatment (with its associated morbidity) should be continued, discontinued or changed to a different regimen.

Surgical treatment planning

Claims have been made that MRS provides important information for guidance of gamma knife therapy. It has been suggested that MRS has improved accuracy in determining tumor extent and better delineates the area to be treated with focused radiation.

1.3.4 Factors that may affect performance of MRS

Location of lesion including proximity to bone and sinuses

The technique of MRS requires careful “shimming” of the magnetic fields --- adjusting the magnetic fields around the tissue of interest so that these fields are homogeneous. Variations in the magnetic fields mis-register the spectral peaks, as the frequency sensitivities of chemical

structures are also affected by the external magnetic field strength. Sudden dramatic changes in tissue composition, such as adjacent air or bone, can result in the inability to correctly shim the magnet field. This can result in distorted and non-usable data. Therefore, lesions that are small, and abut bone or air-filled structures, such as the sinuses, can present problems during MRS analysis.

Operator issues

While standard MRI technologists are seldom specifically trained in MRS, commercial software has become available that is less sensitive to operator error. Nevertheless, many current uses of MRS for brain tumors require precise localization that demands an understanding of MRS positioning requirements that with which many technologists are not acquainted. Multivoxel MRS techniques may have reduced these problems to some degree. However, accurate placement to achieve the desired results is still necessary. It may therefore be necessary for a trained neuroradiologist familiar with MRS to be available for voxel placement.

Size/position of voxel

Current commercial software enables either multivoxel or single voxel spectroscopy to be performed. Manufacturers have pre-set values for slab thickness and voxel size in their software. However, if mandated by conditions, these parameters may be changed by the investigator. Likewise, in single voxel studies, there are default values for voxel size and position. However, specific conditions, such as tumor size, location and relative positioning of the voxels near artifact-producing structures can require changes in size. The investigator must remember that the time of acquisition changes with the cube of the volume or square of the area. Additionally, the voxels must avoid overlapping with structures containing only cerebrospinal fluid, such as the ventricles, Sylvian fissure and choroidal fissures. These regions contain some, but not all, of the chemical compounds analyzed in the brain. Hence they can distort key ratios in the compounds used in interpretation.

Concurrent disease

Concurrent disease can occasionally produce problems when using MRS for evaluating tumors. Tumors lying near areas of old infarcts and ischemic changes can distort chemical ratios used in interpretation.

Similarly, concurrent demyelinating disease can produce additional distortions. In general, with single voxel technique, careful voxel placement, and containing voxels from appropriate control areas can alleviate the problem. Alternatively, selecting appropriate voxels from control areas in a multivoxel study could accomplish the same objective.

Hardware and software

Hardware and software both affect the application of MRS. In general, studies on magnets with field strengths less than 1.5 tesla (unit of magnetic flux) require too much time to be used on a routine basis. High field strength magnets, such as current 3 tesla systems have a time advantage (that can be converted into a space localization advantage).

2. METHODS

2.1 Classification of diagnostic studies

The Medicare Coverage Advisory Committee (MCAC) report on "Recommendations for Evaluating Effectiveness; Executive Committee Working Group Medicare Coverage Policy" (Executive Committee Working Group, 2001) (http://www.cms.hhs.gov/mcac/8b1-i9.asp) developed recommendations for evaluating evidence. It pointed out that although direct evidence is preferable, few studies directly measure the effect of diagnostic tests on health outcomes. Rather, studies typically focus on whether diagnostic tests are technically feasible or on effects on accuracy. These points apply to MRS. Few well-designed studies evaluate the impact of this test on clinical outcomes.

To systematically review the level of assessment of each study, we used a model described by Fineberg et al. (1977), Fryback and Thornbury (1991), and Adams (1997) to categorize the level of assessment achieved by the studies:

CATEGORIES OF DIAGNOSTIC ASSESSMENT

CATEGORY	CATEGORY DESCRIPTION	EXAMPLES OF MEASURES
1	Technical feasibility and optimization	Ability to produce consistent spectra
2	Diagnostic accuracy	Sensitivity and specificity
3	Diagnostic thinking impact	% of times clinicians' subjective assessment of diagnostic probabilities change
4	Therapeutic choice impact	% of times therapy planned prior to MRS changed after MRS
5	Patient outcome impact	% of patients who improved with MRS compared to % without MRS
6	Societal impact	Cost-benefit analysis

Note that the Institute of Medicine has also described similar criteria for evaluating diagnostic tests.

According to the MCAC assessment criteria, the studies most useful for assessing MRS would be Category- 2 or higher. In consultation with AHRQ and CMS, it was decided to review in depth only Category- 2 and higher studies.

2.2 Literature search

An OVID search of the MEDLINE® database was conducted on November 6, 2002. Filters and limitations were used to eliminate inappropriate publications, with inclusion and exclusion criteria developed to identify articles to be reviewed. The search used applicable MeSH headings and textwords with appropriate Boolean operators. After filtering irrelevant publication types, the search resulted in 959 citations for download and screening. Hand screening of the abstracts resulted in accepting 137 citations for complete article retrieval. All abstracts were reviewed to identify full articles that met the criteria.

In addition, abstracts from the following relevant professional society proceedings for the years 2001 and 2002 were reviewed and included in the analyses:

- American Society of Neuroradiology (ASNR)
- Radiological Society of North America (RSNA)
- International Society for Magnetic Resonance in Medicine (ISMRM)

Note that the information available from abstracts in such proceedings is extremely limited in comparison to that available in full articles. Additionally, the peer review process is generally not comparable to the process for full

articles. Finally, the International Network of Agencies for Health Technology Assessment (INAHTA) (**http://www.inahta.org/**) and National Guidelines Clearinghouse (NGC) (**http://www.guideline.gov/index.asp**) databases were searched for relevant citations.

2.3 Inclusion/Exclusion Criteria

The inclusion criteria for accepting studies included the use of hydrogen proton magnetic resonance spectroscopy (hydrogen) MRS on patients with suspected or known brain tumors. Only in vivo studies with a minimum of six adult human subjects were included. Explicitly excluded were studies of only healthy patients or studies of exclusively HIV/AIDS patients. In addition, studies of phosphorus or other types of MRS were excluded.

2.4 Search Results

One hundred thirty-seven publications were retrieved. Further review of those retrieved publications with application of inclusion criteria yielded 85 studies for inclusion in the report. The detailed search strategy follows:

MEDLINE <1966 to October Week 4 2002>

#	Search History	Results
1	exp Magnetic Resonance Spectroscopy/	92891
2	limit 1 to human	22632
3	limit 2 to English language	20499
4	exp neoplasms/	1409117
5	(tumor or cancer$ or neoplasm$ or neoplas$ or lesion$ or mass).tw.	1131920
6	(brain or cranial or cerebr$).tw.	479504
7	5 and 6	71583
8	4 and 6	50293
9	7 or 8	93338
10	exp brain neoplasms/	69674
11	3 and (9 or 10)	1231
12	limit 11 to (addresses or bibliography or biography or dictionary or directory or editorial or festschrift or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	24
13	Case Report/	1059907
14	11 not (12 or 13)	959

Two hundred forty-one abstracts were identified in the search of the three professional society proceedings and fifty-one met the inclusion

criteria and are included in this report. No relevant material was identified in either the INAHTA or NGC databases.

2.5 Data Extraction

As described above, our review entailed classifying each study into five categories. For those studies in Category- 1 we extracted data summarizing the following aspects of each study for later use in an evidence table: study characteristics (design, enrollment, patient characteristics), MRS technical aspects (number and volume of voxels), and study objectives (differential diagnosis and treatment planning).

For the studies in Category- 2 and above, narrative analyses were provided for each study. Studies in these categories were also evaluated with respect to their methodological adequacy.

3. RESULTS: Full Published Studies

The following table shows the number of studies in each of the categories. After reviewing the 959 abstracts and 137 retrieved articles, 75 studies were classified as Category-1 Technical feasibility studies. Ten studies were identified as providing information beyond that of the technical feasibility category. An additional 10 studies were added to Category- 1 and 1 study added to Category- 2 from references given by peer reviewers of the draft version of this report. In this section we report on the 96 published full-length studies classified using the approach described above. There were eight articles for Category-2, two articles for Category-3 (one study also qualify for Category-4), two articles for Category- 4 (one article shared with Category-3), and none for Category- 5 or Category- 6. Nearly all the studies identified were in Categories- 1 and 2, with the vast majority in Category- 1. The following table summarizes these results:

CATEGORY	DESCRIPTION	#
1	Technical feasibility and optimization	85
2	Diagnostic accuracy	8
3	Diagnostic thinking impact	2*
4	Therapeutic choice impact	2*
5	Patient outcome impact	0
6	Societal impact	0

*One study overlapped Category- 3 and Category- 4.

3.1 Category- 1 studies: Technical Feasibility

Evidence Table 1 shows selected characteristics of the technical feasibility (Category- 1) studies. Included in this table are the year of publication, country in which the research was conducted, study characteristics including number of diseased (case) and non-diseased (control) patients, method of patient enrollment, diagnostic status, and age. The table also shows the size of the volume of tissue (voxel) of interest as well as whether single or multiple voxel sampling was used. Finally, the table indicates the principal clinical study objectives: tumor differentiation, tumor grading, distinguishing primary tumor tissue from recurrent tumor and from metastases, and identifying necrotic tissue.

We reviewed 85 Category- 1 studies published from 1988 through 2003 involving approximately 2434 patients; fifty (59%) of the studies were published before 2000. There was extensive international representation in these studies. Twenty-four (28%) were from the US, 15 (18%) were from Japan, and 19 other countries were represented. The ages of patients included in the studies varied considerably; the range was from 1- 88 years, but we excluded studies that consisted predominantly of pediatric patients.

Almost all of the studies were prospective, with several retrospective and several of unknown design. The largest study included 120 cases. Many of the studies did not include control patients; for those studies that did, however, the maximum number of healthy controls was 151. One study reported approximately 300 diagnostic studies of controls. The mechanism used to enroll patients was generally not reported. In almost all of the studies, the disease status of the participants was ascertained via biopsy, although in a few instances the ascertainment was via clinical assessment only.

Single voxel sampling was the predominant methodology, although multiple sampling was also often used, and a combination of the two approaches was sometimes employed. In some articles the technique was not reported. Voxel volumes ranged widely.

Tumor differentiation (36 studies) and grading (30 studies) were the most frequently cited clinical objectives. Identifying necrotic tissue (15 studies) was also a frequent objective. Distinguishing metastases from primary tumors (5 studies) and recurrent from primary tumors (four studies) were less frequent objectives.

While not shown in the table, nearly all of these studies reported that metabolite peaks were obtained and metabolite ratios calculated. The authors analyzed spectral patterns using these measures.

3.2 Category-2: Studies that Evaluate Test Performance

Eleven studies were identified as providing information beyond the technical feasibility category. There were eight articles for Category-2, two articles for Category-3 (one study also qualify for Category-4), two articles for Category-4 (one article shared with Category-3), and none for Category-5 or Category-6.

A total of eight studies provided data for Category-2. Studies in this category could be further grouped into studies with the main purpose of differentiating tumors from non-tumors (three), grading of tumors (two), differentiating intracranial cystic lesions (one), and assessing the incremental value of MRS added to MRI (one). The purposes of the studies within the same group were sufficiently different so that combining or comparing studies within the same group was infeasible.

One group of investigators from the Medical College of Wisconsin published three articles (Rand et al., 1997; Adamson et al., 1998; Butzen et al., 2000) using overlapping patient samples but addressing different

research issues. Fifty-five MRS spectra belonging to 53 patients in the 1997 article were included in the 99 MRS spectra evaluated in the 2000 article. The study by Adamson et al. (1998) was a retrospective analysis of 78 patients from the same study population and is discussed under the Category-4 section.

3.2.1 Studies Differentiating Neoplasm from Non-neoplasm

Rand et al. (1997) evaluated 55 brain lesions in a consecutive series of 53 patients between September 1994 and December 1995. The patients included 31 males and 22 females between the ages of 14 and 81 years (mean 45 years), and they had suspected brain neoplasm or recurrent neoplasia. The purpose of the study was to measure the accuracy of single-voxel, image-guided proton MRS in distinguishing normal from abnormal brain tissue and neoplastic from non-neoplastic brain disease.

Using voxel sizes of 1 to 3 cm^3, MRS spectra were obtained using a clinical 0.5 Tesla MR system (manufacturer not stated) with a prototype head coil or a receive-only conformal surface coil. The voxel was centered over solid portions of the lesion and avoided necrotic debris or edema.

Spectra were interpreted by visual inspection. At the time of MRS, one of the four neuroradiologists and one MR spectroscopist prospectively

wrote a formal report using available clinical data and imaging studies. The unblinded readers interpreted the spectra as diagnostic or not, and if diagnostic, as neoplasia or non-neoplasia. Four neuroradiologists blinded to the clinical data and MRI results interpreted spectra retrospectively. The blinded readers classified the spectra as diagnostic or not, if diagnostic as normal or abnormal, and when abnormal as neoplasia or non-neoplasia.

For blinded interpretations, control and patient spectra were presented in random order. Blinded readers interpreted the results independently. Additional measures were taken to minimize biases in the interpretation of results.

The blinded readers rated the spectra from one to 100 as normal or abnormal, and as neoplastic or non-neoplastic, respectively. For the purpose of estimating test performance, a score of less than 50 was defined as negative (normal or non-neoplastic), a score of 50 and above was defined as positive (abnormal or neoplastic). The full range of the scores from each reader was used to create receiver operating characteristic (ROC) curves.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for the unblinded reader and each blinded reader for untreated patients and treated patients separately.

Spectra from 55 brain lesions in 53 patients were included in the analysis. In two patients, two lesions were studied. Fourteen patients (15 lesions) had received treatments for brain neoplasia before undergoing MRS. Histological diagnoses were available for 50 lesions. Diagnoses were established in three cases of infarcts by clinical follow-up and serial radiologic studies (CT, MRI, MR angiography, catheter angiography, or a combination) in which the lesions diminished in size. Diagnoses were established in two cases of acute demyelinating disease by clinical follow-up and reduction of lesion size on serial MRI.

The distribution of 42 neoplasia final diagnoses included: one astrocytoma-not otherwise specified, four astrocytoma grade I, four astrocytoma grade II, two astrocytoma grade III, 10 astrocytoma grade IV – one glioblastoma multiforme, one giant cell astrocytoma, one oligodendroglioma, four mixed glioma, one ganglioglioma, one ependymoma, six meningioma, four metastases, and two dysembryoblastic neuroepithelial tumor. The distribution of 13 non-neoplasia final diagnoses included: one Rathke's pouch cyst, three infarct, one parasitic infection, one sarcoidosis, one acute inflammation and gliosis, two demyelinating disease, one radiation necrosis without neoplasm, one vasculitis, one

arteriovenous malformation with old hemorrhage, and one neuroglial (gyral) dysplasia.

Blinded readers disqualified 20 (9%) of 213 patient spectra as non-diagnostic because of unacceptably low signal to noise ratios, ambiguous resonance assignments, unacceptably broad resonances, lack of detectable metabolite resonance, equivocal findings of neoplasm versus non-neoplasm, or a combination of the above.

Unblinded readers produced 40 true-positive, 12 true-negative, no false-positive, and two false-negative diagnoses. One spectrum was interpreted as nondiagnostic. Compared to the reference standard, the sensitivity, specificity, PPV, NPV, and accuracy of MRS to distinguish between neoplastic and non-neoplastic spectra for the unblinded readers were 0.95, 1.00, 1.00, 0.86, and 0.96, respectively.

Compared to the reference standard, the four blinded readers accumulated 12 false-positive interpretations on eight spectra and 22 false-negative interpretations on 13 spectra. The sensitivity, specificity, PPV, NPV, and accuracy of MRS to distinguish between neoplastic and non-neoplastic spectra for the four blinded readers averaged 0.85, 0.74, 0.92, 0.61, and 0.83, respectively. The test performance showed better results when only untreated patients were analyzed.

This study was exemplary for many aspects in this category. This was a prospective study and included a variety of diagnoses, used ROC analysis and multiple blinded readers to interpret the spectra results, and used well-defined reference standards and methods to minimize bias. The number of patients with and without neoplasm and the number of diagnoses was relatively small, however. The lack of a quantitative analysis of the MRS spectra profile also diminishes the ability to compare their results with other studies.

The population studied by Butzen et al. (2000) from the Medical College of Wisconsin is a superset of the patient population studied by Rand et al. in 1997. The purpose of this study was to compare a logistic regression (LR) model with blinded and unblinded qualitative MRS interpretations for the discrimination of neoplastic from non-neoplastic brain lesions using MRI-guided single voxel proton MRS data. The MR system and technique used were described in the paper by Rand et al. Ninety-nine consecutive patient spectra (the number of patients was not reported) with suspected brain neoplasms or recurrent neoplasia referred for MRS were evaluated by the LR model, of which 55 were evaluated by Rand et al. in the earlier study.

The LR model computed the probability of neoplasm ranging from zero to one. A cutoff probability of 0.8 for a positive MRS examination for neoplasia was determined by adjusting the cutoff to obtain equal rates of false-negative and false-positive results. Qualitative interpretations were made by two blinded neurologists and by one of five unblinded staff neuroradiologists and one staff spectroscopist.

The LR model was applied to 99 spectra with a sensitivity of 87% and a specificity of 85%. One blinded reader evaluated 86 spectra with a sensitivity of 75% and a specificity of 90%. The second blinded reader evaluated 90 spectra with a sensitivity of 88% and a specificity of 58%. The unblinded reader evaluated 95 spectra with a sensitivity of 89% and a specificity of 92%. The results of the blinded and unblinded readers were similar to those in the earlier study. Using a threshold of greater than one for the metabolite ratio Cho/NAA (NAA = N-acetylated compounds) to classify tumors, the sensitivity for 99 spectra was 79% and the specificity was 77%.

McKnight et al. (2002) tested a statistical index derived from a linear model of choline vs. NAA for discriminating neoplastic from non-neoplastic brain lesions. A subset of 26 patients in this study with high grade tumors were also reported on by Pirzkall et al. in a Category-1 study. Multi-voxel (1

700 cm^3) 3D-MRSI was performed with a 1.5 Tesla General Electric Medical
701 Systems Signa scanner (General Electric Medical Systems, Signa;
702 Milwaukee, WI) on 68 patients (ages unknown) with suspected gliomas.
703 The statistical model yielded an MRS-derived score (Cho-NAA Index—the
704 "CNI") summarizing the degree of difference between relative Cho and
705 NAA levels in a specific voxel and that of a population of control voxels for
706 each patient.

707 Of the original 68 patients, biopsies revealed that 26 had Grade II
708 gliomas, 26 had Grade III gliomas, and 16 had Grade IV gliomas. Only 44
709 patients gave consent for their surgeons to be guided during the biopsy by
710 MRS-guided instructions to sample four voxels --- one each with a high CNI
711 score, one with a low score and two with intermediate values. (The
712 remaining 24 patients' MR images and CNI scores were used in another
713 analysis of the distribution of metabolic abnormality with hyper intense
714 lesions on T_2-weighted MR images and contrast-enhancing lesions.)

715 The one hundred biopsy samples from the 44 patients yielded the
716 following histological classification of gliomas: Grade II: 36; Grade III: 34;
717 and Grade IV: 23. Seven of the samples were nontumorous. The patient-
718 level distribution of gliomas was: Grade II: 12; Grade III: 21; and Grade IV:
719 11. None of the patients were tumor-free.

The difference between CNIs of tumor and non-tumorous samples was highly significant. An analysis to assess the ability of the CNI to differentiate between tumor and non-tumorous samples yielded an ROC area of .94. With a CNI cutoff of 2.5, the sensitivity of this test was 90% and the specificity was 86%. The 95% bootstrap confidence interval for the sensitivity was 84 -96% and for specificity was 56-100%. These sensitivities were tumor-level, not patient-level.

This study also used the MRS CNI methodology to examine the proportion of patients of all 66 patients with evidence of tumor outside the area of contrast enhancement. Regardless of tumor grade, 41-45% of hyperintense lesions showed metabolic evidence of tumor (CNI >2.5), and 36-45% of non-enhancing lesions also showed such evidence.

Finally, a sub-analysis analyzed grade. There were 7 tumors with heterogeneous histological findings; in three of these cases, the CNIs did not correlate with the histological grade.

This study had several limitations. The authors do not describe how patients were enrolled in the study, nor was the analysis of MRS results blinded to final diagnosis. The small number of non-tumorous samples limited statistical power, and the restriction of tumors to gliomas limited generalizability. There may have been bias due to the number of dropouts.

Kimura et al. (2001) retrospectively evaluated the accuracy of single-voxel MRS spectra in patients with ring-like enhanced lesion using gadolinium-enhanced MRI. Forty-five patients including 29 men and 16 women between the ages of 26 to 75 years with various brain lesions were studied. The diagnoses included 19 metastases, 10 glioblastoma,seven radiation necrosis, five brain abscesses, and four cerebral infarctions.

MRS was performed with a 1.5 Tesla Signa Horizon System (GE Medical System, Milwaukee, WI). The investigators evaluated two types of volume of interest (VOI). One VOI was selected to include the whole ring-like enhanced rim and the central region of the lesion (whole lesion). The second type of VOI was selected to include only the non-enhanced inner region. The size of the voxel was not reported in the article. Quantitative analyses of spectra were performed on Cho, Cr, NAA, Lac, and Lip signals (Cho = choline; Cr = total creatine; NAA = N-acetylated compounds; Lac=lactate; Lip = lipids, protein, and lactate). Three metabolite ratios (Cho/Cr, Lac/Cr, NAA/Cr) were calculated and used for analyses.

For the whole lesions, the mean Cho/Cr ratio of metastases was 4.56 and 4.12 for glioblastoma. The mean Cho/Cr ratio for radiation necrosis was 2.33 and 1.48 for cerebral infarction. Significant differences were found for: metastases and radiation necrosis, metastases and cerebral infarction,

and glioblastoma and cerebral infarction. Significant differences in the Cho/Cr ratios between the whole lesion and inner region were found in the spectra of metastases and glioblastoma. There were no significant differences among the lesion types for the Cho/Cr ratios in the inner region.

The investigators found that using a Cho/Cr ratio of 2.48 for the whole lesion, the lowest rate of misdiagnosis was achieved in differentiating neoplasm from non-neoplasm. The positive predictive value using this threshold for metastatic brain tumors and glioblastoma was 89% (95% CI, 65 - 99%) and 60% (95% CI, 26 - 88%), respectively. The positive predictive value of a Cho/Cr ratio of less than 2.48 for diagnosing radiation necrosis and cerebral infarction were 71% (95% CI, 29 - 96%) and 100% (95% CI, 40 - 100%), respectively.

The lowest rate of misdiagnosis in differentiating metastases and radiation necrosis was achieved using a Cho/(Lip or Lac) ratio of 0.3 for the whole lesion. The positive predictive value of using a threshold value of greater than 0.3 to diagnose metastases was 94% (95% CI, 73 - 99%). The positive predictive value of using a threshold value of less than 0.3 to diagnose radiation necrosis was 100% (95% CI, 59 - 100%).

The relatively small sample size, narrow spectrum of brain lesions, and retrospective nature of this study limited the generalizability of this study. In addition, abscesses were excluded from the analyses.

3.2.2 Clinical Utility of MRS added to MRI

Moller-Hartman et al. (2002) evaluated the clinical utility of MRS added to MRI for the differentiation of intracranial neoplastic and non-neoplastic mass lesions. The study population consisted of a consecutive series of 176 patients presented to the neuroradiology department with focal intracranial mass lesions following MRI and/or CT imaging. Spectroscopic studies were performed using a 1.5 Tesla whole-body MR scanner (Magnetom Vision, Siemens). All patients underwent a single voxel MRS with a mean voxel volume of 8 cm^3 (range 4 - 12 cm^3). The voxel was placed in the solid part of the lesion excluding necrotic or cystic tumor parts or adjacent edematous areas. An acceptable voxel had to contain at least an estimated 70 percent tumor tissue. Whenever feasible, a reference spectrum of the same voxel size was acquired in the homologous region in the contralateral brain.

Within 10 days of MRS, histological diagnosis was obtained by stereotactic biopsy or craniotomy and open biopsy, except in nine (of 25)

cases of brain abscesses or focal inflammatory brain disease and nine (of nine) cases of cerebral infarction. Features on MRI or CT, clinical course, cerebrospinal fluid findings, and blood tests made the final diagnoses of the non-biopsied cases. Twelve out of the 176 spectra were of poor quality and were excluded from further evaluation. Final diagnoses for the remaining 164 interpretable spectra included 23 low-grade astrocytomas, 28 anaplastic astrocytomas, 39 glioblastomas, four PNETs or medulloblastomas, 18 metastases,nine meningiomas, nine neurinomas, 25 cerebral abscesses and nine brain infarctions.

Two neuroradiologists independently reviewed the combined MRI and MRS results blinded to the final diagnoses and two other neuroradiologists independently reviewed only the MRI results blinded to the final diagnoses. A diagnosis was classified as “correct” if the reader correctly assigned the case to the type of intracranial mass lesion and the tumor grade, according to the WHO classification of the final diagnoses. A “no evidence diagnosis” was assigned if the neuroradiologist could not decide between several diagnoses. The article did not report whether the two neuroradiologists read all the images or spectra in the same group or how discrepancies between the readers were resolved.

Tumor metabolite signal intensities were expressed as the percentage of the corresponding metabolites of the reference spectrum using measurements of the peak area signal intensity of each metabolite (NAA, Cr, and Cho) in the lesion. Two metabolite ratios (Cho/Cr and NAA/Cr) were also calculated.

Compared with the reference spectrum on the contralateral side of the brain, the Cr level was about 75-80% among the gliomas and there were no significant differences between the different tumor grades. The levels of Cr in the metastases, abscesses, and infarctions were about 40-50%, compared to the reference. The Cho levels decreased to 70-80% in infarctions and abscesses, and increased in metastases, PNET, and gliomas. The Cho level progressively increased with the tumor grade. The Cho/Cr ratios were: infarction = 1.45; astrocytoma I = 1.33; astrocytoma II = 2.13; astrocytoma IV = 3.93; PNET = 18.4; metastases = 3.97; abscesses = 1.52; meningioma = 4.81; neurinoma = 3.08.

Of the 176 spectra, conventional MRI alone made 97 (55.1%) correct diagnoses, 27 (15.3%) incorrect diagnoses, 52 (29.6%) no evidence diagnoses, and no examinations without diagnostic value. MRS added to MRI produced 124 (70.5%) correct diagnoses, 16 (9.1%) incorrect diagnoses, 24 (13.6%) no evidence diagnoses, and 12 (6.8%)

examinations without diagnostic value. There was no case in which a correct diagnosis made by MRI alone was interpreted incorrectly by the combination of MRI and MRS.

3.2.3 Studies on Tumor Grading

Roser et al. (1997) prospectively evaluated 35 MRS spectra in 17 patients with suspected glial brain tumors. The purpose of the study was “to apply the metabolic features found in a previous study of 21 healthy controls and humans with gliomas to a new cohort of patients with a suspected glial brain tumor and other healthy volunteers.” The age and sex of the patient population were not reported. None of the patients had received stereotactic biopsy, open surgery, or radiation therapy before MRS. Sterotactic biopsy or open surgery was performed within a few days after MRS.

MRS spectra of single-voxel size 8 cm^3 were acquired using a 1.5 Tesla MR system (Siemens Magnetom SP 400, Siemens Medical Systems, Erlangen, Germany). The VOI was placed as close as possible to the tumor center and covered at least 75% of the tumor tissue.

Using “training” data from an earlier study of 21 healthy controls and patients with gliomas, the investigators calculated five ratios (NAA/Cr,

MGG/Cr, Cho/Cr, GI/Cr, Lip/Cr) using 6 metabolite resonance measurements (NAA = N-acetylated compounds; Cr = total creatine; MGG = macromolecules, glutamine, and glutamate; Cho = choline; GI = glycine and myo-inositol; Lip = lipids, protein, and lactate). These five metabolite ratios were used in an orthonormal discriminant vector (ODV) analysis (Kauppinen et al., 1993) to construct a graph of two-dimensional metabolite space. The two axes were the ODV results based on a linear combination of the five metabolite ratios. By plotting the two ODV results of the metabolite ratios of individual patients from the training data, different tumor grades and healthy controls occupy distinct regions in the graph that could be classified as high grade, low grade and healthy volunteers.

In the validation study, the correlation of superimposing new patients' data onto the classification derived from the training data was noted. Histological diagnoses of the new patients included ten glioblastoma multiforme, two astrocytoma grade III, and five astrocytoma grade II. All ten cases of glioblastoma multiforme were in the proximity of the high grade region defined by the training data. Four of five astrocytoma grade II were classified as low grade gliomas, and one was classified as high grade. One of the two astrocytoma grade III was classified as high grade and the other as low grade. In addition, the contralateral normal-appearing matter of

879 tumor patients was assigned as normal in six cases and low grade in two
880 cases.

881 The results of this study cannot readily be generalized. Only 21
882 healthy subjects and patients with glial brain tumor were selected in the
883 development of the ODV equations. In the prospective validation study, all
884 17 patients also had glial brain tumors; thus the results of this study cannot
885 be generalized to populations with a broader spectrum of brain lesions. A
886 much larger number of patients with a broader spectrum of brain lesions is
887 needed to develop the diagnostic criteria and to verify the results.

888 Tedeschi et al. (1997) prospectively studied 27 patients with known
889 brain gliomas to test the hypothesis that MRS can help detect malignant
890 degeneration and/or recurrence (progressions). The 27 patients received
891 from two to five MRS studies, a total of 72 MRS imaging studies were
892 performed over 3.5 years. Repeated MRS studies were not based on a
893 fixed time interval and the reasons for the repeated studies were not
894 explicitly stated.

895 A 1.5 Tesla MR imager (manufacturer not stated) was used to
896 acquire multi-voxel spectra. Nominal voxel size was 0.83 cm^3. At the time
897 of each MRS study, a combination of clinical examination, MRI, positron
898 emission tomography with 18F-fluorodeoxyglucose, and biopsy findings

(when available) were used to categorize each patient as having either stable or progressive disease.

The signal amplitude of each metabolite (Cho, NAA, Cr, Lac) in the tumor region of interest was normalized to the corresponding amplitude in a matching region of interest from a normal area of the contralateral brain in order to calibrate the signal intensities from different imaging studies and individuals to a common scale. The investigators used the percentage changes in the normalized Cho signal intensity between two consecutive studies to categorize patients into stable and progressive groups. They found that all progressive cases could be correctly classified using a Cho signal increase of more than 45% and all stable cases had increases of less than 35%. Thus, using a threshold of 40% Cho signal increase between visits, the sensitivity was 100% and specificity was 100%.

In addition to the normalized Cho measurements, the investigators also analyzed normalized NAA, Cr, and Lac, as well as the within-voxel metabolite ratios (NAA/Cho, NAA/Cr, Cho/Cr). Other than the normalized Cho measurement, they found no association of the other measurements with disease progression.

3.2.4 Differentiating Intracranial Cystic Lesions

Shukla-Dave et al. (2001) prospectively evaluated the accuracy of MRS in the differentiation of intracranial cystic lesions. Fifty-one patients including 23 men and 28 women between the ages of eight and 50 years (mean 33 years) with intracranial cystic lesions on conventional MRI were studied. Single-voxel MRS was performed using a 1.5 Tesla MR system (Magnetom, Siemens) on lesions greater than 8 cm^3. A VOI of 4 to 8 cm^3 within the confines (sometimes including the rim) of the lesion was selected for MRS.

The criteria used to establish the diagnosis of cystic lesions were:

- Abscesses: lipid/lactate at 1.3 and amino acids at 0.9 ppm in all with/without additional resonances of succinate, acetate, alanine and glycine
- Glioma: lipid and/or lactate with choline
- Arachnoid cyst: presence of small resonance of lactate with very low signal to noise spectrum
- Hydatid cyst: very large succinate peak with lactate, alanine, acetate with absence of amino acids

Two investigators who did not know the MRI results, except that the lesions were cystic, interpreted the MRS spectra independently. However,

the rate of discrepancies and the method of resolution of discrepancies in the interpretation of the spectra results between the two investigators were not reported. The pre-operative diagnosis was based solely on the MRS results. All patients presumably underwent surgery for the intracranial cystic lesions. The final diagnosis was based on the results of histopathology, aspiration and culture of the contents. Fifty MRS spectra out of 51 were interpretable. Data for one case of acoustic neuroma was of poor quality and not included in the analysis.

Of the 51 cases, MRS correctly identified all 21 cases of abscess, all 19 cases of glioma, all three cases of arachnoid cyst, and all three cases of hydatid cyst. MRS incorrectly diagnosed one case of xanthogranuloma and one case of infarct as glioma. A total of three inconclusive MRS diagnoses were later found to be glioblastoma multiforme, glioependymal cyst, and acoustic neuroma. Thus, MRS correctly diagnosed the pathology of intracranial cystic lesions in 46 of 51 (90%) cases, did not contribute to the diagnosis in three cases (6%) and falsely diagnosed benign lesions as malignant in two cases (4%).

3.3 Category-3: Studies Conducted to Evaluate Diagnostic Thinking Impact

Two small prospective studies qualified for this category. The purpose of the study by Hall et al. (2001) was “to determine the utility of intraoperative MRS for targeting during brain biopsy using a skull-mounted trajectory guide.” The trajectory guide is commercially available and has been approved by the Food and Drug Administration (FDA) for the placement of deep brain stimulators, drug delivery catheters, and brain biopsies (Hall et al., 2001). The successful use of intraoperative MRS-guided brain biopsy might replace the conventional frame-based or frameless stereotactic techniques guided by either computed tomography (CT) or magnetic resonance imaging (MRI). In this setting, the CT or MRI are typically performed immediately or a few days before the biopsy. However, the opening of the dura mater and with the loss of cerebrospinal fluid may result in shifting the position of the lesion identified in the imaging studies (brain shift), which in turn might result in non-diagnostic stereotactic biopsy. A review of stereotactic brain biopsies found a diagnostic yield (proportion of biopsies containing useable diagnostic tissue) of 91% (Hall, 1999).

A total of 17 patients including 13 men and four women between the ages of 16 and 80 years suspected of brain tumors were evaluated in Hall's 2001 prospective study. All patients had "turbo spectroscopic imaging (TSI)" (a multi-voxel MRS method) and seven patients had single-voxel spectroscopy in addition, for purposes of comparison. MRS spectra were obtained using 1.5 Tesla MR system (ACS-NT; Philips Medical Systems, Best, Netherlands) located within an intraoperative MRI suite. The VOI in the single voxel spectroscopy was 1.5x1.5x1.5 cm^3 and the TSI used a 32x32 grid of spectra in a single plane with a spatial resolution of 0.66x0.66x2.0 cm^3.

Turbo spectroscopic imaging was successfully obtained in all 17 patients. The investigators noted that the TSI spectra in one case of radiation necrosis did not correlate well with the single voxel spectra. The TSI spectra in general had lower spectroscopic resolution and often contained lipid signals that were not evident on single voxel spectra. Three lesions did not demonstrate regions of elevated choline on the TSI images, which were later histologically confirmed to be brain tumors.

All 17 biopsies guided by MRS yielded diagnostic tissues, which included six glioblastoma multiforme, three anaplastic astrocytoma, three anaplastic oligodendroglioma, two radiation necrosis, one germinoma, one

ganglioglioma, and one astrocytoma. No radiographically or clinically significant hemorrhage associated with MRS guided brain biopsies using the trajectory guide was reported among the 17 patients.

The authors concluded that “intraoperative MRS-guided brain biopsy using a trajectory guide is a simple, safe, and accurate technique for accessing areas of the brain of diagnostic interest.” They further commented that with the development of intraoperative MRS, it is now possible to biopsy lesions located in the brain without the use of rigidly fixed head frames (traditional stereotaxy) and in near real-time, thus improving the accuracy and diagnostic yield. The use of the trajectory guide with MRS may also reduce intracerebral hemorrhage complications by minimizing the number of needed passages of the biopsy needle.

While the combination of trajectory guide and intraoperative MRS in this study appears promising in achieving high yield in brain biopsies, the number of patients studied was small. The need for an intraoperative MRI suite limits the generalizability. It should also be noted that three of the four authors of this study disclosed a financial interest in the company that produces the trajectory guide.

Lin et al. (1999) prospectively evaluated the utility of single voxel MRS when used as an alternative or adjunct to brain biopsy in patients with

lesions suggestive of brain tumors initially identified by MRI. This study provided information for diagnostic thinking impact (Category- 3) as well as for therapeutic choice impact (Category- 4).

Fifteen patients between the ages of seven and 58 (there was only one child of age 7) were studied. Among the diagnoses based on histology were six anaplastic astrocytoma, one astrocytoma, one oligodendroglioma grade II, one oilgodendroglioma grade III, one glioblastoma multiforme, and one abscess. Three additional patients did not have biopsy and the lesions resolved on serial scans. One patient with a history of treated brain stem mass subsequently died from progressive disease on follow-up. A neurosurgeon defined a treatment plan that would be carried out in the absence of a diagnostic MRS study prior to the MRS examination, to determine whether MRS directly impacted upon and altered clinical decision-making. MRS interpretations were directly incorporated into the clinical decision-making and a treatment plan was determined. Patients were then followed to determine if subsequent treatment and outcomes were in accordance or discordance with the MRS findings.

Single-voxel MRS was performed on a 1.5 Tesla Signa Scanner (GE Medical Systems, Milwaukee, WI). The VOI was determined by the neurosurgeon based on MRI results prior to the MRS exam. The voxel size

was adjusted to optimize the amount of homogeneous abnormal tissues within the voxel, while minimizing the amount of necrotic tissue. Voxel size varied between 2.35 to 9.68 cm^3.

The MRS spectra were quantified with an external standard although it was not described. NAA/Cr ratios were consistently and significantly elevated in non-neoplastic spectra whereas Cho/Cr demonstrated the opposite trend. Lipid and lactate were only observed in abscesses and one-half of neoplastic spectra. They could not reliably differentiate necrotic tumor from radiation necrosis or abscess. Myoinositol/creatine ratios were not significantly different between groups.

Forty-one VOI from 15 patients were analyzed. Thirty-five (85%) of the spectra were considered to be of good or excellent quality,four (9%) of poor but interpretable quality, and two (4%) non-interpretable. For 10 patients with previously documented tumors, MRS was interpreted as consistent with recurrent tumors in seven cases and consistent with radiation necrosis in three cases.

In one patient with two regions of interest on MRI, MRS suggested tumor in one lesion, but interpreted another lesion as edematous white matter without tumor. Disease progression occurred in the edematous white matter lesion 9 months after initial surgery, indicating that MRS was

unsuccessful in identifying infiltrating tumor in this instance. A retrospective review of the spectra in that region suggested that the effect of averaging over a large volume might have resulted in the misinterpretation. The authors suggested that a multi-voxel MRS might have been able to provide a more accurate diagnosis.

In the absence of MRS, the neurosurgeon would have recommended stereotactic biopsy in eight cases, serial MRI at six week intervals in three cases, repeat craniotomy in three cases, and empiric chemotherapy in one case. MRS was used in place of biopsy in seven cases, and correlated with clinical course in six of these cases. Overall, MRS was found to directly alter clinical management in 12 of 15 patients and provided greater support for clinical management in 14 of 15 patients. Had MRS been relied upon in every case, it might have avoided biopsy in nine cases, and influenced clinical management in 13 of 15 patients.

The small number of patients, narrow spectrum of diagnoses, and the inclusion of only one neurosurgeon’s decision limit the generalizability of this study.

3.4 Category-4: Studies Conducted to Evaluate Therapeutic Choice Impact

Prospective studies

The prospective study by Lin et al. (1999) also provided limited information on the use of the test on therapeutic choice impact. See the discussion under Category-3 above.

Retrospective study

Adamson et al., (1998) conducted a retrospective review of medical records to assess the influence of single-voxel MRS findings on the treatment of patients suspected of having a brain tumor. This publication appears to be based on the same overlapping patient population from the Medical College of Wisconsin that had been used in two other Category-2 publications.

The medical records of 90 patients who had MRS between May and December of 1995 were examined. Seventy-eight met the inclusion criteria and provided sufficient data for analysis. The patients were categorized into two groups based on the interpretation of the MRS findings:

- Group 1, MRS findings positive for neoplasm
- Group 2, MRS findings negative for neoplasm

The investigators examined all available medical records, including discharge summaries, progress notes, and outpatient reports to determine the outcome and treatment subsequent to the MRS examination. The patients were further categorized on the basis of whether they underwent biopsy before treatment. Pathology records in those patients who underwent surgical intervention or biopsy were reviewed.

MRS was classified as having a potential positive influence on treatment if no biopsy was needed before the initiation of treatment. If MRS results did not agree with the subsequent clinical diagnosis, the results were considered to have a potential negative influence on patient treatment. In all other cases, the effect of MRS was presumed to be negligible or indeterminate.

Neuroradiologists interpreted MRS spectra on the basis of the relative amplitudes for lactate, lipids, NAA, creatine and phosphocreatine, choline-containing compounds, and myo-inositol. A Cho/NAA ratio greater than 1.0 was considered to be positive for neoplasm. Smaller increases in the choline concentration were not considered diagnostic for neoplasm. The presence of lactic acid or lipid was consistent with relatively high-grade neoplasia if the choline concentration was elevated. Elevation of lactic acid

without elevation of the choline concentration was considered more consistent with infarct than with tumor.

MRS was positive for neoplasm in 49 of the 78 patients. In eight of these 49 patients, MRS was classified as having a potential positive influence. These eight patients received radiation therapy, chemotherapy, or both, for a presumed neoplasm without a biopsy to confirm the presence of a tumor. MRS was negative for neoplasm in 29 of 78 patients. In 15 of these 29 patients, MRS was classified as having a potential positive influence.

MRS was classified as having a potential negative influence on patient treatment in two of the 49 patients diagnosed as having neoplasm by MRS. One of these two patients underwent biopsy, which showed inflammatory reaction as probably being secondary to demyelination. The other patient underwent surgery and was found to have arteriovenous malformation. MRS had no influence on patient treatment in 37 patients diagnosed with brain tumor by MRS.

Because of the nature of retrospective medical record review, there were several problems with this study. Fourteen of the 78 patients had incomplete follow-up information, two from the MRS- diagnosed “tumor” group and 12 from the MRS “non-tumor” group. The patients study were

highly selected. The decision to perform MRS was based on CT and MRI results in which a neoplasm was considered to be the prime candidate in the differential diagnosis.

3.5 Category- 5: Studies Conducted to Evaluate the Impact of Test on Health Outcomes

No study was identified for this category.

3.6 Category 6: Studies Conducted to Evaluate the Use of Test on Societal impact

No study was identified for this category.

The following table summarizes our assessment of the Category-2 and above studies described above.

	Author	Objective	Sample N/gender/ mean age	Design	Assessment of accuracy or usefulness of MRS	Limitations
CATEGORY 2: TEST PERFORMANCE						
• Differentiating neoplasm from non-neoplasm						
	Rand et al. (1997)	Normal vs. non-normal; neoplasm vs. non-neoplasm	31 ♂ 22♀ age=41	Prospective series of patients. with suspected or recurrent neoplasm	Moderate	small sample size
	Butzen et al. (2000)	Neoplasm vs. non-neoplasm	99 spectra 31 ♂ 22♀ age=41	Logistic regression analysis	Moderate	Only study to use Cho/NAA ratio
	McKnight et al.(2002)	Neoplasm vs. non-neoplasm	100 biopsies	Prospective Linear model	Moderate	Unclear enrollment, unblinded, limited generalize-ability
	Kimura et al. (2001)	Neoplasm vs. non-neoplasm	29 ♂ 16♀ age 26-75	Retrospective patients with lesions	Moderate	Selection bias, small sample, homogeneous lesions
• Clinical utility of MRS added to MRI						
	Moller-Hartman et al. (2002)	Neoplasm vs. non-neoplasm	176	Consecutive series of patients with lesions	High	Did not report how reading discrepancies resolved
• Grading of tumors						
	Roser et. al. (1997)	Grading glial tumors	17	Suspected glial tumors	Moderate	Small sample; homogeneity of lesion type
	Tedeschi et al. (1997)	Malignant degeneration and recurrence	27	Prospective 3 yr. follow-up of patients w/known tumors	High	Small sample
• Differentiate intracranial cystic lesions						
	Shukla-Dave et al, (2001)	Differentiating Intracranial cystic lesions	23 ♂ 28♀ age=33	Prospective patients w/intracranial lesions dx. by MRI	High	Possible observer bias due to non reporting of method for resolving difference in interpreting spectra; sample size?

Category	Author	Objective	Sample	Design	Assessment of accuracy or usefulness of MRS	Limitations
CATEGORY 3: DIAGNOSTIC THINKING IMPACT						
	Hall et al. (2001)	Utility of MRS for targeting biopsies	13 ♂ 4♀ age 16-80	Prospective patients w/suspected tumors	High	Small sample; need for intra-operative MRI suite
	Lin et al. (1999) (also Category-4)	Supporting brain biopsy for MRI-identified lesions	15 Age 7-58	Prospective	High	Small sample, homogeneous group of diagnoses, limited observer verification
CATEGORY 4. THERAPEUTIC CHOICE IMPACT						
	Adamson et al. (1998)	Evaluation of impact of MRS on biopsy decision	90 initial; 78 final	Retrospective patients w/suspected neoplasms dx. By CT or MRI See Rand et al.; same data.	Low	Retrospective, losses to follow-up; medical record reviews
	Lin et al. (1999) (also Category-3)	Supporting brain biopsy for MRI-identified lesions; some patients were treated based on MRI findings	15 Age 7-58	Prospective	High	Small sample, homogeneous group of diagnoses, limited observer verification

4. RESULTS: Abstracts

As described above, abstracts and proceedings from following professional societies for the years 2001 and 2002 were reviewed:

- ASNR-American Society of Neuroradiology
- RSNA-Radiological Society of North American
- ISMRM-International Society for Magnetic Resonance in Medicine

Because these were abstracts and not full papers, data on basic study design information such as patient gender and means of enrolling patients were frequently unavailable. Of the 241 proceedings-generated abstracts reviewed, 44 were provided information beyond the technical feasibility category. The following table summarizes the distribution of abstracts by category:

CATE-GORY	DESCRIPTION	(#/%)
1	Technical feasibility and optimization	44
2	Diagnostic accuracy	8*
3	Diagnostic thinking impact	1
4	Therapeutic choice impact	0
5	Patient outcome impact	0
6	Societal impact	0

*One study shown in this category could also be considered a Category-3 study.

4.1 Category-1 Abstracts: Technical Feasibility

Evidence Table 2 shows selected characteristics of the 44 technical feasibility (Category 1) abstracts. Similar to Evidence Table 1 containing technical feasibility studies, it summarizes: year of publication, country in which the research was conducted, study characteristics including number of diseased (cases) and non-diseased (control) patients, method of patient enrollment, diagnostic status, and age. The table also shows the size of the volume of tissue (voxel) of interest as well as whether single or multiple voxel sampling was used. Finally, the table indicates the principal clinical study objectives: tumor differentiation, tumor grading, distinguishing primary tumor tissue from recurrent tumor and from metastases, and identifying necrotic tissue. In addition, there were two instances where there were duplicate abstracts for the same studies from different proceedings.

There were forty-seven abstracts reviewed for Category 1 from 3 different proceedings for 2001 and 2002. Forty-four unique studies remained after removing four duplicate studies. In addition, there were a minimum of four instances of overlapping population represented in the abstracts. The abstracts reported on 1,445 patients. One study reported on

174 diagnostic ‘studies’ without mentioning the number of patients and one reported the results of 14 ‘studies’. Twenty studies (42.5%) were from the US. The ages of patients described in eight of the abstracts varied considerably; ranging was from 8 to 84 years. As in the complete studies reviewed, we excluded abstracts that were predominantly pediatric.

Five studies were reported as prospective and five were retrospective. The remaining abstracts reported no data on study design. The largest sample reported in an abstract was 130 patients. Most abstracts did not include controls. Single voxel and multiple voxel sampling were used approximately equally. In six studies no voxel data were reported and in four a combination of both approaches were employed.

Tumor differentiation (14 studies) and grading (10 studies) were the most frequently cited clinical objectives. Other clinical objectives varied widely such as characterization of metabolite ratios (six abstracts), prognosis (two abstracts), measure of lipid levels (two abstracts), and tumor response to treatment (two abstracts).

4.2 Category-2: Studies that Evaluate Test Performance

The proceedings abstracts described eight studies in this category. Studies in this category could be further grouped into studies with the main

purpose of differentiating tumors from non-tumors, grading of tumors, differentiating intracranial cystic lesions, and to assess the incremental value of MRS added to MRI.

4.2.1 Abstracts of Category-2 Studies Differentiating Neoplasm from Non-neoplasm

Yin et al. (2002) evaluated 40 lesions in 35 patients with suspected brain neoplasms or recurrent neoplasm. The purpose of this study was to measure the accuracy of multivoxel 3D MRS proton MRS in distinguishing neoplastic from non-neoplastic brain lesions (blinded vs. unblinded). Final diagnoses were assessed by clinical examination, biopsy and serial MRI.

The specificity for distinguishing between neoplastic and non-neoplastic lesions was 88.6%. Of the 35 cases, 21 had neoplasms and 19 had non-neoplastic lesions. Of 16 glioma, 14 were correctly identified through increased Cho and decreased NAA for the gliomas. The metabolic profiles of the following types of tissue were studied: abscess (increased Lac), metastasis (increased Cho and Lac and no NAA peak), demyelinating lesion (decreased NAA and normal Cho), lymphoma (high Cho and lipids), and necrosis (high Cho and decreased metabolism). There was also little diversity of lesions, no information about patient ages, no statistical

analysis, and no comparative data. The study did, however, report a form of blinding, but no detail was provided.

Herminghaus et al. (2002a) evaluated 293 consecutive patients diagnosed with focal brain lesions. The purpose of this study was to assess the potential of single voxel MRS (1.5 T Siemens Magnetom Vision) to differentiate between neoplastic and non-neoplastic lesions, between high grade tumors and metastases or lymphomas, and between different types of tumors. The authors studied 25 types of lesions.

Discriminant analysis was used to “confirm significance” of differences between clusters formed by the authors. The analysis yelded five clusters: one containing glioblastoma (unknown grade), gliosarcoma, and embryonal tumors (IV WHO). A second cluster included anaplastic astrocytomas, anaplastic oligoastrocytomas, anaplastic oligodendrogliomas, anaplastic meningeoma (WHO III), and lymphomas. The third cluster included glial low grade tumors, gangliogliomas, gangliocytomas, neurominomas, and glioses and abscesses. The fourth cluster contained tumor necrosis, tumor cysts, infectious cysts, and meningeomas. The fifth cluster contained metastasis, glioblastoma, gliosarcoma, and embryonal tumor grade IV WHO. The authors concluded that MRS can be helpful in differentiating:

- Low grade from high grade tumors
- Metastasis and lymphomas from benign or low grade tumors
- Abscesses from gliobastoma and meastasis
- Silent infarct from low grade tumors
- Tumor cysts, infectious cysts, and necrotic tissue from each other and from other lesions
- WHO I/II meningeomas from metastasis

The authors concluded MRS could not distinguish:

- Between different tumor types of the same grade.
- Lymphomas from grade III tumors
- Metastasis from glioblastoma
- Low grade brain tumors from gliosis

"Success rates" were reported for the above classifications, but the level of detail provided in the abstract is insufficient for meaningful interpretation of these statistics. Finally, the fact that this study did not describe the standard against which the focal brain tumors were diagnosed, makes its difficult to interpret its conclusions.

4.2.2. Abstracts of Category-2 Studies Detecting Tumor Recurrence

Kovanlikaya et al. (2002) prospectively examined 16 lesions in seven men and seven women (mean age 50 yrs) to determine the value of multi-voxel MRS (1.5 T; 1 cm^3 spatial resolution) of glial neoplasms in detecting tumor recurrence after treatment with surgical excision, radiotherapy, and chemotherapy. The neoplasms included 12 astrocytomas, one oligodendroglioma and three mixed tumors of Grade II (5), Grade III (5) and Grade IV (6). Voxels showing the highest choline levels were analyzed for levels of NAA, creatine and lactate/lipid values and compared to the matched contralateral normal side of the brain. The results were assessed pathologically (6 lesions) and clinically (10 lesions).

Tumor recurrence was observed in eight of the 14 patients. Choline levels were much higher (114% elevation) in the recurrent lesions, with much lower levels in stable patients (7% depression). Choline elevation had a high sensitivity for detecting tumor recurrence (100%; positive predictive value = 82%). The specificity of choline depression for detecting stability was 72% (negative predictive value = 100%.) The authors, despite the small numbers, also suggested that the lactate/lipid peak in three

patients was highly specific for detecting necrosis but not sensitive for detecting recurrence. There was no independent verification of the results.

Lefkowitz et al. (2002) prospectively examined 27 lesions in 22 patients whose brain tumors had been surgically excised and/or irradiated to evaluate MRS' usefulness for diagnosing recurrent neoplasms. Single and multivoxel MRS was used to obtain maps of NAA and Cho concentration, ratio maps of Cho/Cr peak areas and heights, and tables of Cho/Cr ratios to identify potential tumor-containing voxels. A Cho/Cr ratio greater than or equal to 2.0, behavior of control voxels, and other spectral features were considered for tumor/non-tumor designations. Biopsy or follow-up imaging was used to confirm tumor status.

For the 27 MRS results, there were 19 gliomas, five metastases, two lymphomas, and one medulloblastoma. Sensitivity for detecting tumor recurrence was 89% (positive predictive value = 73%). Specificity was 33% (negative predictive value = 60%). Overall accuracy was 70%. Tests of statistical significance and confidence intervals were not reported. There was no independent verification of results.

Shah et al. (2002) assessed how well MRS performed in identifying tumor recurrence compared to SPECT and CT/MRI. These authors studied nine patients who had undergone surgery and radiotherapy or radiotherapy

alone for an average of 28 months with tumors suspected of recurrence. The tumors comprised: oligodendroglioma II (two); oligodendroglioma III (one); anaplastic astrocytoma (two); malignant mixed glioma (one); astrocytoma II (two); and glioblastoma multiforme (one). Choline spectra derived from MRS (1.5 T Siemens) sequence voxels ranging from 1.3 ml to 3.8 ml were used as markers for recurrence and were compared with radiological and SPECT results.

The kappa (k) measure of agreement was calculated between MRS and each of the other two tests. The results were: MRS vs. SPECT (k=0.72), MRS vs. CT/MRI (k=0.57) and CT/MRI vs. SPECT (k=0.37). There was no biopsy confirmation of tumor recurrence and therefore no 'reference standard'. In addition, the sample size was small, and no tests of statistical significance or confidence intervals were reported.

Lichy et al. (2002) examined the value of MRS, FDG-PET, and IMT-SPECT in evaluating suspicious brain lesions detected by MRI follow-up of 24 patients with irradiated gliomas. Multivoxel 2D MRS (1.5 T; voxel size = 8.8 x 8.8 x15 mm^3) was used to obtain relative signal intensity ratios of Cho, Cr, and NAA. Eighty-six voxels from suspicious lesions and 147 from 'normal' areas were analyzed. Clinical and MRI/CT follow-up, not biopsy, was used to classify lesions as neoplastic or non-neoplastic.

This study reported that the true positive rate (it is assumed that surgery was the standard of comparison) for identifying neoplastic tissue was 88% for MRS, 73% for FDG-PET, and 100% for IMT-SPECT. The true positive rate for identifying non-neoplastic tissue was 89% for MRS, 100% for FDG-PET and 75% for IMT-SPECT. Cho and Cho/NAA were present in significantly higher levels in neoplastic tissue. Additional information about sensitivity and specificity were reported, but the performance outcomes being evaluated were unclear. In this study three diagnostic techniques were compared only to each other and not to either biopsy or surgical results. In addition, there was no independent verification of results, and no confidence intervals for diagnostic test performance were reported.

4.2.3 Abstracts Of Category-2 Studies Distinguishing Homogeneity, Proliferation, And Grade Of Lesions

Herminghaus et al. (2001a) prior to biopsy evaluated 29 consecutive patients with MRI results and history suggestive of neuroepithelial brain tumors. The purpose of the study was to evaluate MRI's ability to distinguish low from high-grade tumors. Single voxel MRS (1.5 T) was

used to evaluate tumor tissues as well as normal appearing brain tissue in the contralateral hemisphere. NAA, total creatine, Cho, Lip, and Lac were analyzed. Tumor spectroscopic data were classified ("observer-independently") as grade I/II or III/IV according to the World Health Organization system. Biopsies were performed and confirmed by following patients for three years. Tumors showing at least 6 months of stability were defined as low-grade; those tumors showing progression were classified as high-grade.

While the authors reported sensitivity (100%), specificity (86%), and overall accuracy (96%), it is not clear what the reference standard was. Since the authors also report sensitivity (95%), specificity (86%), and overall accuracy (93%) for biopsy, it may be inferred that biopsy was not the reference standard. It is possible that surgery was the reference standard, but the study does not mention whether or how frequently surgery was performed. This ambiguity makes it difficult to assess the meaning of these findings. In addition, there was no independent verification of results. (This study might also be classified as Category 3).

4.3.1 Abstracts of Category-3: Studies Conducted to Evaluate Diagnostic Thinking Impact

Mao et al., (2002) evaluated the utility of single voxel MRS (1.5 T Phillips NT scanner) to guide selection of biopsy target areas in eight patients with a previous biopsy yielding equivocal results. This study might be considered as providing information for thinking about diagnostic impact. Areas of decreased NAA and elevated Cho and Lac were identified so that NAA and Cho maps could be used to target these areas as potential biopsy sites. The maps were superimposed on the stereotactic anatomical image to develop coordinates for the sites. Biopsies were then performed, followed by either CT or MRI.

MRS results showed abnormal metabolite maps for all eight patients, with seven showing decreased NAA and increased CHO. Biopsy sites were chosen from areas showing the most elevated CHO levels, and the biopsies were positive for seven of the eight patients. Tumor types included: two anaplastic astrocytomas (III); glioblastoma multiforme (IV); two infiltrative astrocytomas (II); oligodendroglioma (II).

While the study described in this abstract shows the technical feasibility of using MRI to help select the site of biopsy, the sample size of

eight was small, with no statistical analysis (it mentions a ‘significant’ decrease in NAA and increased CHO, but no quantitative data to support this is presented in the abstract). In addition, there was no comparison group of patients with non-MRS guided biopsy and there was no independent verification of the results.

5. SUMMARY

Ninety-six articles met our inclusion criteria for evaluation, with 11 providing information beyond the level of technical feasibility. Eight articles evaluated the test performance of MRS in various settings. Three articles addressed the impact of MRS on diagnostic thinking and therapeutic decision making. No article was found that addressed improvement of patient outcome.

5.1 For what metabolite profiles does MRS provide equivalent, complementary, or more accurate diagnostic information?

The following table summarizes the peak intensities and ratios of metabolites evaluated in Category-2 and higher studies.

Category 2 and higher studies that reported metabolite profiles

Study	Category	Qualitative interpretation	Quantitative measurements																
			Individual metabolites							Ratios									
			Cho	Cr	NAA	Lac	Lip	GI or MI	MGG	Cho/Cr	NAA/Cr	Cho/NAA	NAA/Cho	Lac/Cr	Lip/Cr	Cho/(Lip or Lac)	GI/Cr or MI/Cr	MGG/Cr
Rand	2	x																	
Butzen	2	x	x	x	x	x	x					x							
Shukla-Dave	2	x																	
Kimura	2		x	x	x	x	x			x	x			x	x	x			
Moller-Hartmann	2		x	x	x	x	x			x	x								
Tedeschi	2		x	x	x	x				x	x		x						
Roser	2		x	x	x		x	x	x	x	x				x		x	x	
Lin (1999)	3,4		x	x	x	x	x	x		x	x						x		

These profiles represent a very heterogeneous mix of signals and ratios, study populations, study purpose, and results. Some of the signals and ratios were unique for a particular study. For example, Butzen et al. used a Cho/NAA ratio of greater than 1.0 to classify lesions as tumors for initial diagnosis and reported a sensitivity of 79% and specificity of 77%. No other study used this metabolite ratio; therefore their results could not be

verified. The most common ratios evaluated were Cho/Cr and NAA/Cr, which were reported in five studies. With so little data and many questions, the above question could be answered only to a very limited extent.

Cho/Cr is the only metabolite ratio that has been found to be useful in differentiating neoplasm and non-neoplasm and supported by several studies. Among all the full articles examined in this technology assessment, Moller-Hartmann et al. provided the most complete reporting of the metabolite signal intensities and ratios for each type of tumor found in their study population. However, no single metabolite or ratio, other than perhaps a very high Cho/Cr ratio to diagnose PNET, by itself could differentiate among different neoplasms, among different tumor grades, or between neoplastic and non-neoplastic lesions. A moderately high Cho/Cr ratio of approximately four was observed for astrocytoma grade IV and metastases, compared to a value of approximately 1.5 for cerebral infarctions and abscesses. Kimura et al. also reported that a Cho/Cr ratio of 2.48 minimized the rate of misdiagnosis of neoplasm and non-neoplasm. Lin et al. reported that the Cho/Cr ratio was the single most accurate spectral measurement for differentiating neoplastic from non-neoplastic lesions. Unfortunately, the results were presented only as a bar graph.

In the only study that addressed the incremental diagnostic yield, Moller-Hartmann et al. demonstrated that MRS added to conventional MRI improved the number of correct diagnoses and reduced the number of incorrect or equivocal diagnoses.

5.2 Does The Use Of MRS Lead To An Improved Net Health Outcome?

Three studies addressed the potential impact of MRS results on diagnostic thinking or therapeutic decision making. Conclusions that can be drawn from these studies are severely limited due to the fact that the two prospective studies had only 15 and 17 patients, respectively, and the only large study was a retrospective analysis of medical records to identify potential opportunities for MRS to influence diagnostic thinking.

5.3 Are Voxel Positions And Operator Error Important Factors In Obtaining Diagnostic Images? If So, How Do They Impact MRS Accuracy?

No study explicitly evaluated the impact of voxel position on the accuracy of MRS. The retrospective study by Kimura et al. came closest to this objective. This study evaluated the differences of measurements between the whole lesion and the inner region of the same tumor.

Significant differences between the inner region and the whole lesion were found for various types of lesions. Although not specifically reported, the voxel sizes of the inner regions obviously were smaller than those of the whole lesions.

No study commented on the potential impact of operator error in placement of the voxel.

5.4 Strengths And Weaknesses Of The Studies

Most of the studies on Proton MRS were Category- 1 studies that addressed technical feasibility. The stated purpose of some of the studies classified as technical feasibility studies was to examine the impact of MRS on practice, but limitations of these studies' designs kept them from meeting the criteria necessary to achieve that level. Most of the studies we evaluated in categories 2 to 4 concluded that MRS has value for the indications studied. One study (Rand et al. 1997), which measured the accuracy of single-voxel, image-guided proton MRS in distinguishing normal from abnormal brain tissue and neoplastic from non-neoplastic brain disease, was an excellent example in some respects of the type of study needed to assess diagnostic efficacy. The use of multiple blinded readers and ROC analyses should be encouraged. Detailed presentation of

quantified spectra intensities and ratios similar to those reported in the article by Moller-Hartmann et al. would help the interpretation of results across studies.

Sample size is also an important limitation. Sample sizes that might be adequate for investigating one type of tumor are not necessarily adequate for investigating multiple types of tumors in the same study. This applies to tumor grades as well.

In summary, while there are a large number of studies that confirm MRS' technical feasibility, there are very few published studies to evaluate the diagnostic accuracy and whether it can positively affect diagnostic thinking and therapeutic choice. Those studies that do address these areas often have significant design flaws including inadequate sample size, retrospective design and other limitations that could bias the results.

5.5 Implications for future research

The relative rarity of brain tumors, the relatively low installed base of MRS software and the constraints of clinical practice have precluded the establishment of large, double-blinded controlled trials that would go beyond exploring technical feasibility. Experience with MRS has only become available to the general community of radiologists within the past

five years. Prior to this time, commercial software for shimming and analyzing spectra was not reliable, except in the hands of trained specialists. The current commercial software is vastly improved and can be mastered with a reasonable amount of additional training. Prior to about 1995, MRS was available at only a few research-oriented institutions. Hence studies were typically single institution feasibility studies or small case series. The recent change in the availability of MRS is only now reaching enough centers to allow more advanced investigations using the technique. MRS is still not available in many community hospitals, and even some academic centers.

The reason that the research is not more advanced may be that in addition to the relatively recent availability of MRS, its use in brain tumor evaluation evolved by using techniques that were not straightforward. Initially, it was hoped that tumors would have a characteristic “signature” that would allow rapid MRS diagnoses. Because the sensitivity of MRS allows demonstration of only a limited set of chemical compounds in the brain, such signatures have not been found. However, means of using the chemical information that is provided by MRS for tumor evaluation has progressed as new ideas have evolved for effective use of this information.

6. CONCLUSION

Human studies conducted on the use of MRS for brain tumors demonstrate that this non-invasive method is technically feasible and suggest potential benefits for some of the proposed indications. There is a paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision making. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized. The table below summarizes the current state of evidence.

CATEGORY	DESCRIPTION	EVIDENCE SUMMARY
1	Technical feasibility and optimization	Large amount of evidence
2	Diagnostic accuracy	
	Distinguish neoplasm from non-neoplasm	Limited evidence
	MRS added to MRI	Limited evidence
	Tumor grading	Limited evidence
	Differentiate intracranial cystic lesions	Limited evidence
3	Diagnostic thinking impact	Limited evidence
4	Therapeutic choice impact	Limited evidence
5	Patient outcome impact	No evidence
6	Societal impact	No evidence

APPENDIX A: ANALYTIC FRAMEWORK: POTENTIAL USES OF MRS

Newly Diagnosed Space-Occupying Brain Mass Identified By CT or MRI*	*Follow-Up Of Patients with Previously Diagnosed Brain Tumor Undergoing Treatment*
Potential use of MRS in **diagnostic evaluation and prognostication**	

• Replacement of diagnostic biopsy by MRS
  o *Outcome measure: same or improved accuracy/less invasiveness*
• Differentiating masses
  • Distinguishing malignant neoplasms from non-malignant neoplasms and vascular lesions (e.g. ring-enhancing primary tumors from abscesses)
  • Distinguishing single metatstatic lesions such as gliomas from primary tumors
  • Distinguishing among types of neoplasm (e.g. PNET from astrocytoma or neurofibroma bright spots from astroglial tumors)
  • *Outcome measure: Higher sensitivity and specificity in differentiating masses*
• MRS-guided biopsy to improve biopsy yield
  • *Outcome measure: Success rate of MRS-guided biopsies*
• Tumor grading: degree of malignancy
  • *Outcome measure: % of inappropriate biopsies avoided; biopsy yield*
	• Determining whether tumor has recurred
	• Differentiate recurrence from radiation injury (necrosis)
	• *Outcome measure: Higher sensitivity and specificity in differentiating masses*
	• MRS-guided biopsy to improve biopsy yield
	• *Outcome measure: Success rate of MRS-guided biopsies*

Potential use of MRS in **patient management**	

• Planning treatment
  o Choosing among therapies
  o Identifying tumor margin and volume for radiosurgery planning/surgical resection
  o Identifying tumor margin and volume for radiotherapy (gamma knife therapy) planning
  o Identifying target volume (isolating most active portions of tumor) for radiosurgery
	• Re-initiating radiosurgery when recurrence differentiated from necrosis
	• Rapidly assessing treatment effectiveness to optimize treatment
	  o Monitor response to treatment
	• *Outcome measures: survival, quality of life*

Newly Diagnosed Space-Occupying Brain Mass Identified By CT or MRI*	*Follow-Up Of Patients with Previously Diagnosed Brain Tumor Undergoing Treatment*
planning o Tumor grading: timing interventions • *Outcome measures: survival, quality of life*	
Factors potentially **affecting MRS performance**	
• Lesion location (e.g. proximity to bone and sinuses) and voxel positions • Concurrent disease (suspicion of known Ca elsewhere, e.g. lung, breast); suspicion of HIV • Operator error • Machine used/software and equation version	• Lesion location (e.g. proximity to bone and sinuses) and voxel positions • Concurrent disease (suspicion of known Ca elsewhere, e.g. lung, breast); suspicion of HIV • Operator error • Machine used/software and equation version

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APPENDIX B: Glossary

Cho – choline

cm^3 – cubic centimeter

Cr – creatine and phosphocreatine

CT – computed tomography

Gl – glycine

Lac – lactate

Lip – lipid

MGG – macromolecules, glutamine, and glutamate

MI – myo-inositol

MR – magnetic resonance

MRI – magnetic resonance imaging

MRS – magnetic resonance spectroscopy

NAA – N-acetyl-aspartate

ODV – orthonormal discriminant vector

PET – positron emission tomography

PNET – peripheral neuroectodermal tumor

ROC – receiver operating characteristic

VOI – volume of interest

Tesla – unit of magnetic flux

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Evidence Table 1. Summary of studies examining technical feasibility for magnetic resonance spectroscopy

				Study characteristics						Technique		Study objective(s)					
Author	UI	Pub Yr	Country	Study design	N (cases)	N (ctrls)	Enrollment	Dx status	Mean Age, range	Voxel volume (cm^3)	S / M	Tumor diff	Tumor grading	Recur vs Prim.	Met vs Primary	Necrosis	Other
Alger	2243962	1990	US	p	40	0	u	k	42, 18-81	27	s					x	
Barba	11147898	2001	England	p	27	0	u	k	ND	2x2x2	s					x	
Barbarella	9458376	1998	Italy	u	19	20	u	k	21-69	2x2x3	s		x			x	
Bruhn	2748837	1989	Germany	p	9	0	u	k	33-61	3x3x3	s	x					
Burtscher	10669230	2000	Sweden	p	26	0	u	k	52, 31-80	1.5x1.5x1.5-2 / 3x4x1.5 - 10x9x1.5	s/m	x					x
Castillo	11039343	2000	US	p	34	5	u	k	2-75	3-27	s		x				
Chang	9541289	1998	Korea	p	39	0	u	k	43, 26-60	2x2x2	s			x		x	
Chumas	9219744	1997	Scotland	p	9	0	u	k	54	21	s					x	
Croteau	11564242	2001	US	p	31	0	u	k	>18	0.8	m	x				x	x
Demaerel	1846155	1991	Belgium	p	50	0	u	k	53.4, 16-79	8-64	s	x					
Domingo	10070443	1998	UK	p	8	0	u	k	58, 41-70	1x1x1.5	s						x
Dowling	11290466	2001	US	p	29	0	u	k	16-68	1	m	x					
Esteve	9457810	1998	France	p	11	0	u	k	30-63	1x0.9x2	s						
Falini	8923303	1996	Italy	p	70	0	u	M	ND	8	s	x	x		x		
Fountas	11251398	2000	US/Greece	p	120	0	u	k	61.3, 29-76	8	s	x	x				
Frahm	92042946	1991	Germany	p	19	~300 studies	u	k	ND	2-8	s	x					
Fulham	1438744	1992	US	r	50	0	u	k	43, 18-76	0.675-2.0	m	x	x		x	x	
Furuya	9251112	1997	Japan	r	17	0	u	k	ND	8[1]	m	x					
Galanaud	12593610	2003	France	p	9	9 & 25	u	k	52, 15-69	ND / 2.0x2.0x1.5	s/m	x					
Go	7603595	1995	The Netherlands	u	32	0	u	k	ND	3x3x1, 1	m		x				
Go	9416313	1997	The Netherlands	u	18	0	u	u	ND	3x3x1, 1	m						x
Gotsis	8694527	1996	Greece	u	76 tumors	0	u	u	ND	2-8	s	x					x
Graves[2]	10690720	2000	US	p	36	0	u	k	45.5, 24-68	1	m						x
Graves[2]	11290467	2001	US	p	18	0	u	k	24-62	1	m			x			x
Gupta	10025604	1999	US	r	20	0	na	k	27-68	1x1x1.2	m	x				x	
Gupta	11263501	2000	US	p	18	0	u	M	28-62	1x1x1.2	m		x				
Hagberg	7476084	1995	Switzerland	p	32	8	u	k	55	8-18	s		x				x
Hall	10853123	1999	US	u	6	0	u	k	ND	ND	u			x		x	
Harada	95263377	1995	Japan	p	25	0	u	k	ND	15.6	s	x	x				
Heesters	8120569	1993	The Netherlands	u	11	0	u	k	ND	27 cc / 9 cc / 1	s/m						x
Heesters	9541920	1998	The Netherlands	p	8	0	u	k	29-66	1	m						x
Herminghaus	12546355	2003	Germany	p	90	0	c	n	ND	4.2 - 12.7	s		x				
Henriksen	2031809	1991	Denmark	p	17	0	u	k	49, 24-77	3x3x3	s	x					x
Houkin	7761009	1995	Japan	u	11	0	u	k	ND	2x2x2 - 3x3x3	s						x
Howe	12541241	2003	UK	p	42	8	u	n	ND	4 - 8	s	x	x				
Hubesch	2558086	1989	US	u	45	13	u	k	ND	18 - 40	s						x
Ikehira	8848553	1995	Japan	p	16	3	u	k	46.4, 14-71	8-27	s						x
Ishimaru	11511902	2001	Japan	p	56	0	u	k	55.8, 12-88	1.3x1.3x1.3 - 1.5x1.5x1.5	s				x		
Isobe	12165353	2002	Japan	p	23	7	u	k	20-26	2.2 - 31.5	s		x				x
Kadota	11372554	2001	Japan	p	10	0	u	k	12-73	2x2x2 - 3x3x3	s	x					x
Kamada	9095625	1997	Japan	p	11	20	u	k	7-76	8-27	s					x	
Kamada	11412866	2001	Germany	p	7	10	u	k	37-61	1.25x1.25x1.5	m						x
Kaminogo	11396738	2001	Japan	p	25	0	u	k	13-82	12x12x12 - 15x15x15	s		x				x
Kim	9205254	1998	Korea	p	14	0	c	k	25-70	2x2x2	s					x	x
Kinoshita	9367328	1997	Japan	p	12	16	u	k	50, 43-62	1	s			x		x	
Kizu	9508276	1998	Japan	r	6	0	n	k	50, 13-63	0.38-0.47	m					x	
Kugel	1584924	1992	Germany	p	36	27	u	k	27-81	8-18	s	x	x				
Langkowski	2607903	1989	Germany	p	16	0	u	k	22-74	4-20	s						x
Law	11867790	2002	US	p	17	34	c	k	51.9, 15-80	1x1x1.5 - 1x1x2	m				x		
Lin	11584229	2001	US	p	49	14	c	k	50	variable	s						x
Luan	10322655	1998	China	p	13	0	u	k	42, 13-68	2x2x2	s	x	x				
Mader	97029389	1996	Switzerland	p	17	7	u	n	50.3, 20-74	8 / 3.4-4.5	s/m	x	x				
Majos	12594562	2003	Spain	p	25	0	c	u	ND	1.5 - 2	s	x			x		
Manton	11252030	2000	UK	p	23	0	u	k	ND	variable	s	x					
McBride	7502203	1995	US	p	23	16	u	k	ND	27	s	x	x				
McKnight	11169821	2001	US	p	30	14	u	k	42	1	m	x	x				

Types of tu

Evidence Table 1. Summary of studies examining technical feasibility for magnetic resonance spectroscopy (Continued)

				Study characteristics						Technique		Study objective(s)					
Author	UI	Pub Yr	Country	Study design	N (cases)	N (ctrls)	Enrollment	Dx status	Mean Age, range	Voxel volume (cm^3)	S / M	Tumor diff	Tumor grading	Recur vs Prim.	Met vs Primary	Necrosis	Other
Meyerand	9974066	1999	US	p	27	0	u	k	43, 19-72	1 - 6.2	s	x	x				
Murphy	11973038	2002	UK	p	19	0	c	k	ND	8 - 16	s		x				
Negendank	8609557	1996	US/Europe/Japan	p	86	0	u	k	41, 3-75	8	s	x	x				
Ng	11820651	2001	Taiwan	p	58	0	u	k	ND	2 - 20	s	x				x	x
Pirzkall	11429219	2001	US/Germany	p	34	0	c	k	ND	1	m						x
Pirzkall	12128127	2002	US	p	20	0	u	k	39, 23-57	1	m						x
Poptani	7502961	1995	India	p	120	40	u	n	1-65	4.09 - 8	s	x	x				
Poptani	8583866	1995	India	p	34	30	u	n	1-65	4.09 - 8	s	x	x				
Preul	8612232	1996	Canada	u	91	14	u	u	ND	0.1	m	x					
Preul	10690729	2000	Canada	p	16	0	n	M	48.2, 24-70	0.7 - 1.2	m						x
Prost	9205253	1997	US	p	18	8	u	n	16-73	1.0 - 11.47	s						x
Rabinov	12461273	2002	US	p	14	0	u	k	40.4, 28-51	1.25	m						x
Ricci	10696025	2000	US	r	19	0	c	k	55, 42-70	4 - 8	s						x
Rock	12234397	2002	US	p	27	31	u	M	>18	0.9	m	x				x	
Schlemmer	11498420	2001	US/Germany	p	56	0	u	k	42.5	1.5 - 2x2x3	s	x					x
Segebarth	2319936	1990	Europe	p	10	12	u	k	ND	30 / 9-30	m						x
Shimizu	10782774	2000	Japan	p	26	0	c	n	46, 24-79	1.2x1.2x1.6 - 2x2x2	s		x				
Shimizu	8730195	1996	Japan	p	25	17	u	k	ND	1.3x1.3x1.5 - 2x2x2	s		x				
Sijens	9001146	1997	The Netherlands	u	17	0	u	k	ND	1x1x2 cm	m						
Sijens	7651119	1995	US/Europe	u	40	151	u	k	24-73	8	s	x					
Sijens	8748188	1995	The Netherlands	u	13	0	u	k	ND	3.4-64 / 10.2-13.6	s/m						x
Tamiya	10872152	2000	Japan	p	23	14	n	M	42.5, 15-68	1	s	x	x				
Tarnawski	11955739	2002	Poland	p	51	30	c	k	47, 20-68	1.5x1.5x1.5	s		x				x
Thomsen	2831923	1988	Europe	u	8	8	u	n	14-66	ND	ND	x	x				
Tien	8659372	1996	US	p	46	10	n	k	46, 17-78	6-8	s		x				
Tomoi	9140749	1997	Japan	u	8	0	u	k	62.5, 32-83	1.5x1.5x1.5	s						x
Vigneron	11295350	2001	US	p	31	8	u	n	ND	0.24 - 0.54, 1 - 2	m	x	x				
Wald	9322843	1997	US	p	12	0	u	k	ND	0.34 - 2	m						x
Walecki	10401596	1999	Poland	p	10	30	u	k	28-51	8	s						x

[1] Voxel size data unclear or incomplete

[2] Possible overlapping patient population

Abbreviations: c, consecutive; k, known; M, mixed; m, multiple; n, nonconsecutive; n, no histological diagnosis; ND, no data; p, prospective; r, retrospective; s, single; u, unknown

Evidence Table 2. Summary of abstracts examining technical feasibility for magnetic resonance spectroscopy

				Study characteristics						Technique		Study objective(s)					
Author	Proceedings	Pub Yr	Country	Study design	N (cases)	N (ctrls)	Enrollment	Dx status	Mean Age, range	Voxel volume (cm^3)	S / M	Tumor diff	Tumor grading	Recur vs Prim.	Met vs Primary	Necrosis	Other
Antiniw	ISMRM	2002	US	p	22	0	u	k	22-84	ND	m						x
Ben Sira	RSNA	2002	Israel	r	35	0	c	k	ND	ND	s	x					
Bizzi[1]	RSNA	2001	Italy	u	22	0	u	u	44	ND	m		x				
Bizzi[1]	ASNR	2001	Italy	u	20	0	u	u	40	ND	m						
Castillo	ASNR	2001	US	r	17	0	u	k	ND	ND	s	x					
Catalaa	ISMRM	2001	US	u	67	0	u	u	23-78	1	m		x				
Cha	ASNR	2002	US	r	10 gliomas	0	u	k	ND	ND	u	x					
Cruz	RSNA	2001	Brazil	r	15	0	u	k	ND	ND	s	x	x				
Fan	RSNA	2002	China	p	22	0	u	u	36.7mdn, 8-62	ND	u	x					
Fatterpekar	ASNR	2001	US	r	14 studies	0	u	u	ND	ND	u	x					
Fujiwara	ISMRM	2001	Brazil	u	22	5	u	u	ND	8	s						x
Gomori	RSNA	2001	Israel	u	10	12	u	k	ND	ND	u						x
Graves	ISMRM	2002	US	u	10	0	u	u	ND	ND	m						x
Hakyemez	ASNR	2001	Turkey	u	23	0	u	u	ND	2x2x2	s	x					
Hearshen[2]	ISMRM	2001	US	u	35	0	u	k	ND	.9x.9x1.5	m						
Herminghaus	ASNR	2002	Germany	u	174 lesions		u	u	ND	ND	s	x					
Herminghaus[3]	ASNR	2001	Germany	u	83	0	c	M	ND	ND	s						x
Herminghaus[3]	ASNR ISMRM	2001	Germany	u	31	0	u	u	52.8, 11-75	ND	s						x
Hiltunen	ISMRM	2001	Finland	u	8	2	u	k	ND		m		x				
Hiwatashi	ASNR	2002	US	u	24	0	u	u	ND	1	m						
Howe	ISMRM	2002	UK	u	25	8	u	k	ND	ND	u						x
Law	ISMRM	2002	US	u	20	10	u	k	ND	1x1x1.5 - 1x1x2	m		x				
Leeds	ASNR	2002	US	u	9	0	u	k	ND	ND	m		x				x
Li[4]	ISMRM	2001	US	u	18	0	u	M	ND	ND	s/m	x					
Li[4]	ISMRM	2002	US	u	19	0	u	k	ND	ND	m						x
Lim	ASNR	2001	Singapore	u	59	0	u	u	ND	ND	m						x
Lim	ISMRM	2002	Singapore	u	20	15	u	k	ND	1	m	x					
Lin	ISMRM	2001	US	p	7	15	u	u	43, 25-64 (cntrl)	4.5 (cntrl) 2-4.5 (case)	s						x
Lin	ISMRM	2001	US	u	50	50	c	k	ND	4-12.5	s						x
Londono	ASNR	2002	US	u	15 meningiomas		u	M	24-81	ND	s/m						x
Majos	RSNA	2002	Spain	u	130	0	u	u	ND	ND	s	x					
Majos	RSNA	2001	Spain	p	108	0	u	u	ND	ND	s						x
McKnight	ASNR	2001	US	u	58	0	u	u	ND	1	m	x	x				
McKnight	ISMRM	2002	US	u	20	0	u	u	ND	ND	m		x				
Peck	ISMRM RSNA	2001	US	u	10	0	u	k	ND	ND	u						x
Pilatus	ASNR ISMRM	2001	Germany	u	95	0	c	u	ND	ND	s						x
Scatliff	ASNR	2001	US	u	12	0	u	k	ND	1.5-2	s/m						x
Shah	ISMRM	2002	India	u	10	0	u	n	ND	3-6	s	x					
Shah[5]	ISMRM	2001	India	u	72	0	u	n	ND	1.7-8	s						x
Shah[5]	ISMRM	2002	India	u	52	0	u	n	ND	2.2 - 8	s		x				
Smith	RSNA	2003	US	u	25	5	u	u	ND	ND	s/m						
Szabo De Edelenyi	ISMRM	2001	France	u	56	7	u	n	ND	ND	m		x				
Tate	ISMRM	2001	UK/Spain	u	51	0	u	u	ND	ND	s	x					
Waldman	ISMRM	2002	UK	p	28	0	u	n	ND	1-8	s						x

[1, 3, 4, 5] Potential overlap of patient population

[2] Potential overlap of patient population with Rock, Hearshen, Scarpace et al., 2002

Abbreviations: ASNR, American Society of Neuroradiology; c, consecutive; k, known; M, mixed; m, multiple; mdn, median; n, nonconsecutive; N, no histological diagnosis; ISMRM, International Society for Magnetic Resonance in Medicine; NA, not applicable; ND, no data; p, prospective; r, retrospective; RIBI, radiation-induced brain injury; RSNA, Radiological Society of North America; s, single; u, unknown.