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3 **MAGNETIC RESONANCE SPECTROSCOPY FOR BRAIN TUMORS**
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40

41

Abstract

42

43 Magnetic Resonance Spectroscopy For Brain Tumors

44

45

46 Introduction

47

Diagnosing and treating space-occupying tumors of the brain

48

presents special challenges due to the similarities of tumors to other

49

pathologic entities on conventional imaging, the similarities of individual

50

tumor cell types on conventional imaging, the inaccessibility of these

51

lesions, and their proximity to complex brain structures. A non-invasive

52

technique that could provide information about the chemical and histologic

53

composition of brain tissue could greatly aid diagnosis and treatment of

54

brain tumors by helping to avoid unnecessary biopsies, by helping to guide

55

biopsies, and by providing additional information for improving treatment.

56

The Centers for Medicare & Medicaid Services (CMS) requested a

57

technology assessment by the Agency for Healthcare Research and

58

Quality (AHRQ) to assess the value of Magnetic Resonance Spectroscopy

59

(MRS) for diagnostic evaluation, surgical planning, and patient

60

management of space-occupying brain tumors. The Tufts-New England

61

Medical Center Evidence-based Practice Center was asked to conduct an

62

assessment of this technology.

63

64 **Methods**

65

66 An OVID search of the MEDLINE® database was conducted on
67 November 6, 2002. Filters and limitations were used to eliminate
68 inappropriate publications, with inclusion and exclusion criteria developed
69 to identify articles to be reviewed. The search used applicable MeSH
70 headings and textwords with appropriate Boolean operators. After filtering
71 irrelevant publication types (such as publications not containing original
72 clinical data), the search resulted in 959 citations for download and
73 screening. Hand screening of the abstracts resulted in accepting 137
74 citations for complete article retrieval. All abstracts were reviewed to
75 identify full articles that met the criteria. In addition, abstracts from the
76 following relevant professional society proceedings for the years 2001 and
77 2002 were reviewed and included in the analyses: American Society of
78 Neuroradiology (ASNR), Radiological Society of North America (RSNA),
79 and the International Society for Magnetic Resonance in Medicine
80 (ISMRM).

81

82

Results

83

84

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

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

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

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

105

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

115 **Conclusion**

116
117 Human studies conducted on the use of MRS for brain tumors
118 demonstrate that this non-invasive method is technically feasible and
119 suggest potential benefits for some of the proposed indications. However,
120 there is a paucity of high quality direct evidence demonstrating the impact
121 on diagnostic thinking and therapeutic decision making. In addition, the
122 techniques of acquiring the MRS spectra and interpreting the results are
123 not well standardized. In summary, while there are a large number of
124 studies that confirm MRS' technical feasibility, there are very few published
125 studies to evaluate its diagnostic accuracy and whether it can positively
126 affect diagnostic thinking and therapeutic choice. Those studies that do

127 address these areas often have significant design flaws including
128 inadequate sample size, retrospective design and other limitations that
129 could bias the results.
130

131
132

1. INTRODUCTION

133

1.1 Background

134

Diagnosing and treating space-occupying tumors of the brain

135

presents special challenges due to the similarities of tumors to other

136

pathologic entities on conventional imaging, the similarities of individual

137

tumor cell types on conventional imaging, the inaccessibility of these

138

lesions and their proximity to complex brain structures. Standard imaging

139

diagnostic procedures include computerized tomography (CT), magnetic

140

resonance imaging (MRI), single photon emission computed tomography

141

(SPECT), and positron emission tomography (PET) imaging. Following is a

142

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). |

143

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

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

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

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

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

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

180

181 **1.2 Requests by the Centers for Medicare and Medicaid Services**

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

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

- 198 • Avoiding unnecessary biopsy
199 • Obtaining appropriate biopsy, from appropriate location
200 • Directing biopsy to an appropriate location
201 • Receiving appropriate treatment
202 • Avoiding an inappropriate treatment

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

206

207 **1.3 Analytic Framework**

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

218 **1.3.1 Diagnostic evaluation**

219 Experimentation with in-situ Magnetic Resonance Spectroscopy
220 (MRS) for tumor assessment has been ongoing since 1985 (Maris et al.,
221 1985). It was initially hoped that MRS would provide definitive
222 spectrographic signatures of tumor histologic types. Clinical MRS research
223 has led to multiple specific applications of MRS for both diagnostic work-
224 ups and treatment follow-up of CNS tumor. Combined with findings from
225 conventional anatomic MRI, MRS may have the potential to improve the
226 diagnosis and management of brain tumors.

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

229

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

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

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

239

240 **In distinguishing abscesses from CNS tumors**

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

248

249 **Tumor grade**

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

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

261

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

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

275

276 **Biopsies**

277 MRS has also been recently investigated for use in biopsies. Biopsy

278 guidance is an area where MRS may reduce sampling error associated

279 with determination of tumor grade (and prognosis) in primary CNS tumors.

280 Accurate determination of tumor grade is important in determining

281 prognosis and adjuvant therapy.

282

283 **1.3.3 Patient management and planning for surgery**

284 The management of CNS tumors depends on tumor type and

285 multiplicity. In primary astrocytomas of the CNS, treatment depends on

286 grade. Low-grade tumors (WHO classification grades 1-2) are usually

287 observed, with follow-up, if small, and do not represent an immediate

288 neurological crisis. In cases of neurologic crisis, tumors are either excised

289 or debulked. In high-grade astrocytomas, tumors are debulked surgically,

290 followed by whole-brain radiation.

291 Single metastatic brain lesions have conventionally been excised

292 when in accessible locations. Excision is often accompanied by

293 chemotherapy. Multiple lesions have conventionally been treated with

294 whole brain radiation and chemotherapy. Gamma knife therapy (focused

295 stereotactical radiation) has become an important and increasingly used

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

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

301

302 **Determining tumor recurrence**

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

309

310 **Distinguishing radiation necrosis from tumor recurrence**

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

316 distinguish recurrent tumor from radiation necrosis under some
317 circumstances.

318

319 **Determining tumor response to therapy**

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

323

324 **Surgical treatment planning**

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

329

330 **1.3.4 Factors that may affect performance of MRS**

331

332 **Location of lesion including proximity to bone and sinuses**

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

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

343

344 **Operator issues**

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

354

355 **Size/position of voxel**

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

370

371 **Concurrent disease**

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

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

380

381 **Hardware and software**

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

387 **2. METHODS**

388
389 **2.1 Classification of diagnostic studies**
390
391 The Medicare Coverage Advisory Committee (MCAC) report on
392 “Recommendations for Evaluating Effectiveness; Executive Committee
393 Working Group Medicare Coverage Policy” (Executive Committee Working
394 Group, 2001) (<http://www.cms.hhs.gov/mcac/8b1-i9.asp>) developed
395 recommendations for evaluating evidence. It pointed out that although
396 direct evidence is preferable, few studies directly measure the effect of
397 diagnostic tests on health outcomes. Rather, studies typically focus on
398 whether diagnostic tests are technically feasible or on effects on accuracy.
399 These points apply to MRS. Few well-designed studies evaluate the impact
400 of this test on clinical outcomes.

401
402 To systematically review the level of assessment of each study, we
403 used a model described by Fineberg et al. (1977), Fryback and Thornbury
404 (1991), and Adams (1997) to categorize the level of assessment achieved
405 by the studies:

406

407 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 |

408

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

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

415

416

417

418

419 **2.2 Literature search**

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

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

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

435
436 Note that the information available from abstracts in such proceedings is
437 extremely limited in comparison to that available in full articles. Additionally,
438 the peer review process is generally not comparable to the process for full

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

443

444 **2.3 Inclusion/Exclusion Criteria**

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

452

453 **2.4 Search Results**

454 One hundred thirty-seven publications were retrieved. Further review
455 of those retrieved publications with application of inclusion criteria yielded
456 85 studies for inclusion in the report. The detailed search strategy follows:

457

458

459 MEDLINE <1966 to October Week 4 2002>

460

| 461 # | Search History | Results |
|--------|---|---------|
| 463 1 | exp Magnetic Resonance Spectroscopy/ | 92891 |
| 464 2 | limit 1 to human | 22632 |
| 465 3 | limit 2 to English language | 20499 |
| 466 4 | exp neoplasms/ | 1409117 |
| 467 5 | (tumor or cancer\$ or neoplasm\$ or neoplas\$ or lesion\$ or mass).tw. | 1131920 |
| 469 6 | (brain or cranial or cerebr\$).tw. | 479504 |
| 470 7 | 5 and 6 | 71583 |
| 471 8 | 4 and 6 | 50293 |
| 472 9 | 7 or 8 | 93338 |
| 473 10 | exp brain neoplasms/ | 69674 |
| 474 11 | 3 and (9 or 10) | 1231 |
| 475 12 | limit 11 to (addresses or bibliography or biography or | |

476

477

| 478 # | Search History | Results |
|--------|--|---------|
| 480 | 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 |
| 484 13 | Case Report/ | 1059907 |
| 485 14 | 11 not (12 or 13) | 959 |

486

487

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

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

492
493
494
495

2.5 Data Extraction

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

502
503 For the studies in Category- 2 and above, narrative analyses were
504 provided for each study. Studies in these categories were also evaluated
505 with respect to their methodological adequacy.

506 **3. RESULTS: Full Published Studies**

507

508 The following table shows the number of studies in each of the

509 categories. After reviewing the 959 abstracts and 137 retrieved articles, 75

510 studies were classified as Category-1 Technical feasibility studies. Ten

511 studies were identified as providing information beyond that of the technical

512 feasibility category. An additional 10 studies were added to Category- 1

513 and 1 study added to Category- 2 from references given by peer reviewers

514 of the draft version of this report. In this section we report on the 96

515 published full-length studies classified using the approach described above.

516 There were eight articles for Category-2, two articles for Category-3 (one

517 study also qualify for Category-4), two articles for Category- 4 (one article

518 shared with Category-3), and none for Category- 5 or Category- 6. Nearly

519 all the studies identified were in Categories- 1 and 2, with the vast majority

520 in Category- 1. The following table summarizes these results:

521

| 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 |

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

523 **3.1 Category- 1 studies: Technical Feasibility**

524

525 Evidence Table 1 shows selected characteristics of the technical

526 feasibility (Category- 1) studies. Included in this table are the year of

527 publication, country in which the research was conducted, study

528 characteristics including number of diseased (case) and non-diseased

529 (control) patients, method of patient enrollment, diagnostic status, and age.

530 The table also shows the size of the volume of tissue (voxel) of interest as

531 well as whether single or multiple voxel sampling was used. Finally, the

532 table indicates the principal clinical study objectives: tumor differentiation,

533 tumor grading, distinguishing primary tumor tissue from recurrent tumor

534 and from metastases, and identifying necrotic tissue.

535 We reviewed 85 Category- 1 studies published from 1988 through

536 2003 involving approximately 2434 patients; fifty (59%) of the studies were

537 published before 2000. There was extensive international representation in

538 these studies. Twenty-four (28%) were from the US, 15 (18%) were from

539 Japan, and 19 other countries were represented. The ages of patients

540 included in the studies varied considerably; the range was from 1- 88

541 years, but we excluded studies that consisted predominantly of pediatric

542 patients.

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

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

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

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

564

565 **3.2 Category-2: Studies that Evaluate Test Performance**

566 Eleven studies were identified as providing information beyond the
567 technical feasibility category. There were eight articles for Category-2, two
568 articles for Category-3 (one study also qualify for Category-4), two articles
569 for Category-4 (one article shared with Category-3), and none for Category-
570 5 or Category-6.

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

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

581 research issues. Fifty-five MRS spectra belonging to 53 patients in the
582 1997 article were included in the 99 MRS spectra evaluated in the 2000
583 article. The study by Adamson et al. (1998) was a retrospective analysis of
584 78 patients from the same study population and is discussed under the
585 Category-4 section.

586

587 **3.2.1 Studies Differentiating Neoplasm from Non-neoplasm**

588

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

596 Using voxel sizes of 1 to 3 cm³, MRS spectra were obtained using a
597 clinical 0.5 Tesla MR system (manufacturer not stated) with a prototype
598 head coil or a receive-only conformal surface coil. The voxel was centered
599 over solid portions of the lesion and avoided necrotic debris or edema.

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

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

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

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

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

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

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

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

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

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

654 Compared to the reference standard, the four blinded readers
655 accumulated 12 false-positive interpretations on eight spectra and 22 false-
656 negative interpretations on 13 spectra. The sensitivity, specificity, PPV,
657 NPV, and accuracy of MRS to distinguish between neoplastic and non-
658 neoplastic spectra for the four blinded readers averaged 0.85, 0.74, 0.92,
659 0.61, and 0.83, respectively. The test performance showed better results
660 when only untreated patients were analyzed.

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

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

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

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

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

700 cm³) 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 T₂-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.

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

727 This study also used the MRS CNI methodology to examine the
728 proportion of patients of all 66 patients with evidence of tumor outside the
729 area of contrast enhancement. Regardless of tumor grade, 41-45% of
730 hyperintense lesions showed metabolic evidence of tumor ($CNI >2.5$), and
731 36-45% of non-enhancing lesions also showed such evidence.

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

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

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

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

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

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

764 The investigators found that using a Cho/Cr ratio of 2.48 for the whole
765 lesion, the lowest rate of misdiagnosis was achieved in differentiating
766 neoplasm from non-neoplasm. The positive predictive value using this
767 threshold for metastatic brain tumors and glioblastoma was 89% (95% CI,
768 65 - 99%) and 60% (95% CI, 26 - 88%), respectively. The positive
769 predictive value of a Cho/Cr ratio of less than 2.48 for diagnosing radiation
770 necrosis and cerebral infarction were 71% (95% CI, 29 - 96%) and 100%
771 (95% CI, 40 - 100%), respectively.

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

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

781

782 **3.2.2 Clinical Utility of MRS added to MRI**

783

784 Moller-Hartman et al. (2002) evaluated the clinical utility of MRS
785 added to MRI for the differentiation of intracranial neoplastic and non-
786 neoplastic mass lesions. The study population consisted of a consecutive
787 series of 176 patients presented to the neuroradiology department with
788 focal intracranial mass lesions following MRI and/or CT imaging.

789 Spectroscopic studies were performed using a 1.5 Tesla whole-body MR
790 scanner (Magnetom Vision, Siemens). All patients underwent a single voxel
791 MRS with a mean voxel volume of 8 cm³ (range 4 - 12 cm³). The voxel was
792 placed in the solid part of the lesion excluding necrotic or cystic tumor parts
793 or adjacent edematous areas. An acceptable voxel had to contain at least
794 an estimated 70 percent tumor tissue. Whenever feasible, a reference
795 spectrum of the same voxel size was acquired in the homologous region in
796 the contralateral brain.

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

799 cases of brain abscesses or focal inflammatory brain disease and nine (of
800 nine) cases of cerebral infarction. Features on MRI or CT, clinical course,
801 cerebrospinal fluid findings, and blood tests made the final diagnoses of the
802 non-biopsied cases. Twelve out of the 176 spectra were of poor quality and
803 were excluded from further evaluation. Final diagnoses for the remaining
804 164 interpretable spectra included 23 low-grade astrocytomas, 28
805 anaplastic astrocytomas, 39 glioblastomas, four PNETs or
806 medulloblastomas, 18 metastases, nine meningiomas, nine neurinomas, 25
807 cerebral abscesses and nine brain infarctions.

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

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

823 Compared with the reference spectrum on the contralateral side of
824 the brain, the Cr level was about 75-80% among the gliomas and there
825 were no significant differences between the different tumor grades. The
826 levels of Cr in the metastases, abscesses, and infarctions were about 40-
827 50%, compared to the reference. The Cho levels decreased to 70-80% in
828 infarctions and abscesses, and increased in metastases, PNET, and
829 gliomas. The Cho level progressively increased with the tumor grade. The
830 Cho/Cr ratios were: infarction = 1.45; astrocytoma I = 1.33; astrocytoma II =
831 2.13; astrocytoma IV = 3.93; PNET = 18.4; metastases = 3.97; abscesses
832 = 1.52; meningioma = 4.81; neurinoma = 3.08.

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

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

841

842 **3.2.3 Studies on Tumor Grading**

843
844 Roser et al. (1997) prospectively evaluated 35 MRS spectra in 17
845 patients with suspected glial brain tumors. The purpose of the study was “to
846 apply the metabolic features found in a previous study of 21 healthy
847 controls and humans with gliomas to a new cohort of patients with a
848 suspected glial brain tumor and other healthy volunteers.” The age and sex
849 of the patient population were not reported. None of the patients had
850 received stereotactic biopsy, open surgery, or radiation therapy before
851 MRS. Sterotactic biopsy or open surgery was performed within a few days
852 after MRS.

853 MRS spectra of single-voxel size 8 cm³ were acquired using a 1.5
854 Tesla MR system (Siemens Magnetom SP 400, Siemens Medical Systems,
855 Erlangen, Germany). The VOI was placed as close as possible to the tumor
856 center and covered at least 75% of the tumor tissue.

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

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

870 In the validation study, the correlation of superimposing new patients'
871 data onto the classification derived from the training data was noted.
872 Histological diagnoses of the new patients included ten glioblastoma
873 multiforme, two astrocytoma grade III, and five astrocytoma grade II. All ten
874 cases of glioblastoma multiforme were in the proximity of the high grade
875 region defined by the training data. Four of five astrocytoma grade II were
876 classified as low grade gliomas, and one was classified as high grade. One
877 of the two astrocytoma grade III was classified as high grade and the other
878 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 cm³. At the time
897 of each MRS study, a combination of clinical examination, MRI, positron
898 emission tomography with 18F-fluorodeoxyglucose, and biopsy findings

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

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

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

917

918 **3.2.4 Differentiating Intracranial Cystic Lesions**
919
920

921 Shukla-Dave et al. (2001) prospectively evaluated the accuracy of
922 MRS in the differentiation of intracranial cystic lesions. Fifty-one patients
923 including 23 men and 28 women between the ages of eight and 50 years
924 (mean 33 years) with intracranial cystic lesions on conventional MRI were
925 studied. Single-voxel MRS was performed using a 1.5 Tesla MR system
926 (Magnetom, Siemens) on lesions greater than 8 cm³. A VOI of 4 to 8 cm³
927 within the confines (sometimes including the rim) of the lesion was selected
928 for MRS.

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

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

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

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

947 Of the 51 cases, MRS correctly identified all 21 cases of abscess, all
948 19 cases of glioma, all three cases of arachnoid cyst, and all three cases of
949 hydatid cyst. MRS incorrectly diagnosed one case of xanthogranuloma and
950 one case of infarct as glioma. A total of three inconclusive MRS diagnoses
951 were later found to be glioblastoma multiforme, gloependymal cyst, and
952 acoustic neuroma. Thus, MRS correctly diagnosed the pathology of
953 intracranial cystic lesions in 46 of 51 (90%) cases, did not contribute to the
954 diagnosis in three cases (6%) and falsely diagnosed benign lesions as
955 malignant in two cases (4%).

956

957 **3.3 Category-3: Studies Conducted to Evaluate Diagnostic
958 Thinking Impact**

959 Two small prospective studies qualified for this category. The
960 purpose of the study by Hall et al. (2001) was “to determine the utility of
961 intraoperative MRS for targeting during brain biopsy using a skull-mounted
962 trajectory guide.” The trajectory guide is commercially available and has
963 been approved by the Food and Drug Administration (FDA) for the
964 placement of deep brain stimulators, drug delivery catheters, and brain
965 biopsies (Hall et al., 2001). The successful use of intraoperative MRS-
966 guided brain biopsy might replace the conventional frame-based or
967 frameless stereotactic techniques guided by either computed tomography
968 (CT) or magnetic resonance imaging (MRI). In this setting, the CT or MRI
969 are typically performed immediately or a few days before the biopsy.
970 However, the opening of the dura mater and with the loss of cerebrospinal
971 fluid may result in shifting the position of the lesion identified in the imaging
972 studies (brain shift), which in turn might result in non-diagnostic stereotactic
973 biopsy. A review of stereotactic brain biopsies found a diagnostic yield
974 (proportion of biopsies containing useable diagnostic tissue) of 91% (Hall,
975 1999).

976 A total of 17 patients including 13 men and four women between the
977 ages of 16 and 80 years suspected of brain tumors were evaluated in Hall's
978 2001 prospective study. All patients had "turbo spectroscopic imaging
979 (TSI)" (a multi-voxel MRS method) and seven patients had single-voxel
980 spectroscopy in addition, for purposes of comparison. MRS spectra were
981 obtained using 1.5 Tesla MR system (ACS-NT; Philips Medical Systems,
982 Best, Netherlands) located within an intraoperative MRI suite. The VOI in
983 the single voxel spectroscopy was 1.5x1.5x1.5 cm³ and the TSI used a
984 32x32 grid of spectra in a single plane with a spatial resolution of
985 0.66x0.66x2.0 cm³.

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

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

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

999 The authors concluded that “intraoperative MRS-guided brain biopsy
1000 using a trajectory guide is a simple, safe, and accurate technique for
1001 accessing areas of the brain of diagnostic interest.” They further
1002 commented that with the development of intraoperative MRS, it is now
1003 possible to biopsy lesions located in the brain without the use of rigidly
1004 fixed head frames (traditional stereotaxy) and in near real-time, thus
1005 improving the accuracy and diagnostic yield. The use of the trajectory guide
1006 with MRS may also reduce intracerebral hemorrhage complications by
1007 minimizing the number of needed passages of the biopsy needle.

1008 While the combination of trajectory guide and intraoperative MRS in
1009 this study appears promising in achieving high yield in brain biopsies, the
1010 number of patients studied was small. The need for an intraoperative MRI
1011 suite limits the generalizability. It should also be noted that three of the four
1012 authors of this study disclosed a financial interest in the company that
1013 produces the trajectory guide.

1014 Lin et al. (1999) prospectively evaluated the utility of single voxel
1015 MRS when used as an alternative or adjunct to brain biopsy in patients with

1016 lesions suggestive of brain tumors initially identified by MRI. This study
1017 provided information for diagnostic thinking impact (Category- 3) as well as
1018 for therapeutic choice impact (Category- 4).

1019 Fifteen patients between the ages of seven and 58 (there was only
1020 one child of age 7) were studied. Among the diagnoses based on histology
1021 were six anaplastic astrocytoma, one astrocytoma, one oligodendrogloma
1022 grade II, one oilgodendrogloma grade III, one glioblastoma multiforme, and
1023 one abscess. Three additional patients did not have biopsy and the lesions
1024 resolved on serial scans. One patient with a history of treated brain stem
1025 mass subsequently died from progressive disease on follow-up. A
1026 neurosurgeon defined a treatment plan that would be carried out in the
1027 absence of a diagnostic MRS study prior to the MRS examination, to
1028 determine whether MRS directly impacted upon and altered clinical
1029 decision-making. MRS interpretations were directly incorporated into the
1030 clinical decision-making and a treatment plan was determined. Patients
1031 were then followed to determine if subsequent treatment and outcomes
1032 were in accordance or discordance with the MRS findings.

1033 Single-voxel MRS was performed on a 1.5 Tesla Signa Scanner (GE
1034 Medical Systems, Milwaukee, WI). The VOI was determined by the
1035 neurosurgeon based on MRI results prior to the MRS exam. The voxel size

1036 was adjusted to optimize the amount of homogeneous abnormal tissues
1037 within the voxel, while minimizing the amount of necrotic tissue. Voxel size
1038 varied between 2.35 to 9.68 cm³.

1039 The MRS spectra were quantified with an external standard although
1040 it was not described. NAA/Cr ratios were consistently and significantly
1041 elevated in non-neoplastic spectra whereas Cho/Cr demonstrated the
1042 opposite trend. Lipid and lactate were only observed in abscesses and one-
1043 half of neoplastic spectra. They could not reliably differentiate necrotic
1044 tumor from radiation necrosis or abscess. Myoinositol/creatinine ratios were
1045 not significantly different between groups.

1046 Forty-one VOI from 15 patients were analyzed. Thirty-five (85%) of
1047 the spectra were considered to be of good or excellent quality, four (9%) of
1048 poor but interpretable quality, and two (4%) non-interpretable. For 10
1049 patients with previously documented tumors, MRS was interpreted as
1050 consistent with recurrent tumors in seven cases and consistent with
1051 radiation necrosis in three cases.

1052 In one patient with two regions of interest on MRI, MRS suggested
1053 tumor in one lesion, but interpreted another lesion as edematous white
1054 matter without tumor. Disease progression occurred in the edematous
1055 white matter lesion 9 months after initial surgery, indicating that MRS was

1056 unsuccessful in identifying infiltrating tumor in this instance. A retrospective
1057 review of the spectra in that region suggested that the effect of averaging
1058 over a large volume might have resulted in the misinterpretation. The
1059 authors suggested that a multi-voxel MRS might have been able to provide
1060 a more accurate diagnosis.

1061 In the absence of MRS, the neurosurgeon would have recommended
1062 stereotactic biopsy in eight cases, serial MRI at six week intervals in three
1063 cases, repeat craniotomy in three cases, and empiric chemotherapy in one
1064 case. MRS was used in place of biopsy in seven cases, and correlated with
1065 clinical course in six of these cases. Overall, MRS was found to directly
1066 alter clinical management in 12 of 15 patients and provided greater support
1067 for clinical management in 14 of 15 patients. Had MRS been relied upon in
1068 every case, it might have avoided biopsy in nine cases, and influenced
1069 clinical management in 13 of 15 patients.

1070 The small number of patients, narrow spectrum of diagnoses, and the
1071 inclusion of only one neurosurgeon's decision limit the generalizability of
1072 this study.

1073

1074 **3.4 Category-4: Studies Conducted to Evaluate Therapeutic**

1075 **Choice Impact**

1076 **Prospective studies**

1077 The prospective study by Lin et al. (1999) also provided limited

1078 information on the use of the test on therapeutic choice impact. See the

1079 discussion under Category-3 above.

1080

1081 **Retrospective study**

1082 Adamson et al., (1998) conducted a retrospective review of medical

1083 records to assess the influence of single-voxel MRS findings on the

1084 treatment of patients suspected of having a brain tumor. This publication

1085 appears to be based on the same overlapping patient population from the

1086 Medical College of Wisconsin that had been used in two other Category-2

1087 publications.

1088 The medical records of 90 patients who had MRS between May and

1089 December of 1995 were examined. Seventy-eight met the inclusion criteria

1090 and provided sufficient data for analysis. The patients were categorized into

1091 two groups based on the interpretation of the MRS findings:

- 1092 • Group 1, MRS findings positive for neoplasm

- 1093 • Group 2, MRS findings negative for neoplasm

1094 The investigators examined all available medical records, including
1095 discharge summaries, progress notes, and outpatient reports to determine
1096 the outcome and treatment subsequent to the MRS examination. The
1097 patients were further categorized on the basis of whether they underwent
1098 biopsy before treatment. Pathology records in those patients who
1099 underwent surgical intervention or biopsy were reviewed.

1100 MRS was classified as having a potential positive influence on
1101 treatment if no biopsy was needed before the initiation of treatment. If MRS
1102 results did not agree with the subsequent clinical diagnosis, the results
1103 were considered to have a potential negative influence on patient
1104 treatment. In all other cases, the effect of MRS was presumed to be
1105 negligible or indeterminate.

1106 Neuroradiologists interpreted MRS spectra on the basis of the relative
1107 amplitudes for lactate, lipids, NAA, creatine and phosphocreatine, choline-
1108 containing compounds, and myo-inositol. A Cho/NAA ratio greater than 1.0
1109 was considered to be positive for neoplasm. Smaller increases in the
1110 choline concentration were not considered diagnostic for neoplasm. The
1111 presence of lactic acid or lipid was consistent with relatively high-grade
1112 neoplasia if the choline concentration was elevated. Elevation of lactic acid

1113 without elevation of the choline concentration was considered more
1114 consistent with infarct than with tumor.

1115 MRS was positive for neoplasm in 49 of the 78 patients. In eight of
1116 these 49 patients, MRS was classified as having a potential positive
1117 influence. These eight patients received radiation therapy, chemotherapy,
1118 or both, for a presumed neoplasm without a biopsy to confirm the presence
1119 of a tumor. MRS was negative for neoplasm in 29 of 78 patients. In 15 of
1120 these 29 patients, MRS was classified as having a potential positive
1121 influence.

1122 MRS was classified as having a potential negative influence on
1123 patient treatment in two of the 49 patients diagnosed as having neoplasm
1124 by MRS. One of these two patients underwent biopsy, which showed
1125 inflammatory reaction as probably being secondary to demyelination. The
1126 other patient underwent surgery and was found to have arteriovenous
1127 malformation. MRS had no influence on patient treatment in 37 patients
1128 diagnosed with brain tumor by MRS.

1129 Because of the nature of retrospective medical record review, there
1130 were several problems with this study. Fourteen of the 78 patients had
1131 incomplete follow-up information, two from the MRS- diagnosed “tumor”
1132 group and 12 from the MRS “non-tumor” group. The patients study were

1133 highly selected. The decision to perform MRS was based on CT and MRI
1134 results in which a neoplasm was considered to be the prime candidate in
1135 the differential diagnosis.

1136

1137 **3.5 Category- 5: Studies Conducted to Evaluate the Impact of**
1138 **Test on Health Outcomes**

1139 No study was identified for this category.

1140

1141 **3.6 Category 6: Studies Conducted to Evaluate the Use of Test**
1142 **on Societal impact**

1143 No study was identified for this category.

1144

1145 The following table summarizes our assessment of the Category-2 and
1146 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 generalizability |
| | 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? |

1147

| 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 |

1148

1149

1150

1151
1152 **4. RESULTS: Abstracts**

1153 As described above, abstracts and proceedings from following
1154 professional societies for the years 2001 and 2002 were reviewed:
1155 • ASNR-American Society of Neuroradiology
1156 • RSNA-Radiological Society of North American
1157 • ISMRM-International Society for Magnetic Resonance in Medicine

1158

1159 Because these were abstracts and not full papers, data on basic study
1160 design information such as patient gender and means of enrolling patients
1161 were frequently unavailable. Of the 241 proceedings-generated abstracts
1162 reviewed, 44 were provided information beyond the technical feasibility
1163 category. The following table summarizes the distribution of abstracts by
1164 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 |

1165 *One study shown in this category could also be considered a Category-3
1166 study.

1167

1168

1169 **4.1 Category-1 Abstracts: Technical Feasibility**

1170 Evidence Table 2 shows selected characteristics of the 44 technical
1171 feasibility (Category 1) abstracts. Similar to Evidence Table 1 containing
1172 technical feasibility studies, it summarizes: year of publication, country in
1173 which the research was conducted, study characteristics including number
1174 of diseased (cases) and non-diseased (control) patients, method of patient
1175 enrollment, diagnostic status, and age. The table also shows the size of
1176 the volume of tissue (voxel) of interest as well as whether single or multiple
1177 voxel sampling was used. Finally, the table indicates the principal clinical
1178 study objectives: tumor differentiation, tumor grading, distinguishing
1179 primary tumor tissue from recurrent tumor and from metastases, and
1180 identifying necrotic tissue. In addition, there were two instances where
1181 there were duplicate abstracts for the same studies from different
1182 proceedings.

1183

1184 There were forty-seven abstracts reviewed for Category 1 from 3
1185 different proceedings for 2001 and 2002. Forty-four unique studies
1186 remained after removing four duplicate studies. In addition, there were a
1187 minimum of four instances of overlapping population represented in the
1188 abstracts. The abstracts reported on 1,445 patients. One study reported on

1189 174 diagnostic ‘studies’ without mentioning the number of patients and one
1190 reported the results of 14 ‘studies’. Twenty studies (42.5%) were from the
1191 US. The ages of patients described in eight of the abstracts varied
1192 considerably; ranging was from 8 to 84 years. As in the complete studies
1193 reviewed, we excluded abstracts that were predominantly pediatric.

1194 Five studies were reported as prospective and five were
1195 retrospective. The remaining abstracts reported no data on study design.
1196 The largest sample reported in an abstract was 130 patients. Most
1197 abstracts did not include controls. Single voxel and multiple voxel sampling
1198 were used approximately equally. In six studies no voxel data were
1199 reported and in four a combination of both approaches were employed.

1200 Tumor differentiation (14 studies) and grading (10 studies) were the
1201 most frequently cited clinical objectives. Other clinical objectives varied
1202 widely such as characterization of metabolite ratios (six abstracts),
1203 prognosis (two abstracts), measure of lipid levels (two abstracts), and
1204 tumor response to treatment (two abstracts).

1205
1206
1207 **4.2 Category-2: Studies that Evaluate Test Performance**
1208
1209 The proceedings abstracts described eight studies in this category.
1210 Studies in this category could be further grouped into studies with the main

1211 purpose of differentiating tumors from non-tumors, grading of tumors,
1212 differentiating intracranial cystic lesions, and to assess the incremental
1213 value of MRS added to MRI.

1214

1215 **4.2.1 Abstracts of Category-2 Studies Differentiating Neoplasm**
1216 **from Non-neoplasm**

1217
1218 Yin et al. (2002) evaluated 40 lesions in 35 patients with suspected
1219 brain neoplasms or recurrent neoplasm. The purpose of this study was to
1220 measure the accuracy of multivoxel 3D MRS proton MRS in distinguishing
1221 neoplastic from non-neoplastic brain lesions (blinded vs. unblinded). Final
1222 diagnoses were assessed by clinical examination, biopsy and serial MRI.

1223 The specificity for distinguishing between neoplastic and non-
1224 neoplastic lesions was 88.6%. Of the 35 cases, 21 had neoplasms and 19
1225 had non-neoplastic lesions. Of 16 glioma, 14 were correctly identified
1226 through increased Cho and decreased NAA for the gliomas. The metabolic
1227 profiles of the following types of tissue were studied: abscess (increased
1228 Lac), metastasis (increased Cho and Lac and no NAA peak), demyelinating
1229 lesion (decreased NAA and normal Cho), lymphoma (high Cho and lipids),
1230 and necrosis (high Cho and decreased metabolism). There was also little
1231 diversity of lesions, no information about patient ages, no statistical

1232 analysis, and no comparative data. The study did, however, report a form
1233 of blinding, but no detail was provided.

1234 Herminghaus et al. (2002a) evaluated 293 consecutive patients
1235 diagnosed with focal brain lesions. The purpose of this study was to
1236 assess the potential of single voxel MRS (1.5 T Siemens Magnetom Vision)
1237 to differentiate between neoplastic and non-neoplastic lesions, between
1238 high grade tumors and metastases or lymphomas, and between different
1239 types of tumors. The authors studied 25 types of lesions.

1240 Discriminant analysis was used to “confirm significance” of
1241 differences between clusters formed by the authors. The analysis yielded
1242 five clusters: one containing glioblastoma (unknown grade), gliosarcoma,
1243 and embryonal tumors (IV WHO). A second cluster included anaplastic
1244 astrocytomas, anaplastic oligoastrocytomas, anaplastic
1245 oligodendrogliomas, anaplastic meningioma (WHO III), and lymphomas.
1246 The third cluster included glial low grade tumors, gangliogliomas,
1247 gangliocytomas, neurominomas, and glioses and abscesses. The fourth
1248 cluster contained tumor necrosis, tumor cysts, infectious cysts, and
1249 meningiomas. The fifth cluster contained metastasis, glioblastoma,
1250 gliosarcoma, and embryonal tumor grade IV WHO. The authors concluded
1251 that MRS can be helpful in differentiating:

1252

- 1253 • Low grade from high grade tumors
- 1254 • Metastasis and lymphomas from benign or low grade tumors
- 1255 • Abscesses from glioblastoma and metastasis
- 1256 • Silent infarct from low grade tumors
- 1257 • Tumor cysts, infectious cysts, and necrotic tissue from each other and
1258 from other lesions
- 1259 • WHO I/II meningiomas from metastasis

1260

1261 The authors concluded MRS could not distinguish:

- 1262 • Between different tumor types of the same grade.
- 1263 • Lymphomas from grade III tumors
- 1264 • Metastasis from glioblastoma
- 1265 • Low grade brain tumors from gliosis

1266

1267 “Success rates” were reported for the above classifications, but the
1268 level of detail provided in the abstract is insufficient for meaningful
1269 interpretation of these statistics. Finally, the fact that this study did not
1270 describe the standard against which the focal brain tumors were
1271 diagnosed, makes it difficult to interpret its conclusions.

1272

1273 **4.2.2. Abstracts of Category-2 Studies Detecting Tumor**

1274 **Recurrence**

1275 Kovanlikaya et al. (2002) prospectively examined 16 lesions in seven
1276 men and seven women (mean age 50 yrs) to determine the value of multi-
1277 voxel MRS (1.5 T; 1 cm³ spatial resolution) of glial neoplasms in detecting
1278 tumor recurrence after treatment with surgical excision, radiotherapy, and
1279 chemotherapy. The neoplasms included 12 astrocytomas, one
1280 oligodendrogloma and three mixed tumors of Grade II (5), Grade III (5) and
1281 Grade IV (6). Voxels showing the highest choline levels were analyzed for
1282 levels of NAA, creatine and lactate/lipid values and compared to the
1283 matched contralateral normal side of the brain. The results were assessed
1284 pathologically (6 lesions) and clinically (10 lesions).

1285 Tumor recurrence was observed in eight of the 14 patients. Choline
1286 levels were much higher (114% elevation) in the recurrent lesions, with
1287 much lower levels in stable patients (7% depression). Choline elevation
1288 had a high sensitivity for detecting tumor recurrence (100%; positive
1289 predictive value = 82%). The specificity of choline depression for detecting
1290 stability was 72% (negative predictive value = 100%). The authors, despite
1291 the small numbers, also suggested that the lactate/lipid peak in three

1292 patients was highly specific for detecting necrosis but not sensitive for
1293 detecting recurrence. There was no independent verification of the results.

1294 Lefkowitz et al. (2002) prospectively examined 27 lesions in 22
1295 patients whose brain tumors had been surgically excised and/or irradiated
1296 to evaluate MRS' usefulness for diagnosing recurrent neoplasms. Single
1297 and multivoxel MRS was used to obtain maps of NAA and Cho
1298 concentration, ratio maps of Cho/Cr peak areas and heights, and tables of
1299 Cho/Cr ratios to identify potential tumor-containing voxels. A Cho/Cr ratio
1300 greater than or equal to 2.0, behavior of control voxels, and other spectral
1301 features were considered for tumor/non-tumor designations. Biopsy or
1302 follow-up imaging was used to confirm tumor status.

1303 For the 27 MRS results, there were 19 gliomas, five metastases, two
1304 lymphomas, and one medulloblastoma. Sensitivity for detecting tumor
1305 recurrence was 89% (positive predictive value = 73%). Specificity was 33%
1306 (negative predictive value = 60%). Overall accuracy was 70%. Tests of
1307 statistical significance and confidence intervals were not reported. There
1308 was no independent verification of results.

1309 Shah et al. (2002) assessed how well MRS performed in identifying
1310 tumor recurrence compared to SPECT and CT/MRI. These authors studied
1311 nine patients who had undergone surgery and radiotherapy or radiotherapy

1312 alone for an average of 28 months with tumors suspected of recurrence.
1313 The tumors comprised: oligodendro glioma II (two); oligodendro glioma III
1314 (one); anaplastic astrocytoma (two); malignant mixed glioma (one);
1315 astrocytoma II (two); and glioblastoma multiforme (one). Choline spectra
1316 derived from MRS (1.5 T Siemens) sequence voxels ranging from 1.3 ml to
1317 3.8 ml were used as markers for recurrence and were compared with
1318 radiological and SPECT results.

1319 The kappa (κ) measure of agreement was calculated between MRS
1320 and each of the other two tests. The results were: MRS vs. SPECT
1321 ($\kappa=0.72$), MRS vs. CT/MRI ($\kappa=0.57$) and CT/MRI vs. SPECT ($\kappa=0.37$).
1322 There was no biopsy confirmation of tumor recurrence and therefore no
1323 'reference standard'. In addition, the sample size was small, and no tests of
1324 statistical significance or confidence intervals were reported.

1325 Lichy et al. (2002) examined the value of MRS, FDG-PET, and IMT-
1326 SPECT in evaluating suspicious brain lesions detected by MRI follow-up of
1327 24 patients with irradiated gliomas. Multivoxel 2D MRS (1.5 T; voxel size =
1328 $8.8 \times 8.8 \times 15 \text{ mm}^3$) was used to obtain relative signal intensity ratios of
1329 Cho, Cr, and NAA. Eighty-six voxels from suspicious lesions and 147 from
1330 'normal' areas were analyzed. Clinical and MRI/CT follow-up, not biopsy,
1331 was used to classify lesions as neoplastic or non-neoplastic.

1332
1333 This study reported that the true positive rate (it is assumed that
1334 surgery was the standard of comparison) for identifying neoplastic tissue
1335 was 88% for MRS, 73% for FDG-PET, and 100% for IMT-SPECT. The
1336 true positive rate for identifying non-neoplastic tissue was 89% for MRS,
1337 100% for FDG-PET and 75% for IMT-SPECT. Cho and Cho/NAA were
1338 present in significantly higher levels in neoplastic tissue. Additional
1339 information about sensitivity and specificity were reported, but the
1340 performance outcomes being evaluated were unclear. In this study three
1341 diagnostic techniques were compared only to each other and not to either
1342 biopsy or surgical results. In addition, there was no independent verification
1343 of results, and no confidence intervals for diagnostic test performance
1344 were reported.

1345
1346 **4.2.3 Abstracts Of Category-2 Studies Distinguishing**
1347 **Homogeneity, Proliferation, And Grade Of Lesions**
1348 Herminghaus et al. (2001a) prior to biopsy evaluated 29 consecutive
1349 patients with MRI results and history suggestive of neuroepithelial brain
1350 tumors. The purpose of the study was to evaluate MRI's ability to
1351 distinguish low from high-grade tumors. Single voxel MRS (1.5 T) was

1352 used to evaluate tumor tissues as well as normal appearing brain tissue in
1353 the contralateral hemisphere. NAA, total creatine, Cho, Lip, and Lac were
1354 analyzed. Tumor spectroscopic data were classified (“observer-
1355 independently”) as grade I/II or III/IV according to the World Health
1356 Organization system. Biopsies were performed and confirmed by following
1357 patients for three years. Tumors showing at least 6 months of stability were
1358 defined as low-grade; those tumors showing progression were classified as
1359 high-grade.

1360 While the authors reported sensitivity (100%), specificity (86%), and
1361 overall accuracy (96%), it is not clear what the reference standard was.
1362 Since the authors also report sensitivity (95%), specificity (86%), and
1363 overall accuracy (93%) for biopsy, it may be inferred that biopsy was not
1364 the reference standard. It is possible that surgery was the reference
1365 standard, but the study does not mention whether or how frequently
1366 surgery was performed. This ambiguity makes it difficult to assess the
1367 meaning of these findings. In addition, there was no independent
1368 verification of results. (This study might also be classified as Category 3).
1369

1370 **4.3.1 Abstracts of Category-3: Studies Conducted to Evaluate**
1371 **Diagnostic Thinking Impact**

1372 Mao et al., (2002) evaluated the utility of single voxel MRS (1.5 T
1373 Phillips NT scanner) to guide selection of biopsy target areas in eight
1374 patients with a previous biopsy yielding equivocal results. This study might
1375 be considered as providing information for thinking about diagnostic impact.
1376 Areas of decreased NAA and elevated Cho and Lac were identified so that
1377 NAA and Cho maps could be used to target these areas as potential biopsy
1378 sites. The maps were superimposed on the stereotactic anatomical image
1379 to develop coordinates for the sites. Biopsies were then performed,
1380 followed by either CT or MRI.

1381 MRS results showed abnormal metabolite maps for all eight patients,
1382 with seven showing decreased NAA and increased CHO. Biopsy sites were
1383 chosen from areas showing the most elevated CHO levels, and the
1384 biopsies were positive for seven of the eight patients. Tumor types
1385 included: two anaplastic astrocytomas (III); glioblastoma multiforme (IV);
1386 two infiltrative astrocytomas (II); oligodendrogioma (II).

1387
1388 While the study described in this abstract shows the technical
1389 feasibility of using MRI to help select the site of biopsy, the sample size of

1390 eight was small, with no statistical analysis (it mentions a ‘significant’
1391 decrease in NAA and increased CHO, but no quantitative data to support
1392 this is presented in the abstract). In addition, there was no comparison
1393 group of patients with non-MRS guided biopsy and there was no
1394 independent verification of the results.

1395

1396

1397 **5. SUMMARY**

1398 Ninety-six articles met our inclusion criteria for evaluation, with
1399 11 providing information beyond the level of technical feasibility. Eight
1400 articles evaluated the test performance of MRS in various settings. Three
1401 articles addressed the impact of MRS on diagnostic thinking and
1402 therapeutic decision making. No article was found that addressed
1403 improvement of patient outcome.

1404

1405 **5.1 For what metabolite profiles does MRS provide equivalent,
1406 complementary, or more accurate diagnostic information?**

1407 The following table summarizes the peak intensities and ratios of
1408 metabolites evaluated in Category-2 and higher studies.

1409

1410 Category 2 and higher studies that reported metabolite profiles

| Study | Category | Qualitative interpretation | Quantitative measurements | | | | | | | | | | | | | | |
|-----------------|----------|----------------------------|---------------------------|----|-----|-----|-----|----------|--------|--------|--------|---------|---------|--------|--------|------------------|----------------|
| | | | Individual metabolites | | | | | | Ratios | | | | | | | | |
| | | | Cho | Cr | NAA | Lac | Lip | Gl or MI | MGG | Cho/Cr | NAA/Cr | Cho/NAA | NAA/Cho | Lac/Cr | Lip/Cr | Cho/(Lip or Lac) | Gl/Cr or MI/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 | | |

1411

1412 These profiles represent a very heterogeneous mix of signals and
 1413 ratios, study populations, study purpose, and results. Some of the signals
 1414 and ratios were unique for a particular study. For example, Butzen et al.
 1415 used a Cho/NAA ratio of greater than 1.0 to classify lesions as tumors for
 1416 initial diagnosis and reported a sensitivity of 79% and specificity of 77%. No
 1417 other study used this metabolite ratio; therefore their results could not be

1418 verified. The most common ratios evaluated were Cho/Cr and NAA/Cr,
1419 which were reported in five studies. With so little data and many questions,
1420 the above question could be answered only to a very limited extent.

1421 Cho/Cr is the only metabolite ratio that has been found to be useful
1422 in differentiating neoplasm and non-neoplasm and supported by several
1423 studies. Among all the full articles examined in this technology assessment,
1424 Moller-Hartmann et al. provided the most complete reporting of the
1425 metabolite signal intensities and ratios for each type of tumor found in their
1426 study population. However, no single metabolite or ratio, other than
1427 perhaps a very high Cho/Cr ratio to diagnose PNET, by itself could
1428 differentiate among different neoplasms, among different tumor grades, or
1429 between neoplastic and non-neoplastic lesions. A moderately high Cho/Cr
1430 ratio of approximately four was observed for astrocytoma grade IV and
1431 metastases, compared to a value of approximately 1.5 for cerebral
1432 infarctions and abscesses. Kimura et al. also reported that a Cho/Cr ratio of
1433 2.48 minimized the rate of misdiagnosis of neoplasm and non-neoplasm.
1434 Lin et al. reported that the Cho/Cr ratio was the single most accurate
1435 spectral measurement for differentiating neoplastic from non-neoplastic
1436 lesions. Unfortunately, the results were presented only as a bar graph.

1437 In the only study that addressed the incremental diagnostic yield,
1438 Moller-Hartmann et al. demonstrated that MRS added to conventional MRI
1439 improved the number of correct diagnoses and reduced the number of
1440 incorrect or equivocal diagnoses.

1441

1442 **5.2 Does The Use Of MRS Lead To An Improved Net Health**
1443 **Outcome?**

1444

1445 Three studies addressed the potential impact of MRS results on
1446 diagnostic thinking or therapeutic decision making. Conclusions that can be
1447 drawn from these studies are severely limited due to the fact that the two
1448 prospective studies had only 15 and 17 patients, respectively, and the only
1449 large study was a retrospective analysis of medical records to identify
1450 potential opportunities for MRS to influence diagnostic thinking.

1451

1452 **5.3 Are Voxel Positions And Operator Error Important Factors In**
1453 **Obtaining Diagnostic Images? If So, How Do They Impact MRS**
1454 **Accuracy?**

1455 No study explicitly evaluated the impact of voxel position on the
1456 accuracy of MRS. The retrospective study by Kimura et al. came closest to
1457 this objective. This study evaluated the differences of measurements
1458 between the whole lesion and the inner region of the same tumor.

1459 Significant differences between the inner region and the whole lesion were
1460 found for various types of lesions. Although not specifically reported, the
1461 voxel sizes of the inner regions obviously were smaller than those of the
1462 whole lesions.

1463 No study commented on the potential impact of operator error in
1464 placement of the voxel.

1465

1466 **5.4 Strengths And Weaknesses Of The Studies**

1467 Most of the studies on Proton MRS were Category- 1 studies that
1468 addressed technical feasibility. The stated purpose of some of the studies
1469 classified as technical feasibility studies was to examine the impact of MRS
1470 on practice, but limitations of these studies' designs kept them from
1471 meeting the criteria necessary to achieve that level. Most of the studies we
1472 evaluated in categories 2 to 4 concluded that MRS has value for the
1473 indications studied. One study (Rand et al. 1997), which measured the
1474 accuracy of single-voxel, image-guided proton MRS in distinguishing
1475 normal from abnormal brain tissue and neoplastic from non-neoplastic
1476 brain disease, was an excellent example in some respects of the type of
1477 study needed to assess diagnostic efficacy. The use of multiple blinded
1478 readers and ROC analyses should be encouraged. Detailed presentation of

1479 quantified spectra intensities and ratios similar to those reported in the
1480 article by Moller-Hartmann et al. would help the interpretation of results
1481 across studies.

1482 Sample size is also an important limitation. Sample sizes that might
1483 be adequate for investigating one type of tumor are not necessarily
1484 adequate for investigating multiple types of tumors in the same study. This
1485 applies to tumor grades as well.

1486 In summary, while there are a large number of studies that confirm
1487 MRS' technical feasibility, there are very few published studies to evaluate
1488 the diagnostic accuracy and whether it can positively affect diagnostic
1489 thinking and therapeutic choice. Those studies that do address these areas
1490 often have significant design flaws including inadequate sample size,
1491 retrospective design and other limitations that could bias the results.

1492

1493 **5.5 Implications for future research**

1494 The relative rarity of brain tumors, the relatively low installed base of
1495 MRS software and the constraints of clinical practice have precluded the
1496 establishment of large, double-blinded controlled trials that would go
1497 beyond exploring technical feasibility. Experience with MRS has only
1498 become available to the general community of radiologists within the past

1499 five years. Prior to this time, commercial software for shimming and
1500 analyzing spectra was not reliable, except in the hands of trained
1501 specialists. The current commercial software is vastly improved and can be
1502 mastered with a reasonable amount of additional training. Prior to about
1503 1995, MRS was available at only a few research-oriented institutions.
1504 Hence studies were typically single institution feasibility studies or small
1505 case series. The recent change in the availability of MRS is only now
1506 reaching enough centers to allow more advanced investigations using the
1507 technique. MRS is still not available in many community hospitals, and
1508 even some academic centers.

1509 The reason that the research is not more advanced may be that in
1510 addition to the relatively recent availability of MRS, its use in brain tumor
1511 evaluation evolved by using techniques that were not straightforward.
1512 Initially, it was hoped that tumors would have a characteristic “signature”
1513 that would allow rapid MRS diagnoses. Because the sensitivity of MRS
1514 allows demonstration of only a limited set of chemical compounds in the
1515 brain, such signatures have not been found. However, means of using the
1516 chemical information that is provided by MRS for tumor evaluation has
1517 progressed as new ideas have evolved for effective use of this information.

1518

1519 **6. CONCLUSION**

1520

1521 Human studies conducted on the use of MRS for brain tumors

1522 demonstrate that this non-invasive method is technically feasible and
1523 suggest potential benefits for some of the proposed indications. There is a
1524 paucity of high quality direct evidence demonstrating the impact on
1525 diagnostic thinking and therapeutic decision making. In addition, the
1526 techniques of acquiring the MRS spectra and interpreting the results are
1527 not well standardized. The table below summarizes the current state of
1528 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

| <i>Newly Diagnosed Space-Occupying Brain Mass* Identified By CT or MRI</i> | <i>Follow-Up Of Patients with Previously Diagnosed Brain Tumor Undergoing Treatment</i> |
|--|---|
| Potential use of MRS in diagnostic evaluation and prognostication | |
| <ul style="list-style-type: none"> • Replacement of diagnostic biopsy by MRS <ul style="list-style-type: none"> ◦ <i>Outcome measure: same or improved accuracy/less invasiveness</i> • Differentiating masses <ul style="list-style-type: none"> • 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) • <i>Outcome measure: Higher sensitivity and specificity in differentiating masses</i> • MRS-guided biopsy to improve biopsy yield <ul style="list-style-type: none"> • <i>Outcome measure: Success rate of MRS-guided biopsies</i> • Tumor grading: degree of malignancy <ul style="list-style-type: none"> • <i>Outcome measure: % of inappropriate biopsies avoided; biopsy yield</i> | <ul style="list-style-type: none"> • Determining whether tumor has recurred • Differentiate recurrence from radiation injury (necrosis) • <i>Outcome measure: Higher sensitivity and specificity in differentiating masses</i> • MRS-guided biopsy to improve biopsy yield • <i>Outcome measure: Success rate of MRS-guided biopsies</i> |
| Potential use of MRS in patient management | |
| <ul style="list-style-type: none"> • Planning treatment <ul style="list-style-type: none"> ◦ Choosing among therapies ◦ Identifying tumor margin and volume for radiosurgery planning/surgical resection ◦ Identifying tumor margin and volume for radiotherapy (gamma knife therapy) planning ◦ Identifying target volume (isolating most active portions of tumor) for radiosurgery | <ul style="list-style-type: none"> • Re-initiating radiosurgery when recurrence differentiated from necrosis • Rapidly assessing treatment effectiveness to optimize treatment <ul style="list-style-type: none"> ◦ Monitor response to treatment • <i>Outcome measures: survival, quality of life</i> |

| <i>Newly Diagnosed Space-Occupying Brain Mass* Identified By CT or MRI</i> | <i>Follow-Up Of Patients with Previously Diagnosed Brain Tumor Undergoing Treatment</i> |
|---|---|
| <ul style="list-style-type: none"> planning ◦ Tumor grading: timing interventions • <i>Outcome measures: survival, quality of life</i> | |
| Factors potentially affecting MRS performance | |
| <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 |

1533

1534

APPENDIX B: Glossary

1535 **Cho** – choline

1536 **cm³** – cubic centimeter

1537 **Cr** – creatine and phosphocreatine

1538 **CT** – computed tomography

1539 **Gl** – glycine

1540 **Lac** – lactate

1541 **Lip** – lipid

1542 **MGG** – macromolecules, glutamine, and glutamate

1543 **MI** – myo-inositol

1544 **MR** – magnetic resonance

1545 **MRI** – magnetic resonance imaging

1546 **MRS** – magnetic resonance spectroscopy

1547 **NAA** – N-acetyl-aspartate

1548 **ODV** – orthonormal discriminant vector

1549 **PET** – positron emission tomography

1550 **PNET** – peripheral neuroectodermal tumor

1551 **ROC** – receiver operating characteristic

1552 **VOI** – volume of interest

1553 **Tesla** – unit of magnetic flux

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

| Author | UI | Publ Yr | Country | Study characteristics | | | Technique | Study objective(s) | | | | | | | |
|-------------|-----------|---------|-----------------|-----------------------|-----------|--------------|-----------|--------------------|-------------|---------------------------------------|-------------------------------------|-------|------------|-----------------------------|--------|
| | | | | Study design | N (cases) | N (controls) | | Enrolment | Dx status | Mean Age range | Vessel volume (cm ³) | S/I M | Turnaround | Turnaround Mean or ratio | Biopsy |
| Alger | 2243962 | 1990 | US | p | 40 | 0 | u | k | 42; 18-81 | 27 | s | x | x | x | |
| Barba | 11147598 | 2001 | England | p | 27 | 0 | u | k | ND | 2x2x2 | s | x | x | x | |
| Bastianelli | 10932439 | 1993 | US | u | 19 | 0 | u | k | 24; 29 | 2x2x3 | s | x | x | x | |
| Bruhn | 2746837 | 1989 | Germany | p | 9 | 0 | u | k | 33-61 | 3x3x3 | s | x | x | x | |
| Burnscher | 10689230 | 2000 | Sweden | p | 26 | 0 | u | k | 52; 31-80 | 1.5x1.5x1.5-2 / 3x4x1.5 - 10x6x1.5 | s/m | x | x | x | |
| Castello | 11035943 | 2000 | US | p | 34 | 5 | 1 | u | k | 53.4; 16-73 | 8x8x5 | s | x | x | x |
| Chang | 9541269 | 1998 | Korea | p | 39 | 0 | 1 | k | 43; 26-60 | 2x2x2 | s | x | x | x | |
| Chumas | 9219744 | 1987 | Scotland | p | 9 | 0 | u | k | 54 | 21 | s | x | x | x | |
| Croiseu | 11564242 | 2001 | US | p | 31 | 0 | u | k | >17 | 0.8 | m | x | x | x | |
| Denehael | 1846152 | 1991 | Belgium | p | 50 | 0 | u | k | 53.4; 16-73 | 8x8x5 | s | x | x | x | |
| Doucet | 10932438 | 1993 | UK | p | 3 | 0 | u | k | 50-60 | 11x11.5 | m | x | x | x | |
| Downing | 11230468 | 2001 | US | p | 29 | 0 | u | k | 16-68 | 1 | m | x | x | x | |
| Eisner | 9457810 | 1986 | France | p | 11 | 0 | u | k | 30-63 | 1x0.5x2 | s | x | x | x | |
| Falini | 6923303 | 1998 | Italy | p | 70 | 0 | u | M | ND | 8 | s | x | x | x | |
| Fournier | 11251398 | 2000 | US/Greece | p | 120 | 0 | u | k | 61.3; 29-78 | 8 | s | x | x | x | |
| Frahm | 9204294 | 1991 | Germany | p | 19 | ~300 | studies | u | k | ND | 2-8 | s | x | x | x |
| Fujihara | 1438744 | 1992 | US | r | 50 | 0 | u | k | 43; 16-76 | 0.675-2.0 | m | x | x | x | |
| Furuya | 9251112 | 1992 | Japan | r | 17 | 0 | u | k | ND | 8 | m | x | x | x | |
| Gadomski | 12230467 | 2001 | Poland | p | 9 | 0 | u | k | 52-60 | ND / 1x1.5x1.5 | m | x | x | x | |
| Go | 7603595 | 1991 | The Netherlands | u | 32 | 0 | u | k | ND | 3x3x1.1 | m | x | x | x | |
| Go | 9416313 | 1991 | The Netherlands | u | 18 | 0 | u | k | ND | 3x3x1.1 | m | x | x | x | |
| Gobis | 8694527 | 1990 | Greece | u | 76 | 0 | u | k | ND | 2-8 | s | x | x | x | |
| Graves | 10890720 | 2000 | US | p | 36 | 0 | u | k | 45.5; 24-68 | 1 | m | x | x | x | |
| Graves | 11230467 | 2001 | US | p | 18 | 0 | u | k | 24-62 | 1 | m | x | x | x | |
| Gupta | 10055604 | 1995 | US | r | 20 | 0 | n/a | k | 27-68 | 1x1x1.2 | m | x | x | x | |
| Gupta | 1263591 | 2000 | US | p | 18 | 0 | u | M | 28-62 | 1x1x1.2 | m | x | x | x | |
| Häggberg | 12230467 | 2001 | Switzerland | p | 32 | 0 | u | k | 26-68 | 8-18 | s | x | x | x | |
| Hall | 10853173 | 1998 | US | p | 10 | 0 | u | k | ND | ND | u | x | x | x | |
| Harada | 95283377 | 1993 | Japan | p | 25 | 0 | u | k | ND | 15.6 | s | x | x | x | |
| Heestern | 8120569 | 1993 | The Netherlands | u | 11 | 0 | u | k | ND | 27 cc / 9 cc / 1 | s/m | x | x | x | |
| Heestern | 1641922 | 1990 | The Netherlands | p | 90 | 0 | u | k | 29-66 | 1 | m | x | x | x | |
| Heijnen | 11230467 | 2001 | US | p | 90 | 0 | u | k | ND | 4.2 - 12.7 | s | x | x | x | |
| Henrikson | 2021809 | 1991 | Denmark | p | 17 | 0 | u | k | 49; 24-77 | 3x3x3 | s | x | x | x | |
| Houkin | 7761009 | 1995 | Japan | u | 11 | 0 | u | k | ND | 2x2x2 - 3x3x3 | s | x | x | x | |
| Howe | 12541241 | 2003 | UK | p | 42 | 8 | u | n | ND | 4-8 | s | x | x | x | |
| Hultsch | 10853173 | 1998 | US | p | 65 | 0 | u | k | ND | 18-60 | s | x | x | x | |
| Ikebara | 8848553 | 1995 | Japan | p | 16 | 3 | u | k | 46.4; 14-71 | 8-27 | s | x | x | x | |
| Ishimaru | 11511902 | 2001 | Japan | p | 56 | 0 | u | k | 55.8; 12-81 | 1.3x1.3x1.3 - 1.5x1.5x1.5 | s | x | x | x | |
| Itoh | 12165353 | 2002 | Japan | p | 23 | 7 | u | k | 20-26 | 2.2 - 31.5 | s | x | x | x | |
| Kanda | 11230467 | 2001 | Japan | p | 10 | 0 | u | k | 12-27 | 2x2x2 - 3x3x3 | s | x | x | x | |
| Kaneda | 2029655 | 1997 | Japan | p | 11 | 20 | 1 | u | ND | 8-24 | s | x | x | x | |
| Kaneda | 11412868 | 2001 | Germany | p | 7 | 10 | u | k | 37-81 | 1.25x1.25x1.5 | m | x | x | x | |
| Kaneko | 11398738 | 2001 | Japan | p | 25 | 0 | u | k | 13-82 | 1.2x1.2x1.2 - 1.5x1.5x1.5 | s | x | x | x | |
| Kim | 9205254 | 1998 | Korea | p | 14 | 0 | c | k | 25-43 | 2x2x2 | s | x | x | x | |
| Kimura | 9205257 | 1998 | Korea | p | 12 | 0 | u | k | 50-62 | 1 | s | x | x | x | |
| Kiku | 9508276 | 1998 | Japan | u | 6 | 0 | n | k | 50, 13-63 | 0.38-0.47 | m | x | x | x | |
| Kugel | 1584924 | 1993 | Germany | p | 36 | 27 | u | k | 27-81 | 8-18 | s | x | x | x | |
| Lankowski | 2607903 | 1989 | Germany | p | 16 | 0 | u | k | 22-74 | 4-20 | s | x | x | x | |
| Li | 10853173 | 1998 | US | p | 8 | 0 | u | k | 51.4; 15-80 | 1x1x1.5 - 1.5x1.5x1.2 | s | x | x | x | |
| Lin | 11564279 | 2001 | US | p | 49 | 14 | 1 | u | k | 50 | 1.5x1.5x1.2 | s/m | x | x | x |
| Luan | 10326955 | 1998 | China | p | 13 | 0 | u | k | 42; 13-68 | 2x2x2 | s | x | x | x | |
| Maeder | 97029398 | 1996 | Switzerland | p | 17 | 7 | u | n | 50.3; 20-74 | 8 / 3.4-4.5 | s/m | x | x | x | |
| Magill | 12594562 | 2003 | Spain | p | 25 | 0 | c | u | ND | 1.5 - 2 | s | x | x | x | |
| Marin | 10853173 | 1998 | US | p | 20 | 0 | u | k | ND | 1.5x1.5x1.5 | s | x | x | x | |
| McBride | 7502203 | 1993 | US | p | 23 | 16 | u | k | ND | 27 | s | x | x | x | |
| McNaught | 111686821 | 2001 | US | p | 30 | 14 | u | k | 42 | 1 | m | x | x | x | |

Types of tu

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

| Author | UI | Pub Yr | Country | Study characteristics | | | | | Technique | Study objective(s) | | | | |
|-----------|----------|--------|-----------------|-----------------------|-----------|-----------|------------|-----------|-------------|---------------------------------|-------|------------|---------------|----------------|
| | | | | Study design | N (cases) | N (ctrls) | Enrollment | Dx status | | Voxel volume (cm ³) | S / M | Tumor diff | Tumor grading | Recur vs Prim. |
| 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

| Author | Proceedings | Pub Yr | Country | Study design | Study characteristics | | | Mean Age, range | Technique | Study objective(s) | | | | | |
|--------------------------|---------------|--------|-----------|--------------|-----------------------|-----------|------------|-----------------|-------------------|-----------------------------|------------|---------------|----------------|----------------|----------|
| | | | | | N (cases) | N (ctrls) | Enrollment | Dx status | | S / M | Tumor diff | Tumor grading | Recur vs Prim. | Met vs Primary | Necrosis |
| 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 |
| L ⁴ | ISMRM | 2001 | US | u | 18 | 0 | u | M | ND | ND | s/m | x | | | |
| L 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.