Magnetic Resonance Spectroscopy as an Imaging Tool for Cancer: A Review of the Literature

Naishadh Shah, DO, MBA; Ayesha Sattar, BS; Michael Benanti, DO; Scott Hollander, DO; and Lanna Cheuck, DO

Objectives: To review the use of magnetic resonance spectroscopy (MRS) as a clinical tool in the identification of cerebral neoplasia type and grade, as well as neoplasia in the prostate, colon, breast, cervix, pancreas, and esophagus. Also, to review how clinicians are using MRS for surgical planning and longitudinal evaluation of tumors after treatment.

Data Sources: Studies and clinical case reports published within the previous 10 years, targeting publications in radiology and oncology journals within the previous 3 years. Sources identified via MEDLINE and PubMed databases.

Study Selection: Studies that contrasted MRS with conventional diagnostic and prognostic methods were considered to yield the most relevant data for this review. Studies discussing cancer staging and grading were also examined to help determine clinical significance of MRS.

Data Syntheses: A review of the literature reveals that, although MRS has mainly been used in diagnostics and tumor evaluation for brain cancer, it is becoming an increasingly important adjunct to conventional diagnostic and monitoring procedures for cancer of the prostate, colon, breast, cervix, pancreas, and esophagus.

Conclusions: The clinical usefulness of MRS has yet to be fully substantiated. As MRS availability and access increase, appropriate evaluations of its strengths and weaknesses will be made. The authors conclude that research to date and primary observation indicate that MRS is a promising clinical tool for oncologic management of patients.

From Wilhelm Roentgen’s discovery of the form of electromagnetic radiation known as x-rays in 1895 to the modern development of mobile magnetic resonance imaging (MRI) systems, biomedical imaging technology has made great leaps in the past 110 years. The role of biomedical imaging has evolved from diagnostics and guiding therapy to longitudinal evaluation of treatment response. Among the most recent radiologic developments in biomedical imaging is magnetic resonance spectroscopy (MRS), which is also known as nuclear magnetic resonance spectroscopy. Magnetic resonance spectroscopy is an application of MRI that provides chemical information about tissue metabolites. The first clinical uses of MRS came in the 1980s. Since then, patients with brain cancer have become the primary focus of MRS applications. However, the scope of MRS has been expanded to the classification and diagnosis of cancers in other regions of the body, including the prostate, colon, breast, cervix, pancreas, and esophagus.

The biomedical images produced with MRS are the result of an interaction between atomic nuclei and magnetic fields. This phenomenon is superficially similar to the conventional application of MRI, but the key difference involves the substance being detected. Conventional MRI detects the nuclear magnetic resonance spectra of water in tissues, thereby producing an illustration of gross internal anatomy. Magnetic resonance spectroscopy, on the other hand, generally detects the resonance spectra of chemical compounds other than water, allowing for a true depiction of in situ chemistry.

In MRS, a magnetic nuclear isotope—such as carbon 13 (13C), deuterium (2H), fluorine 19 (19F), hydrogen 1 (1H), phosphorus 31 (31P), sodium 23 (23Na), or tritium (3H)—absorbs radio frequency energy when placed in a magnetic field. This energy absorption causes the resonance of the nuclei of the atoms in the chemical compound being examined. Because different atoms resonate at different frequencies, the resonance frequency reveals structural information about the chemical compound.

Methods

A review of the literature was conducted to evaluate the use of MRS as a clinical tool in the identification of cerebral neoplasia type and grade, as well as neoplasia in the prostate, colon, breast, cervix, pancreas, and esophagus. This review also examined how clinicians are using MRS for surgical planning and longitudinal evaluation of tumors after treatment.

Studies and clinical case reports published within the previous 10 years were reviewed, targeting articles that appeared in radiology and oncology journals within the pre-
STUDENT CONTRIBUTION

Interpretation of Brain Metabolites Detected by 1H-Magnetic Resonance Spectroscopy

- **Choline**—High levels indicate increased cellular activity and proliferation among glial cells. Because glial cells are involved in protective and restorative functions, increased glial activity implies a process reactive to a neoplasm.

- **Creatine**—Elevated levels are more consistent with tumor cells than with normal cells.

- **Lactate**—Increased levels indicate tumor metabolism. Neoplasms tend to consume glucose using only anaerobic pathways, thus producing increased lactate levels.

- **Myo-inositol**—High levels indicate glial hypertrophy and proliferation, implying a process reactive to a neoplasm.

- **N-Acetylaspartate**—Reduced levels indicate neuronal damage or functional degeneration.

Figure 1. Alterations in the chemical signals of metabolites detected by hydrogen 1- (1H-) magnetic resonance spectroscopy can be used to identify specific tissue properties of brain neoplasms. Physicians can use this information to make clinical evaluations of the neoplasms.

Previous 3 years. Sources were identified via the United States National Library of Medicine’s MEDLINE and PubMed databases using the keywords cancer imaging, magnetic resonance imaging, neurooncology, nuclear magnetic resonance, and spectroscopy. Studies that contrasted MRS with conventional diagnostic and prognostic methods were considered to yield the most relevant data for this review. Studies evaluating cancer staging and grading were also examined to aid in determining the clinical significance of MRS.

Major Applications of Magnetic Resonance Spectroscopy

The following sections review the major applications of MRS in diagnostic and monitoring procedures for patients with cancerous conditions of the brain, prostate and colon, breast, cervix, pancreas, and esophagus.

**Brain**

The most developed use of MRS to date has been in the study of brain cancer. Early MRS studies of brain cancer relied on the resonance frequency of 31P to obtain structural information on metabolites, but 1H has now become the universal “gold standard” in clinical neurology because of the better volume resolution it offers. In addition, 1H-MRS is compatibility with most standard MRI scanners. The use of 1H-MRS allows researchers to gather data quantifying neuronal loss and demonstrating reversible neuronal damage. This data can then be analyzed and applied to the study of various neurologic conditions, including epilepsy; multiple sclerosis; cerebrovascular, neurodegenerative, and metabolic diseases; and neurologic disorders associated with human immunodeficiency virus type 1 (HIV-1). This same technology can also be used to study neuronal development in the brains of fetuses and children.

Beyond the research opportunities in neuroscience that MRS technology provides, MRS has also been suggested as a clinical tool to identify types and grades of cerebral neoplasms. Preul et al. have described the potential of MRS to improve neurosurgical planning because of its ability to display in fine detail the sizes, dimensions, and locations of neoplasms in the brain. Clinicians are also beginning to realize the advantages of using MRS for longitudinal evaluations of brain tumors in patients after treatment.

Access to MRS technology, along with sufficient knowledge of neoplasm metabolism, can help clinicians evaluate brain tumors because MRS is sensitive to alterations in the chemical signals of various metabolites, including choline, creatine, lactate, myo-inositol, and N-acetylaspartate. Figure 1 shows how the levels of these metabolites, as determined by 1H-MRS, are interpreted to identify the cellular activity and other tissue properties of brain neoplasms. Figure 2 demonstrates normal metabolite levels revealed by MRS of one area of a patient’s brain. These levels can be compared with those in Figure 3, which focuses on another area of the patient’s brain, revealing metabolite levels indicative of recurrent glioma and radiation necrosis.

**Prostate and Colon**

Advancements in MRS have extended into diagnostic procedures for patients with possible cancer of the prostate and colon. Traditionally, histopathology has played the central role in determining the diagnosis of prostate cancer, but the efficacy of this method in predicting patient outcomes is limited. Magnetic resonance spectroscopy can serve as a complement to histopathology, because it is able to consistently distinguish between idle prostate cancer and aggressive prostate cancer. Magnetic resonance spectroscopy can profile tumor location, tumor extent, and biologic cancerous potential by mapping the intensities of resonance spectra assigned to choline, citrate, creatine, lipid, and lysine—all markers for evaluation of the metabolic properties of tumors.

By using MRS to compare the ratios of different molecular markers in tumors, Swindle et al. demonstrated that it is possible to distinguish between stromal benign prostatic hyperplasia, glandular benign prostatic hyperplasia, and adenocarcinoma, as well as to identify the stages of tumors. Having this ability allows physicians to prescribe treatment and predict patient outcome with increased confidence.
The application of MRS to colon cancer has been described by Gluch, who reported that low and high tumorigenic colorectal lines are distinguishable based on the resonances of lipid, choline, and fucose. Beloueche-Babari et al described how MRS has aided in the evaluation and identification of the biochemical pathways that promote colon cancer. The amount of phosphocholine, which is detectable by MRS, is a reflection of altered signaling pathways that play a role in tumor inhibition.

**Breast**

Magnetic resonance spectroscopy has led to advancements in the study of breast cancer similar to the advancements made in prostate and colon cancer research. Two studies by Jacobs et al. have shown concurring evidence that MRS can be used to identify malignant lesions of the breast by detecting the presence of choline metabolites. This method of diagnosis is highly reliable because it is based on the appearance of a single spectroscopic peak, that of phosphocholine. A large increase in the cellular concentration of phosphocholine is one of the earliest responses of tumor cells to growth factor proteins. Breast cancer cells contain at least 10 times more phosphocholine than do normal mammary epithelial cells. Magnetic resonance spectroscopy makes it possible to profile this diagnostic marker for breast cancer.

**Cervix**

Evaluations of cervical cancer in patients are increasingly relying on MRS for diagnostic verification. The conventional method of cervical biopsy sampling is limited in its application because it is highly invasive and there is a high potential for error in such a small sample region. Furthermore, conventional cervical biopsy sampling relies primarily on histology for evaluation. Although histology can accurately determine if a region of mature tumor cells is benign or malignant, distinguishing preinvasive cervical lesions from early invasive tumors requires the more sophisticated technology of MRS. Two studies by Mahon et al. have shown that lipid levels, as measured by MRS, are more elevated in malignant cervical tissue compared with normal cervical tissue. These studies also demonstrated that the presence of elevated in-phase triglycerides—specifically CH₃ and CH₂—may be used in MRS for the detection of cancer in vivo.

**Pancreas**

Although MRS studies have not focused heavily on the abdomen, MRS has been used as a tool in the differentiation of pancreatic cancer from chronic focal pancreatitis and in the detection of hepatopancreaticobiliary cancer. Pancreatic cancer and chronic focal pancreatitis are difficult to discriminate initially because of their similar clinical and radiologic features at presentation. Once definite symptoms of pancreatic cancer are detected, the diagnosis is usually made too late for treatment. Magnetic resonance spectroscopy can differentiate pancreatic cancer from chronic focal pancreatitis by analyzing the lipid content of pancreatic tissue. In vivo ¹H-MRS spectra of chronic focal pancreatitis show less lipid than do the spectra of pancreatic carcinoma, according to Cho et al. These differences in lipid peaks can be explained by differences in fibrous tissue content in the two conditions.
Malignant regions associated with hepatopancreaticobiliary cancer can be detected with the MRS analysis of bile. Both $^1$H-MRS and $^{31}$P-MRS are useful techniques in detecting and mapping changes in phospholipid membrane metabolism and the energy state of cells. Khan et al found in a pilot study that the changes in phospholipid metabolites are a strong indicator of regenerative activity in hepatopancreaticobiliary cancer. In the study, measurable differences in the peak area ratios of phosphatidylcholine, detectable by MRS, were present when patients with pancreatic cancer were compared with patients without pancreatic cancer.

Esophagus
Magnetic resonance spectroscopy is being used as a tool in the differentiation of normal epithelium from both esophageal adenocarcinoma and Barrett’s esophagus (also called Barrett’s epithelium and Barrett’s syndrome). These three conditions can be histologically indistinguishable, but Doran et al. report that the conditions are clearly distinct with MRS. Spectra of malignant tissue or Barrett’s esophagus have an increased choline-to-creatine ratio when compared with spectra of normal esophageal tissue. In addition, a relative decrease in the carbohydrate region of the spectra distinguishes patients with cancer secondary to Barrett’s esophagus from patients with noncancerous tissue and Barrett’s esophagus. Because Barrett’s esophagus is thought to be a precursor to adenocarcinoma, early detection of this condition with MRS can be an important preventive step for patients as well as a diagnostic one.

Comment
Although the primary biomedical application of MRS has been tumor evaluation in patients with brain cancer, MRS has become an adjunct to conventional methods of tumor evaluation for other forms of cancer. Magnetic resonance spectroscopy involving cancer other than that of the brain has certain limitations, including the suppression of metabolite signaling by overlying fat. Still, the studies cited in this review suggest that MRS will become integrated as a standard diagnostic tool in the conventional paradigm of cancer detection for many forms of cancer.

The potential to classify tumor grade and type in patients are among the most valuable functions of MRS. Because conventional MRI and other methods of biomedical imaging technology allow for only vague identification and localization of tumors, biopsies are routinely required. For instance, it is often left with insufficient knowledge of a tumor’s nature. This obstacle has made it virtually impossible to formulate an appropriate intervention plan or prognosis for certain patients.

As MRS technology continues to advance and as knowledge of tumor chemistry increases, biomedical imaging will overcome this obstacle and cancer patients will be provided with more definitive care and prognoses. The grading of tumors with MRS has the additional advantage over biopsies of being a noninvasive diagnostic technique, thereby reducing the complication rate for diagnostic procedures.

The next obvious progression in the application of MRS will be the increased use of this imaging technology to gain greater insight into tumor size and margins. Magnetic resonance spectroscopy is already providing some surgeons with information on dimensions and locations of neoplasms to guide them through surgery. This type of application allows patients to benefit from exact excisions that leave them with a larger amount of retained functional tissue.

Conclusion
Magnetic resonance spectroscopy holds great promise for many clinical applications, but the clinical usefulness of MRS has yet to be fully substantiated. As MRS availability and access increases in major medical centers, appropriate evaluations of its strengths and weaknesses will be made.

A number of concerns regarding MRS can be cited. First, MRS is still in its experimental and preliminary phases, with much more research needed to test its efficacy for various medical conditions. Future studies need to be fine-tuned, optimized for signal-to-noise ratios, and repeated for conclusive findings. Second, because the applications of MRS are so widespread, it would be difficult to create a standardized, unique protocol that could be used to evaluate more than one type of cancer at a time. Third, patient accessibility to MRS is a problem. Magnetic resonance spectroscopy is an expensive medical tool, and there would need to be a steep reduction in its cost to serve the best interests of all patients.

We believe that research to date is sufficient to indicate that the concerns about MRS are outweighed by the many benefits of this technology, including its noninvasive nature and its capacity to identify malignant markers. In the coming years, MRS can be expected to follow the pattern of previous biomedical imaging technologies, advancing from a diagnostic method to a method for longitudinally tracking tumor changes and observing patient response to treatment. Research results and primary observation strongly suggest a promising future for MRS in the oncologic management of patients.

References


