History and Evolution of Brain Tumor Imaging: Insights through *Radiology*[1]

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This review recounts the history of brain tumor diagnosis from antiquity to the present and, indirectly, the history of neuroradiology. Imaging of the brain has from the beginning held an enormous interest because of the inherent difficulty of this endeavor due to the presence of the skull. Because of this, most techniques when newly developed have always been used in neuroradiology and, although some have proved to be inappropriate for this purpose, many were easily incorporated into the specialty. The first major advance in modern neuroimaging was contrast agent–enhanced computed tomography, which permitted accurate anatomic localization of brain tumors and, by virtue of contrast enhancement, malignant ones. The most important advances in neuroimaging occurred with the development of magnetic resonance imaging and diffusion-weighted sequences that allowed an indirect estimation of tumor cellularity; this was further refined by the development of perfusion and permeability mapping. From its beginnings with indirect and purely anatomic imaging techniques, neuroradiology now uses a combination of anatomic and physiologic techniques that will play a critical role in biologic tumor imaging and radiologic genomics.

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Learning Objectives:

After reading the article and taking the test, the reader will be able to:

- Explain how technologic changes over time have influenced imaging diagnosis
- Specify how past innovations have led to the current practice of radiology
- Describe how imaging and imaging-guided therapies can aid in patient care

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The anniversary of the founding of the Radiological Society of North America offers us the opportunity to look at the world of imaging and its progress as portrayed by articles appearing in its preeminent journal, *Radiology*. For this review, I have chosen to approach the history of neuroimaging and brain tumor imaging by dividing the discipline into "eras." These eras are not strictly defined by chronologies but by key imaging advances. For the first 50 years and after the development and adoption of brain air studies and cerebral angiography, only incremental progress was seen in neuroradiology. It was not until the early 1970s, when planar imaging matured with the arrival of computed tomography (CT), that neuroimaging was catapulted into a whirlwind of progress with new technologies and treatments.

For this historical vignette, I was asked to retell this story on the basis of brain tumor imaging since it (together with imaging of aneurysms and vascular malformations) has been a mainstay of neuroradiology throughout the history of neuroimaging. All *Radiology* tables of contents for full length articles and case reports (which *Radiology* published in the past) were studied, and the articles included here are only the ones that initially described a finding or a technique or that resulted in changes to the way we practice. Articles based on animal studies are not cited here unless they are indispensable to understand future clinical advances. It is to be noted that in *Radiology,* neuroradiology-related articles commonly appear under other headings, such as Pediatric Imaging, Nuclear Medicine, Experimental Studies, Ultrasonography (US), and Technical Developments—not only in the Neuroradiology section. The search for appropriate articles was not based on their citations, because if number of citations had been the main criterion, important articles that were never cited or were cited only a few times might have been overlooked. Although a given topic may been addressed in a number of articles, only the first of such articles is included, and subsequent ones are mentioned only if they refined or changed the initial ideas. Of course, I could have missed some articles or decided not to include some, and for this I am solely responsible. I hope that this article accurately recounts the history of brain tumor imaging and, indirectly, of neuroimaging as a specialty.

Diagnosis of Brain Tumors in Antiquity

The oldest medical text, the Edwin Smith Papyrus, dates from the 17th century BCE and describes 48 battlefield head and spine injuries but does not mention brain tumors (1). Similarly, the more recent (albeit also ancient) Ebers Papyrus (1500 BCE) also does not mention brain tumors. In antiquity, brain tumors resulted in death and were preceded by longstanding symptoms of headaches, seizures, and coma. Physicians recognized that these symptoms were caused by increased intracranial pressure and developed skull trepanation to relieve it. Skull trepanation (or trephination) probably originated in ancient Africa and South America (2). Hippocrates, Socrates, Aulus Cornelius Celsus, Galen, and many Byzantine physicians do not mention brain tumors in their treatises but left clear instructions regarding trepanation to alleviate intracranial pressure.

Since many neurosurgical techniques were perfected at a time of a war, it should come as no surprise that the Incas, a military state, not only used trepanation but were proficient in performing craniotomies with exquisite knowledge of anatomy, preserving vital structures such as veins and implanting prosthetic materials with relatively low rates of infection (3). It seems that most Inca surgery was performed for trauma, and no documentation of tumor resections exists.

Meningioma plays an important role in the history of intracranial tumors, because although other tumors disappear as the accompanying brain lyses and disintegrates after death, evidence of meningioma remains in ancient skulls. Hyperostosis, commonly produced by meningioma, has been found in Neolithic, Egyptian, and South American skulls. However, there is no evidence that these tumors were ever treated. The presence of clinically palpable external hyperostosis was used to localize the first documented resected meningioma (an orbital one) in 1881 in Scotland (4). At the same time in Italy and London, similar cases were reported. Then in 1895, everything changed.

X-rays and the Brain

In 1895, Wilhelm Roentgen reported the discovery of x-rays. Shortly thereafter, the great neurosurgeon, Harvey Cushing, stated that x-rays had limited utility in the diagnosis of brain tumors but that they had value in the diagnosis of tumors near the sella turcica (4). At about the same time, Fedor Krause, a German neurosurgeon used x-rays routinely to localize brain tumors and wrote a book chapter entirely dedicated to their use for this purpose. In 1904, an article on the use of x-rays to diagnose cerebral infarctions and tumors appeared in the *Transactions of the American Roentgen Ray Society;* this is probably the first report of neuroimaging in an American scientific imaging journal (5). Also at that time, emulsion-coated glass plates were being used by George Pfahler, MD, a radiologist in the United States, to help diagnose brain tumors. Intracranial calcifications, which can indicate tumors such as oligodendroglioma, astrocytoma, meningioma, choroid plexus neoplasia, and pituitary tumor, are easily seen in images in an article by Merrill Sosman, MD, that appeared in *Radiology* in 1927 (Fig 1) (6). As seen in another article published in 1928 in *Radiology*, cranial nerve VIII schwannomas were diagnosed by demonstrating expanded internal auditory canals on oblique skull radiographs, optic nerve gliomas

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Abbreviation:
DWI = diffusion-weighted imaging

Conflicts of interest are listed at the end of this article.

could be inferred by enlargement of the optic canals, and cranial nerve tumors were suggested by expansion of their corresponding outlet foramina (7). The location of the normally calcified pineal gland also helped in the diagnosis of brain tumors. Measurements, stereo views, proportional and graphic methods of localizing the pineal calcification in patients with brain tumors all documented gland displacements that were abnormal in 30%–50% of cases (8). As late as 1949, the only way to confirm the diagnosis of a pituitary tumor was careful measurement of the sella turcica on radiographs (9).

The Living Brain and Spinal Cord Are Visualized

In 1918–1919 at Johns Hopkins University (Baltimore, Md), the neurosurgeon Walter E. Dandy, MD, noticed that free intraperitoneal air outlined the abdominal organs, and he sought to apply the same principle to brain; thus were born pneumoencephalography and ventriculography. This was the first technique that allowed visualization, albeit indirect, of the living brain, and for this development Dandy was nominated for the Nobel Prize in 1933. The technique was perfected in the early 1940s by another neurosurgeon, Leo M. Davidoff, MD, together with the first American neuroradiologist, Cornelius G. Dyke, MD, at the Neurological Institute of New York in New York City. (The first article published by Dyke in *Radiology* was "Acquired Subtentorial Pressure Diverticulum of a Cerebral Lateral Ventricle." [Radiology 1942;39:167–174].)

The first neuroradiology-related article published in *Radiology* dealt with ventriculography in the setting of brain tumors (10). Written in 1923, the authors, neurosurgeons from the Mayo Clinic (Rochester, Minn), reported on 532 patients and concluded that air ventriculograms were very helpful for diagnosing supratentorial masses but were not helpful for the diagnosis of small and/or cerebellar tumors. A few years later, the authors of one article (11) showed lateral and midline displacement of the ventricles in the presence of gliomas and praised the diagnostic value of pneumoencephalography. In 1936, *Radiology* published a remarkable review (12) on gliomas that dealt with their diagnosis on the basis of radiography and air encephalography, which solidified the use of these techniques as the most important in brain tumor imaging (Fig 2). The August 1943 issue of *Radiology* is remarkable because it contains three articles about localization of brain tumors by using "roentgen methods" (13–15). The conclusion of each of the articles praised the use of air-contrast studies but stressed the need for adequate equipment and rich experience. Blockage of the lateral ventricles and deformity of the aqueduct of Sylvius (cerebral aqueduct) were critical findings for the diagnosis of pineal gland tumors on air studies (16). Trapped air inside a mass signified cystic degeneration and/or necrosis and a high-grade malignancy (17). The first *Radiology* article dedicated to imaging of pediatric brain tumors appeared in 1952 (18). In it, the authors discussed their experience with 34 tumor patients and reviewed the literature. Most of these tumors were diagnosed by using pneumoencephalography.

Across the Atlantic, in Marseilles, France, a radiologist (Jean-Athanase Sicard) and a rheumatologist (Jacques Forestier) had the idea of using positive contrast material to outline the spinal cord. They injected lipiodol into the subarachnoid space, and myelography was born. This technique, reported in *Radiology* in 1928 (19), was the first to illustrate the concept of "spinal block" secondary to lesions that compress the spinal cord or expansile cord lesions that block the flow of contrast material in the subarachnoid space.

At the same time and also in Europe in 1927, Egas Moniz, a Portuguese neurosurgeon intrigued by positive contrast agent–enhanced myelography introduced a technique in which sodium iodide was directly injected into veins first and years later into the carotid arteries via a surgical exposure; thus, cerebral angiography was created. It was not until 1941 that the first report

Figure 1

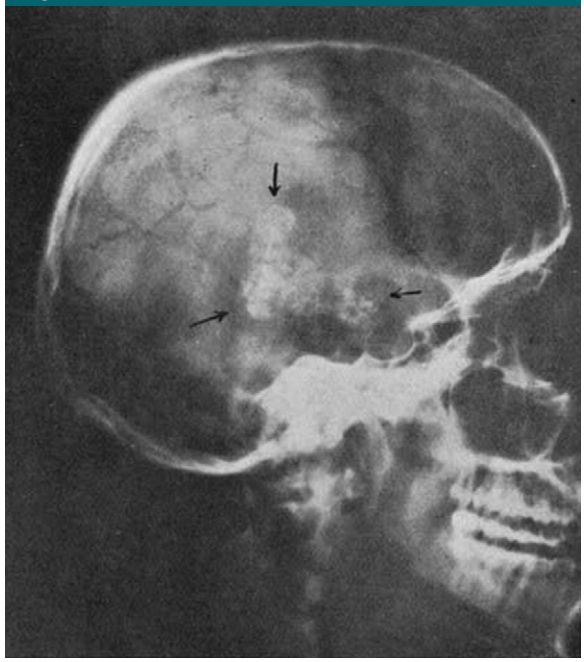


Figure 1: Radiographic aid in the diagnosis intracranial lesions. Radiograph (fig 10 from reference 6) shows a calcified tumor of choroid plexus (arrows) in a 27-year-old woman.

on cerebral arteriography was published in *Radiology* (20). This article, a case report, reported that the patient underwent general anesthesia and the common carotid artery was surgically exposed and a canula inserted. The angiogram was obtained by using Diodrast (iodopyracet), a contrast agent previously used for studies of the kidneys and heart and used at a lower concentration for the brain study. The images shown in the article demonstrated a posterior temporal blush caused by a hypervascular glioma.

Precision Neuroradiology, the Swedish School, and Their Influence on American Neuroradiology

Erik Lysholm (1881–1947) in Stockholm, Sweden developed a "skull table" apparatus capable of exquisitively demonstrating the anatomy of the skull on radiographs. By moving the x-ray source spherically while maintaining a central spot he created planar tomography. An article published in *Radiology* (21) in November 1949 contains several tomograms (called "body sections") and illustrated their utility in the diagnosis of eighth cranial nerve tumors (this issue of the journal was the first to contain five consecutive neuroradiology-related articles). Later, Dr Torgny Greitz measured the cerebral blood circulation time at precisely 4.13 seconds. The first article published in *Radiology* on localization of intracranial tumors by using angiography appeared in October 1946 (22). In the study reported in that article, angiograms in more than 130 patients with cerebral masses in different locations were assessed, and the authors presented beautiful diagrams all of major vascular "shifts" that aided in localizing these tumors with great precision. A few months later, the same two authors published an article on the differential diagnosis of brain tumors based on the angiographic patterns of the tumors (Fig 3) (23). Precise measurements of the cerebellar arteries allowed for diagnosis of posterior fossa tumors (24).

During the same period, Sven-Ivar Seldinger (1921–1998) introduced the technique of threading a guidewire onto a needle and over it into a catheter; thereafter, cerebral angiography via a femoral approach became a relatively risk-free technique. The first *Radiology* article to be entirely

Figure 2

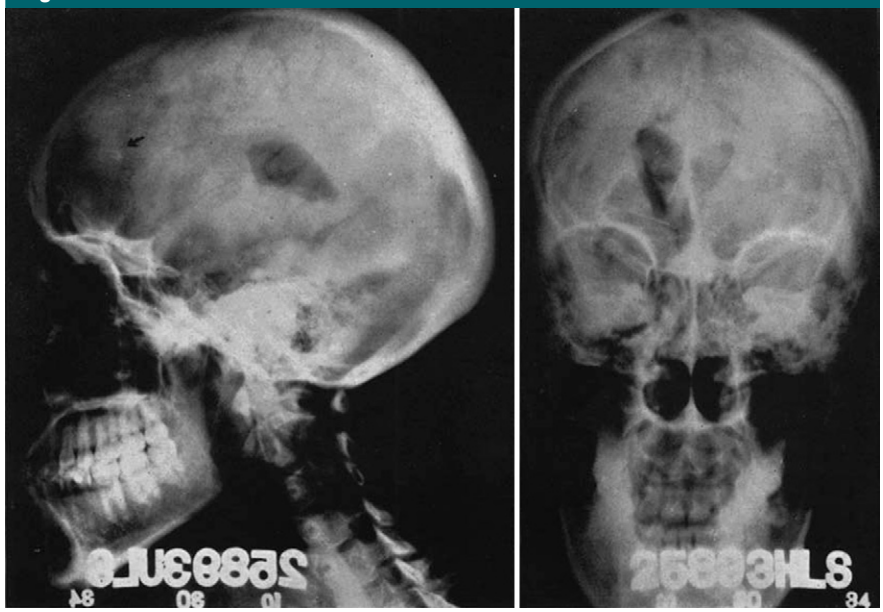


Figure 2: Pneumoencephalograms (figs 5 [left] and 6 [right] from reference 12) show signs of frontal lobe tumor.

Figure 3

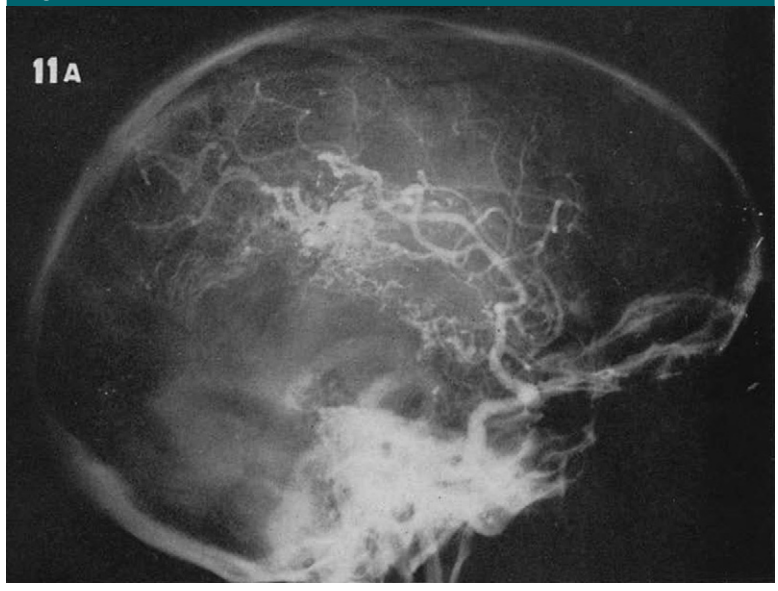


Figure 3: Differential diagnosis of intracranial neoplasms by using cerebral angiography. Arteriogram (fig 11A from reference 23) shows temporoparietal glioblastoma with aneurysmal dilatations of small vessels.

dedicated to this technique appeared in 1960 (25). In it, the technique was used in more than 100 Swedish patients, 20 of whom had brain tumors, and resulted in only one transient complication. Radiologists from the State University of New York Upstate Medical Center (Syracuse, NY) were the first ones to publish an article in *Radiology* describing their experience with femoral catheter neck and cerebral angiography in 1960 (26). Although this was a relatively small series, no complications occurred.

In 1951, *Radiology* published an article (27) that summarized advances in cerebral angiography as follows: improved contrast media (older ones caused blood vessel irritation and disfigurations when extravasated), percutaneous arterial access without need to surgically expose an artery (although all injections were still performed in the neck), and serial x-ray changers with magazines capable of handling rolls of film and faster serial exposures. With these advances, precision neuroangiography became routine in the United States, even in smaller community hospitals (28). In 1959, in an article authored by Paul F. J. New, MB, BS, FFR (29), cerebral angiography was declared safer, less time consuming, and the imaging method of choice when brain tumors were suspected.

Early Physiologic Tumor Neuroimaging

In the late 1940s, George E. Moore, MD, a surgeon in Minneapolis, Minnesota, postulated that some brain tumors could selectively take up a radiotracer. He began by injecting fluorescein, which outlined tumors at the time of surgery, and then tagged the fluorescein with radioactive iodine, which allowed visualization of the tumors before surgery—an event that began the era of brain scanning.

In 1954, the authors of an article in *Radiology* (30) reported the use of nuclear scanning in 200 patients and concluded that accurate localization of brain tumors was possible in 46% (the rate of localization of nontumoral lesions was about the same). By this time, the use of nuclear scanning as the first noninvasive method to localize brain tumors was already fairly routine. Seven years later, an article from Johns Hopkins University compared the results of angiography, pneumoencephalography, and scintigraphy in the diagnosis of 400 brain lesions and found that isotope studies had an accuracy of 73% for the diagnosis of tumors (31). The lack of discomfort and complications were emphasized and suggested that the technique could serve to "screen" patients suspected of harboring brain tumors. Novel isotopes such as mercury 203 (^{203}Hg) were also tried and were very successful in identifying brain tumors (Fig 4) (32).

Figure 4

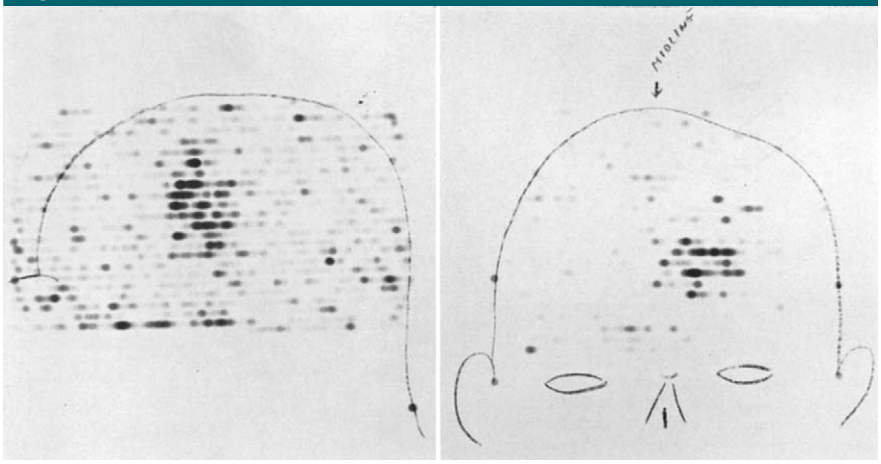


Figure 4: Brain tumor localization by using ^{203}Hg. Lateral (left) and anteroposterior (right) views (fig 3 from reference 32) from brain scan show selective accumulation of ^{203}Hg in left temporal lobe lesion.

Planar Neuroimaging Begins

In the mid-1960s, Kuhl at el (33) reported in *Radiology* the development of the first practical transverse, or cross-sectional, isotopic imaging method for brain lesions, which resulted in improved visualization of tumors located in the posterior fossa. Their report included images of meningiomas and astrocytomas. From the early 1940s to 1970, neuroradiology experienced only small incremental improvements, but in 1971 our ability to image the brain changed radically, and a new era of neuroimaging commenced, especially with regard to the diagnosis of neoplasias.

One of the most famous names in medical imaging is that of Sir Godfrey N. Hounsfield, FRS, an engineer who, while working at EMI in England, created the first CT scanner. In 1971, a head-only scanner was installed in London, England, and was soon thereafter installed in the United States at the Mayo Clinic. A new era of imaging-based diagnosis began, and many articles about with CT scanning of brain tumors, intra- and extraaxial hematomas, abscesses, and hydrocephalus were soon published, forever changing the way we examine patients and diagnose neurologic disorders. Another important event at this time was the introduction of the first iso-osmolar iodinated contrast medium, metrizamide, which made myelography safer and routine. Soon thereafter, its use was extended to CT cisternography which allowed diagnosis of cerebrospinal fluid leaks easily. In 1975, the first whole-body CT units were introduced.

The first article on CT scanning in *Radiology* (January 1974) was written by authors from the Massachusetts General Hospital (Boston) and shows images of an astrocytoma, a metastasis, a meningioma, and a large pituitary adenoma; the authors also detailed their initial experience with imaging in 273 patients, of whom 62 had

Figure 5

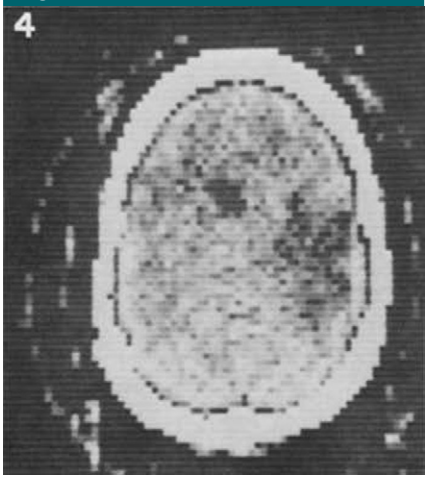


Figure 5: CT scan obtained with the EMI scanner (fig 4 from reference 34). Low-attenuation region involving almost the entire left temporal lobe and extending into parietal and frontal lobes represents astrocytoma.

Figure 6

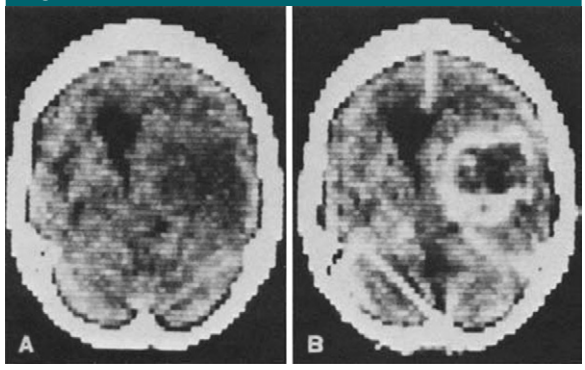


Figure 6: An approach to contrast enhancement for CT of the brain. Transverse scans obtained, *A,* before and, *B,* after contrast agent infusion show right thalamic glioblastoma (fig 1 from reference 38).

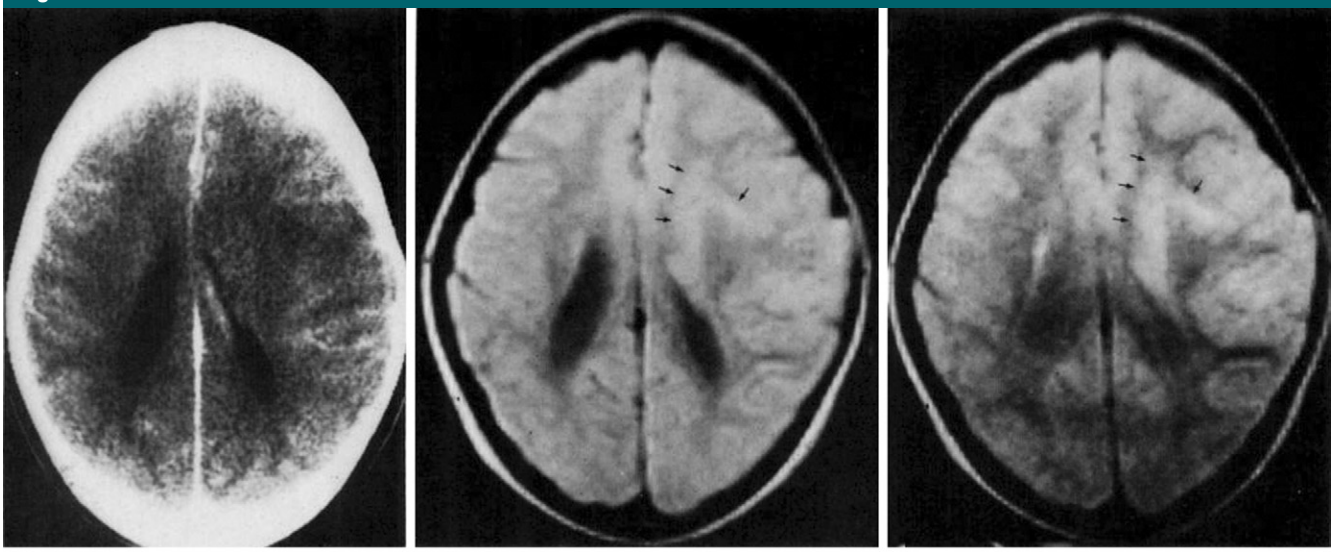
intracranial tumors (Fig 5) (34). At this time, this head imaging–only CT scanner produced 13-mm-thick images with a matrix of 80 × 80. A second article (35) about CT appeared 5 months later, but it dealt with hemorrhage, not brain tumors. The January 1975 issue of *Radiology* contained the first article (36) entirely dedicated to CT imaging of primary and secondary intracranial tumors (600 patients), and the authors reported that in 35 patients with glioma, only one imaging study was false-negative (an optic chiasm glioma) and only one was technically suboptimal owing to motion. With respect to metastases, all CT studies reviewed in that article were positive. In September 1975, an article from Mayo Clinic (37) showed brain images that are not too different from the ones we obtain today with our radiation dose reduction protocols. The authors mention the decreasing numbers of air studies, angiograms, and nuclear brain scans needed to diagnose brain tumors. In that same issue of *Radiology*, the authors of another article (38) detailed the use of CT before and after administration of contrast material and found that, overall, more than 80% of intracranial mass lesions showed contrast enhancement (Fig 6). In November 1978, the first article to show how imaging findings, specifically contrast enhancement, correlated with astrocytoma grade was published in *Radiology* (39). These authors showed that all high-grade supratentorial tumors (grades 3 and 4) enhanced substantially.

The year 1980 was important, because the first two pediatric neuroradiology articles, one on sellar masses (40) and the other on brainstem gliomas (41), appeared in the same issue of *Radiology*. Even at this time, the article on sellar masses (40) still showed skull radiographs and nuclear brain scans! But later that year, an article put an end to radiographs, angiography, and nuclear scans as means of diagnosing intracranial tumors (42). In that article, CT was shown to be the most accurate diagnostic test in over 1000 patients with brain tumors. This article was rapidly followed by two more (43,44) proving that CT was also superior to all other imaging techniques in the diagnosis of brain metastases (43) and meningiomas (44). One last article deserves to be mentioned here. In 1982, Graeb et al (45) described CT changes after tumor treatment that simulated recurrence. This is one of the earliest descriptions of a phenomenon commonly seen in modern brain tumor imaging: pseudoprogression.

More or less at the same time that CT was evolving, the next revolution in neuroimaging was hatching. In 1971 Raymond V. Damadian, MD, reported that nuclear magnetic resonance (MR) could be used to distinguish normal from tumoral tissues and that it would play an important future role in the diagnosis of cancer. Two years later, Paul C. Lauterbur, PhD, reported the first images of a mouse obtained with MR imaging (46). In England, Peter Mansfield, BSc, PhD, FRS, a physicist, developed the mathematic algorithms that allowed rapid imaging and, in 1977, the first human MR images were reported (47). Lauterbur and Mansfield received the Nobel Prize in 2003. In 1984, the first two articles (48,49) dealing with MR imaging of brain tumors appeared in *Radiology*. In the first report (48), T1 measurements of brain masses were performed, and the authors found that astrocytomas had the longest T1 and lipomas had the shortest. The second article (49) was a comparison between the then well-established CT and MR imaging. The authors pointed out that very small tumors and calcifications were missed at MR imaging (the studies were performed with 7-mm-thick sections and a 0.35-T unit) and that differentiation of tumors from surrounding edema was difficult (Fig 7).

The year 1985 saw the publication of an article with a focus on pediatric brain tumors (50), which established the potential of MR imaging in this patient population. The fact that contrast agent administration is essential for detection of primary intraaxial tumors

Figure 7



a. b. c.

Figure 7: MR imaging versus CT in a 10-year-old boy with anaplastic astrocytoma (fig 1 from reference 49). Transverse **(a)** CT and **(b, c)** MR images show compression of left ventricle and displacement of midline due to compression by a mass. No focal lesion is visible on **a,** but **b** (repetition time msec/echo time msec, 2000/28) and **c** (2000/56) clearly show mass extending into frontal and parietal white matter (arrows).

but not for delineation of primary larger extraaxial masses was noted in later in 1985 (51). Not surprisingly, this article (51) came from Europe, where the contrast agent gadopentetate dimeglumine (then known by its chemical name gadolinium–diethylenetriaminepentaacetic acid, or Gd-DTPA) was used for many years before it was approved for use in the United States. Two years later, Russell et al (52) showed that contrast agent administration was essential to depiction of intracerebral metastases, especially those smaller 10 mm in diameter and without accompanying cerebral edema. This was also the case for extraaxial leptomeningeal metastases for which unenhanced MR imaging proved to be inferior to contrast-enhanced CT (the reader should remember that fluid-attenuated inversion-recovery, or FLAIR, imaging had not yet been developed) (53). Because MR imaging allows better characterization of blood products than does CT, an article in 1987 pointed out that complex and atypical bleeds tended to be caused by underlying primary and secondary brain tumors (54). By 1988, several articles clearly advocated the use of gadolinium chelates to help improve tumor identification, as well as identify target areas for biopsies (55,56). In 1990, an article (57) was published in which the authors claimed that the diagnosis of gliomas on the basis of MR imaging findings was similar that for histopathologic findings. The reason for this, the authors claimed, was that MR imaging allowed evaluation of all of the tumor, while histologic examination was subject to sampling errors.

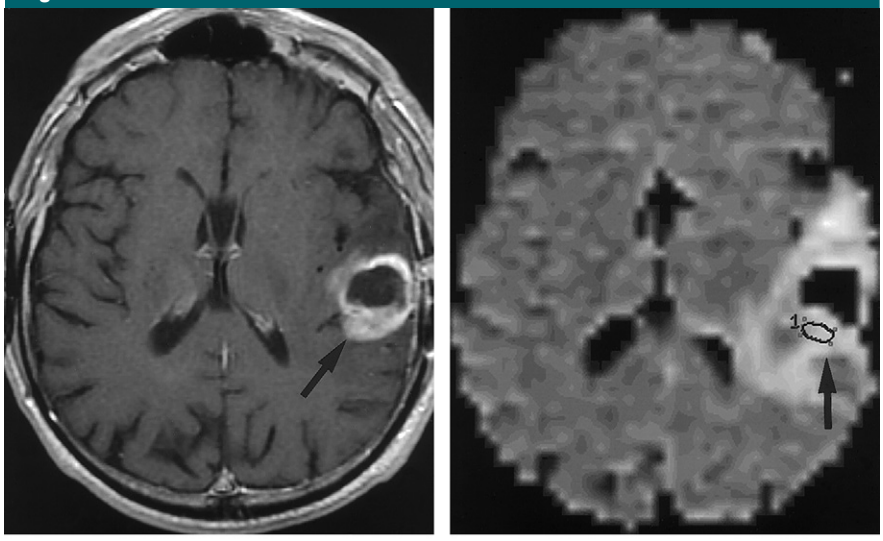
One of the better known MR imaging signs for diagnosing meningioma is the presence of "dural tails." Thickening and contrast enhancement of meninges adjacent to the mass localize it to the extraaxial compartment and provide clues about its nature. However, the authors of one article (58) showed that dural tails were not due to tumor infiltration but rather to reactive changes caused by the neighboring tumor. Thus, the authors concluded that resection of all of enhancing dura at the time of surgery was not needed. It is to be noted that this opinion was controversial. Later that year, the authors of another article (59) concluded that dural tails were due to nodular tumor seeding and that the surrounding dura must be resected (currently, this issue is still controversial).

This section would not be complete without a short mention of US. Although US was and is commonly used to help diagnose brain hemorrhage and hydrocephalus, its utility in tumor evaluation for both the brain and the spinal cord was limited to intraoperative localization. In 1983, Rubin and Dohrmann (60) pointed out the utility of intraopeative US in depicting small (<1-cm) lesions and in helping identify cysts and determine the site for biopsy. Three years later, results of another investigation (61) confirmed that when sampled with biopsy, echogenic areas seen during intraoperative US provided the best sites for tumor grading.

Planar Neuroimaging Matures

The next improvement in CT was spiral (or helical) capability, conceived by Willi A. Kalender, PhD, a medical physicist at the University of Wisconsin–Madison in the 1980s. As the

Figure 8



a. b.

Figure 8: MR imaging demonstration of glioblastoma multiforme in a 70-year-old man (fig 2a [**a**] and 2c [**b**] from reference 64). **(a)** Transverse gadolinium-enhanced T1-weighted MR image (500/11) shows ring-enhancing mass in left temporal lobe (arrow). **(b)** Apparent diffusion coefficient map from DWI (b = 1000 sec/mm^2) at same level as **a** shows high signal intensity in solid posterior portion of tumor (arrow). *1* = region of interest for apparent diffusion coefficient calculation.

patient moved through the spiral CT machine, the x-ray source described a helical trajectory while an array of detectors measured the transmission through the patient. The first 16-section scanner was introduced 2001, and a 64-section scanner became available in 2004. With respect to brain tumor imaging, the greatest advantage of this technique is speed, which allows creation even of CT angiograms and acquisition of time-dependent blood perfusion measurements. Although CT had lost some of its luster in the 1980s, spiral capabilities reaffirmed its importance in neurovascular imaging, particulary in the stroke patient, and also helped in the diagnosis of brain tumors.

Although MR imaging continued to improve, it remained an anatomic imaging method until the clinical deployment of diffusion-weighted imaging (DWI). The first images from DWI were presented by Denis LeBihan, MD, PhD, at the 1985 RSNA Annual Meeting and were later published in *Radiology* (62). Although originally conceived for liver imaging, DWI soon found considerable utility in neuroimaging. Coupled with echo-planar imaging, DWI became the first technique to offer fast, practical, reliable, reproducible, and easy to interpret physiologic imaging. The first article published in *Radiology* on this topic was a report on brain DWI performed in cats, which laid the foundation for understanding the appearance of the normal human brain at DWI (63). Soon DWI became, and remains, the imaging method of choice for patients suspected of having cerebral infarction or abscess and is also very helpful in grading brain tumors. It is now well known that hypercellular tumors such as glioblastoma and lymphoma have a lower apparent diffusion coefficient (ADC) than do benign masses and that lymphomas show a lower ADC than do gliomas (64). Guo et al (64) also showed that tumor cellularity is the main determinant of ADC (Fig 8).

Advanced Physiologic Tumor Neuroimaging

In 1993, Michael E. Moseley, MD (65), reported that water diffusion (movement) in white matter was anisotropic (directional) and that the direction of white matter tracts relative to the orientation of the diffusion gradient could be mapped. Again, it was LeBihan and his group (66) who showed that diffusion-tensor imaging (DTI) could produce maps that show white matter fiber direction. In 1991, the first tractographic images of white matter appeared (66). DTI is useful in displaying the normal anatomy of white matter tracts for surgical planning and in evaluating traumatic injuries, tumors, white matter disorders, and some dementias and provides physiologic information regarding the integrity of brain tissues. With respect to brain tumors, DTI is helpful in assessing the integrity of the white matter around the tumor. Authors of one article (67) reported that DTI enables one to distinguish tumor-infiltrated edema from simply vasogenic edema and thus allowed differentiation of gliomas from metastases. Authors of another article published the same year in *Radiology* (68) also stated that fractional anisotropy (a measurement found in DTI studies) aided in detection of tumoral infiltration of surrounding tissues that is not visible on conventional MR images. In a follow-up article (69) by a different group of authors, peritumoral DTI differences were found in low-and high-grade gliomas. A recent refinement of DWI is diffusion kurtosis imaging, which provides information on the nonlinear, Gaussian, and non-Gaussian components of three-dimensional water motion in the brain. When diffusion kurtosis imaging was applied to tumors, it was found to be better than DWI for helping separate glioma grades (70).

Although the foundations of blood perfusion imaging were reported in 1980 by Leon Axel, MD, PhD, from the University of California, San Francisco, its neuroimaging applications coincided with the development of spiral CT and MR echo-planar imaging capabilities (71). By using dynamic sequential imaging, both MR imaging and CT can be used to measure the amount of contrast agent traveling through blood vessels contained in predetermined voxels. This technique is capable of producing parametric maps

that include relative measurements of cerebral blood flow and volume and mean transit time, as well as time to peak enhancement. The first article published in *Radiology* that addressed dynamic contrast-enhanced perfusion imaging appeared in 1990 (72). Of 12 patients, six had brain tumors, and all masses showed increased perfusion. These findings were later refined in two articles (73,74). In the first (73), it was shown that low-grade gliomas had lower perfusion than did glioblastomas, while the benign but hypervascular hemangioblastomas had the highest perfusion. In the second article (74), high cerebral blood volume in tumors correlated with mitotic activity and vascularity but not with cellular atypia, endothelial proliferation, cellularity, or necrosis (Fig 9). Nevertheless, this latter article hinted at the importance of advanced imaging techniques—that is, the ability of such techniques to provide information about processes, both histologic and physiologic, at cellular levels.

It known that about 5%–10% of glioblastomas arise from malignant transformation of lower-grade gliomas, and in this respect perfusion imaging was reported to be helpful. In an article published in 2008 (75), significantly increased perfusion was noted 12 months before the appearance of contrast enhancement in transforming gliomas. Authors of another similar article (76) reported that gliomas with high perfusion progressed rapidly and showed marked reduction in prognosis and survival.

The above-mentioned perfusion articles used gadolinium bolus–based techniques, however, and in 2003 *Radiology* published an article (77) in which a new technique was reported that did not require administration of contrast material: arterial spin labeling perfusion imaging. In this technique, an inversion pulse is used to label cephalad flowing blood spins, which then provides a quantitative map of cerebral blood flow. The authors of this initial article reported that arterial spin labeling is suitable for measurement of microvascular perfusion and is capable of helping differentiate low-grade from high-grade gliomas.

Figure 9

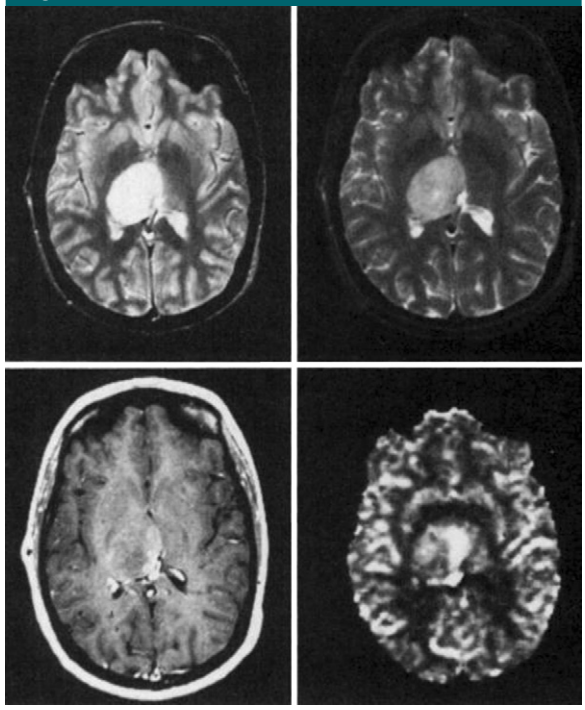


Figure 9: Perfusion MR imaging (fig 6 from reference 73). On proton density–weighted (top left [2000/30]) and T2-weighted (top right [2000/80]) MR images, tumor in right thalamus appears homogeneous and enhances only slightly on contrast-enhanced MR image (bottom left). Cerebral blood volume map (bottom right) shows varying areas of elevated blood volume in tumor, however, consistent with high-grade glioma.

Although we radiologists are accustomed to analyzing images, certain techniques used in neuroimaging—especially metabolic ones—use no images. Most neurospectroscopy examinations have been performed by using water protons, although experiences in using phosphorus, carbon, nitrogen, sodium, and other elements have also been reported. Spectroscopy was first used by chemists and physicists to analyze small molecules. A challenge with human spectroscopy is the need for high uniformity of the magnetic field in relatively large MR units for imaging humans.

The first article on MR spectroscopy to appear in *Radiology* (78) detailed experiments with a 1.4-T whole-body unit in which samples of human brain were characterized with phosphorous 31 MR spectroscopy in only 4.5 minutes. A second challenge to human MR spectroscopy is that when measuring water protons the normal abundant quantity of water may obscure other metabolites. Later in 1986, an article (79) was published in which the authors described a technique to reduce the intensity of the water peak and allow visualization of metabolites such as *N*-acetylaspartate, choline, creatine, and others. This article marked the beginning of clinical brain MR spectroscopy as a technique that was easy to implement and the results of which were easy to interpret. Three years later, another group of investigators (80) clearly showed spectral differences between astrocytoma, meningioma (absence of *N*-acetylaspartate, a neuronal marker in meningioma), metastases, and cysts. The utility of MR spectroscopy in treated brain

Figure 10

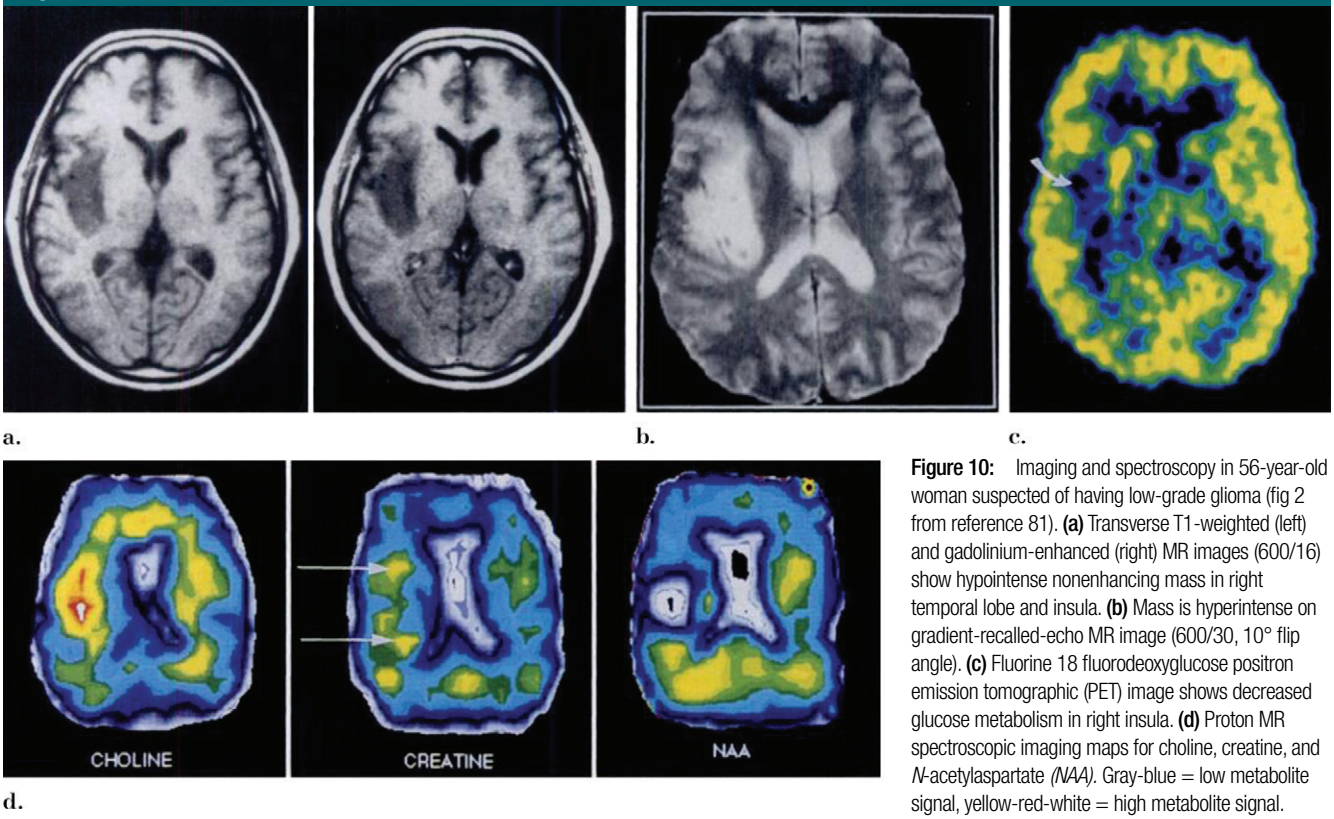


Figure 10: Imaging and spectroscopy in 56-year-old woman suspected of having low-grade glioma (fig 2 from reference 81). **(a)** Transverse T1-weighted (left) and gadolinium-enhanced (right) MR images (600/16) show hypointense nonenhancing mass in right temporal lobe and insula. **(b)** Mass is hyperintense on gradient-recalled-echo MR image (600/30, 10° flip angle). **(c)** Fluorine 18 fluorodeoxyglucose positron emission tomographic (PET) image shows decreased glucose metabolism in right insula. **(d)** Proton MR spectroscopic imaging maps for choline, creatine, and *N*-acetylaspartate *(NAA)*. Gray-blue = low metabolite signal, yellow-red-white = high metabolite signal.

tumors was outlined in yet another (81) article 3 years later (Fig 10). These authors found that treatment-induced necrosis shows a lower choline level than do viable tumors, that lactate is more common in high-grade tumors, and that a progressive decrease in choline during treatment correlates with clinical improvement. Similarly, posttreatment reductions of choline and lactate were also observed in brain lymphomas (82).

Several years later, MR spectroscopy performed at 3.0 T was also judged excellent at enabling distinction of recurrent glioma from radiation effects (83). In addition, when dealing with peripherally enhancing and centrally necrotic cerebral masses, MR spectroscopy was shown to enable differentiation of abscesses from tumors by virtue of demonstrating the presence of amino acids that are byproducts of bacterial metabolism (84). One year later, an article about the clinical influence of MR spectroscopy on the evaluation of brain tumors was published in *Radiology* (85). In that article, MR spectroscopy was reported to help arrive at correct clinical management decisions in most brain tumor patients. Although it seems today that its utility has been well established, MR spectroscopy is still considered an experimental technique by most health insurance companies, and few will reimburse for it.

Another common problem in clinical neuroradiology is attempting to establish the origin of a solitary mass. In 2002, *Radiology* published an article in which MR spectrosocopy together with perfusion measurements of the peritumoral regions (outside the areas of contrast enhancement) together enabled differentiation of primary tumor from solitary metastasis (86). Metastases, which are well defined and often encapsulated, showed no elevation of choline or perfusion in their peritumoral regions.

Refinements in MR spectroscopy allow for identification of other important metabolites. One of these is taurine, the presence of which, particularly in pediatric brain tumors, is indicative of primitive neuroectodermal tumors (87). Another important metabolite is *myo*-inositol which is a glial marker, and its presence offers a glimpse into the difficulty of treating glioblastoma. In one article, *myo*-inositol and glutamine levels were elevated in the normal-appearing cerebral hemisphere contralateral to a glioblastoma, which is consistent with astrocytosis and implies diffuse tumoral infiltration at the time of diagnosis (88).

Although early radionuclide brain tumor imaging was previously discussed, the next advance in nuclear medicine imaging, PET, was established by the ability to detect positron-emitting radionuclides, with three-dimensional images displayed similar to CT images. PET was first implemented in 1961 (the first PET unit was named the "head shrinker") (89). Some years

later, *Radiology* published an article (90) in which fluorodeoxyglucose utilization was found to be as reliable as histologic findings for predicting type, behavior, and recurrence of intracranial meningiomas. Fluorodeoxyglucose has some inherent problems, such as low specificity and low contrast in brain tumors due to the already high uptake by the normal brain. Because of this, an article published in 1995 (91) reported on the use of the novel tracer carbon 11 tyrosine. Uptake of this amino acid permitted visualization of protein synthesis rates in brain tumors, and its sensitivity and specificity for their detection were very high. This tracer also holds promise for assessing the effect of therapy on brain tumors. Conversely, methionine PET was proved to be a better radiotracer for determining the extent, rather than the grade, of tumors (92). I have previously mentioned that MR spectroscopy demonstrates elevated choline metabolism in brain tumors. Similarly, choline can be labeled with ^{18}F, and one study (93) showed that the use of this PET technique could help differentiate among high-grade gliomas, metastases, and benign lesions.

Whereas functional MR imaging is not a technique that is directly used to evaluate the substance of brain tumors, it plays an important role in the evaluation of tumor resectability. With its ability to demonstrate changes in blood oxygenation induced by increased activity in the cerebral cortex, functional MR imaging is capable of mapping some motor and sensory activities. In patients whose tumors are closely associated with eloquent brain regions (ie, motor cortex, language areas), functional MR imaging may help establish their locations and, thus, resection potential. In this regard, the first pertinent functional MR imaging article appeared in *Radiology* in 1999 (94). The authors of this article evaluated lesions around the central sulcus, and functional maps showed expected or deformed activations that were thought to be helpful in surgical planning. Research results (95) from Duke University (Durham, NC) showed that functional MR imaging enables more aggressive surgical treatments in patients with brain tumors by identifying language and motor areas (Fig 11).

Figure 11

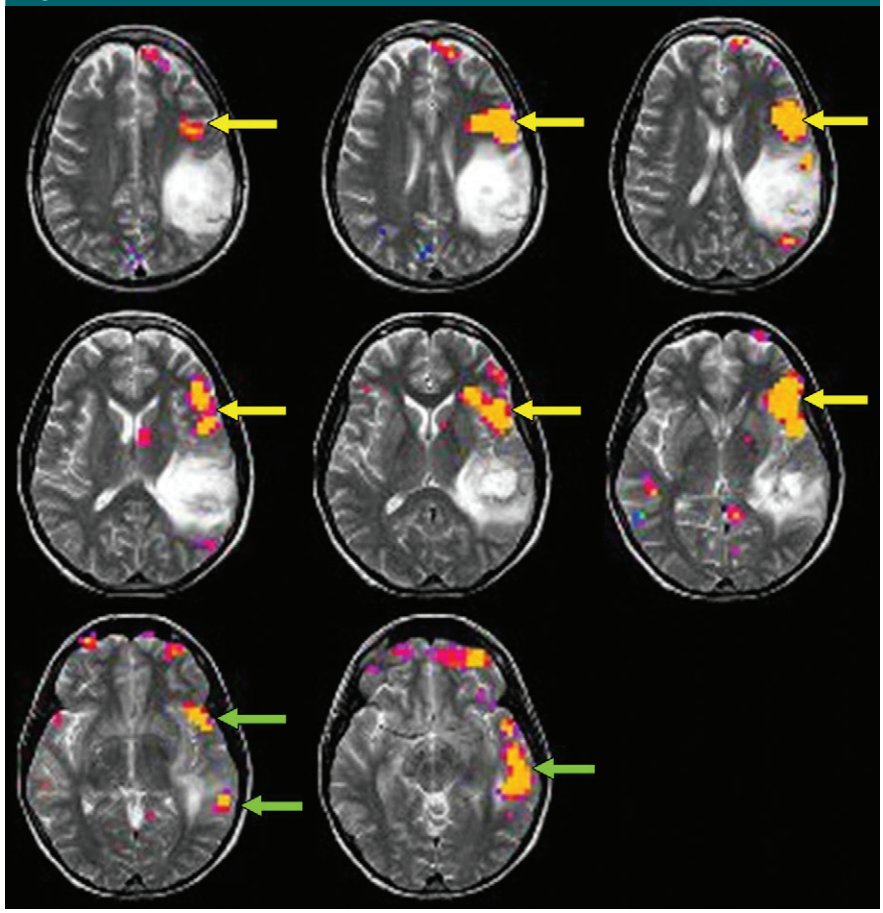


Figure 11: Preoperative functional MR imaging localization of language and motor areas in a 37-year-old woman with recurrent left parietal anaplastic astrocytoma (fig 2 from reference 95). T2-weighted echo-planar MR images (2000/40) displayed as threshold activation maps (red and yellow) overlaid on T2-weighted fast spin-echo images (3000/84). Green arrows = dominant receptive speech areas, yellow arrows = dominant expressive speech areas.

Neuroradiology Goes to the Operating Room

Postoperative MR imaging studies had traditionally been obtained within the first 24 hours after surgery to assess for the presence of residual tumor after resection. The rationale behind this approach was the thought that most contrast enhancement seen before 24 hours was probably tumor and not reactive inflammation. We now know that this is not true. With the possibility of performing neurosurgery with MR imaging guidance beginning in the early 1990s, the exact site of biopsy and the extent of resection could be determined immediately and changed as needed. In 1999, an article (96) describing the use of this technique in 200 patients was published. The authors concluded that the technique was safe and did not affect the incidence of complications nor increase the duration of surgery. Authors of another article (97) reported that assessing the clinical importance of contrast enhancement in the intraoperative tumor bed was challenging and that the correct diagnosis of residual tumor could be made in only 80% of patients.

Genetics and High-Field-Strength MR Imaging of Brain Tumors

Some of the most exciting advances in our understanding of brain tumors have come from the wealth of genetic information that has recently become available, and, not surprisingly, neuroradiologists are working on finding imaging surrogates for many genetic markers. In 2008, a group of investigators from the University of California, Los Angeles, found that incompletely and completely enhancing glioblastomas showed differences in gene expressions and that patients with incompletely enhancing tumors had longer survival (98). In a different study (99), contrast-enhancing regions in glioblastomas were found to overexpress genes that were involved with up-regulation of mitosis, angiogenesis, and apoptosis, all of which contribute to aggressive behavior of tumor (Fig 12). Glioblastomas can be divided into four molecular subtypes, and it is interesting to note that in one study (100) the proneural-expressive type showed lower enhancement, whereas the mesenchymal-expressive type showed more enhancement; in addition larger glioblastomas harbored epidermal growth factor receptor mutations, whereas smaller ones showed *TP53* mutations. Early data from animal studies (101) also showed that specific nanoparticles that

Figure 12

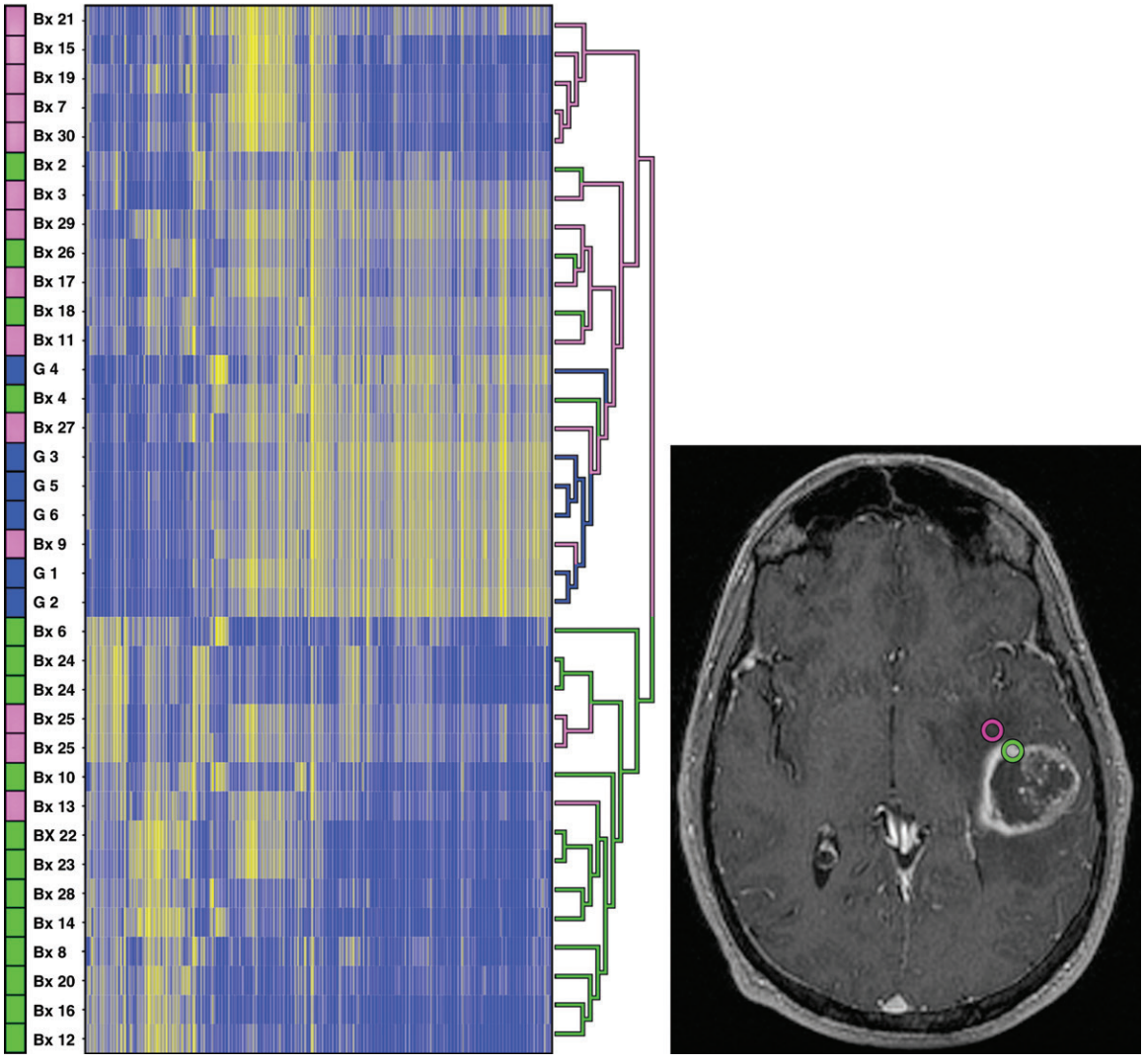


Figure 12: Relationship between contrast enhancement and genetic expression pattern of glioblastoma multiforme (fig 2 from reference 99). Left: Genetic expression map of biopsy samples *(Bx)* with hierarchical clustering of the 500 most-variant genes. Blue = gliosis *(G)* samples, green = enhancing samples, purple = nonenhancing samples. Right: Spoiled gradient-recalled acquisition in the steady state MR image. Green circle = enhancing region for biopsy, purple circle = nonenhancing region for biopsy.

bind to neovascular elements and were labeled with gadolinium may allow visualization of brain tumor vascularity and thus allow identification of those tumors that may benefit from antiangiogenic therapies.

High-field-strength MR imaging may also prove useful for imaging brain tumors. Using gradient-echo sequences at 8 T, Christoforidis et al (102) were able to identify tumoral microvascularity previously only seen at microscopy—a finding that correlates with tumor grade. A recent article (103) detailed the benefits of the integration of MR imaging, messenger RNA expression, and DNA copy number variations.

Conclusion

From this review, it is clear to me that neuroradiology has progressively moved from a strictly anatomy-based discipline to one that combines anatomy and physiology. As early as the 1940s, physiologic parameters such as those seen in cerebral angiography started to play an important role in the diagnosis of neurologic diseases, especially tumors. A true move toward physiologic imaging did not occur until the clinical implementation of MR imaging. Although most efforts to find imaging expressions of cellular, biologic, and genetic markers are being accomplished with MR imaging, it is my belief that our current techniques are still too few and primitive to allow us to use MR imaging as the only means of identifying and quantifying these processes. Yet, there is no doubt in my mind that these answers will be solved in the years to come and that many of these advances will appear in *Radiology* first.

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References

1. Hajdu SI, Darvishian F. Diagnosis and treatment of tumors by physicians in antiquity. Ann Clin Lab Sci 2010;40(4):386–390.
2. Missios S. Hippocrates, Galen, and the uses of trepanation in the ancient classical world. Neurosurg Focus 2007;23(1):E11.
3. Marino R Jr, Gonzales-Portillo M. Preconquest Peruvian neurosurgeons: a study of Inca and pre-Columbian trephination and the art of medicine in ancient Peru. Neurosurgery 2000;47(4):940–950.
4. Kerr PB, Caputy AJ, Horwitz NH. A history of cerebral localization. Neurosurg Focus 2005;18(4):e1.
5. Pfahler G. Cerebral skiagraphy: transactions of the American Roentgen Ray Society – 5th annual meeting. Am J Roentgenol Radium Ther Nucl Med 1904;4:174–186.
6. Sosman MC. Radiology as an aid in the diagnosis of skull and intracranial lesions. Radiology 1927;9(5):396–407.
7. Mayer EG, Wolcott HR. Roentgenographic examination of the base of the cranium in the presence of basal tumors: technic and method of diagnosis. Radiology 1928;10(4):319–341.
8. Fray WW. A roentgenological study of pineal orientation: II. A comparison of the graphic and proportional methods in proven cases of brain tumor. Radiology 1938;30(5):579–587.
9. Hare HF, Silveus E, Smedal MI. Roentgenologic diagnosis of pituitary tumors. Radiology 1949;52(2):193–198.
10. Adson AW, Ott WO, Crawford AS. A study of ventriculography. Radiology 1924;2(2):65–73.
11. Bethea WR. Intracranial studies by ventriculograms. Radiology 1929;12(2):142–150. Abbott WD. The value of encephalography as a diagnostic and therapeutic agent. Radiology 1934;23(6):672–676.
12. Schwartz CW. The gliomas roentgenologically considered. Radiology 1936;27(4):419–432.
13. Boldrey EB. The pathology of brain tumor and its relationship to roentgenologic diagnosis. Radiology 1943;41(2):107–116.
14. Johnson VC, Hodges FJ. Reliability of brain tumor localization by Roentgen methods. Radiology 1943;41(2):117–129.
15. Witner ER, Derbyshire AJ, Corrigan KE. Application of some new technics to study brain tumors. Radiology 1943;41(2):130–143.
16. Horrax G. The diagnosis and treatment of pineal tumors. Radiology 1949;52(2):186–192.
17. Lodwick GS. Cystic degeneration in glioblastoma multiforme: trapped-air sign. Radiology 1958;70(1):74–76.
18. Smith AB. Brain tumors in children. Radiology 1952;58(5):688–695, 95; discussion 711–713.
19. Forestier J. Actual technic of examination of the spinal cavities with lipiodol. Radiology 1928;11(6):481–489.
20. Gross SW. Cerebral arteriography with diodrast, fifty per cent. Radiology 1941;37(4):487–488.
21. Hodes PJ, Pendergrass EP, Young BR. Eighth nerve tumors; their roentgen manifestations. Radiology 1949;53(5):633–665, illust707–710.
22. List CF, Hodges FJ. Angiographic diagnosis of expanding intracranial lesions by vascular displacement. Radiology 1946;47(4):319–333.
23. List CF, Hodges FJ. Differential diagnosis of intracranial neoplasms by cerebral angiography. Radiology 1947;48(5):493–508.
24. Tristan TA, Hodes PJ. Meningiomas of the posterior cranial fossa. Radiology 1958;70(1):1–14.
25. Elfvin P. Angiography of the internal carotid with use of the catheter technic. Radiology 1960;75(1):80–84.
26. Gensini GG, Ecker A. Percutaneous aortocerebral angiography. A diagnostic and physiologic method. Radiology 1960;75(6):885–893.
27. Scott WG, Seaman WB. Developments in cerebral angiography with rapid serialized X-ray exposures on roll film 9 1/2 inches wide. Radiology 1951;56(1):15–30.
28. Moore RC. Cerebral arteriography in general hospital practice. Radiology 1951;57(4):487–499.
29. New PF. Carotid angiography in the localisation of supratentorial neoplasms and hamartomata. Radiology 1959;72(1):35–41.
30. Seaman WB, Ter-Pogossian MM, Schwartz HG. Localization of intracranial neoplasms with radioactive isotopes. Radiology 1954;62(1):30–36.
31. McAfee JG, Taxdal DR. Comparison of radioisotope scanning cerebral angiography and air studies in brain tumor localization. Radiology 1961;77(2):207–222.
32. Croll MN, Brady LW, Hand BM. Brain tumor localization utilizing mercury 203. Radiology 1962;78(4):635–637.
33. Kuhl DE, Pitts FW, Sanders TP, Mishkin MM. Transverse section and rectilinear brain scanning with Tc-99-m pertechnetate. Radiology 1966;86(5):822–829.
34. New PF, Scott WR, Schnur JA, Davis KR, Taveras JM. Computerized axial tomography with the EMI scanner. Radiology 1974;110(1):109–123.

35. Scott WR, New PF, Davis KR, Schnur JA. Computerized axial tomography of intracerebral and intraventricular hemorrhage. Radiology 1974;112(1):73–80.

36. New PF, Scott WR, Schnur JA, Davis KR, Taveras JM, Hochberg FH. Computed tomography with the EMI scanner in the diagnosis of primary and metastatic intracranial neoplasms. Radiology 1975;114(1):75–87.

37. Baker HL Jr. The impact of computed tomography on neuroradiologic practice. Radiology 1975;116(3):637–640.

38. Kramer RA, Janetos GP, Peristein G. An approach to contrast enhancement in computed tomography of the brain. Radiology 1975;116(3):641–647.

39. Butler AR, Horii SC, Kricheff II, Shannon MB, Budzilovich GN. Computed tomography in astrocytomas. A statistical analysis of the parameters of malignancy and the positive contrast-enhanced CT scan. Radiology 1978;129(2):433–439.

40. Miller JH, Peña AM, Segall HD. Radiological investigation of sellar region masses in children. Radiology 1980;134(1):81–87.

41. Bilaniuk LT, Zimmerman RA, Littman P, et al. Computed tomography of brain stem gliomas in children. Radiology 1980;134(1):89–95.

42. Baker HL Jr, Houser OW, Campbell JK. National Cancer Institute study: evaluation of computed tomography in the diagnosis of intracranial neoplasms. I. Overall results. Radiology 1980;136(1):91–96.

43. Potts DG, Abbott GF, von Sneidern JV. National Cancer Institute study: evaluation of computed tomography in the diagnosis of intracranial neoplasms. III. Metastatic tumors. Radiology 1980;136(3):657–664.

44. New PF, Aronow S, Hesselink JR. National Cancer Institute study: evaluation of computed tomography in the diagnosis of intracranial neoplasms. IV. Meningiomas. Radiology 1980;136(3):665–675.

45. Graeb DA, Steinbok P, Robertson WD. Transient early computed tomographic changes mimicking tumor progression after brain tumor irradiation. Radiology 1982;144(4):813–817.

46. Lauterbur PC. Image formation by induced interactions: examples employing nuclear magnetic resonance. Nature 1973;242:190–191.

47. Mansfield P. Multi-planar image formation using NMR spin echoes. J Phys C Solid State Phys 1977;10(3):L55.

48. Araki T, Inouye T, Suzuki H, Machida T, Iio M. Magnetic resonance imaging of brain tumors: measurement of T1—work in progress. Radiology 1984;150(1):95–98.

49. Brant-Zawadzki M, Badami JP, Mills CM, Norman D, Newton TH. Primary intracranial tumor imaging: a comparison of magnetic resonance and CT. Radiology 1984;150(2):435–440.

50. Kucharczyk W, Brant-Zawadzki M, Sobel D, et al. Central nervous system tumors in children: detection by magnetic resonance imaging. Radiology 1985;155(1):131–136.

51. Felix R, Schörner W, Laniado M, et al. Brain tumors: MR imaging with gadolinium-DTPA. Radiology 1985;156(3):681–688.

52. Russell EJ, Geremia GK, Johnson CE, et al. Multiple cerebral metastases: detectability with Gd-DTPA-enhanced MR imaging. Radiology 1987;165(3):609–617.

53. Davis PC, Friedman NC, Fry SM, Malko JA, Hoffmann JC Jr, Braun IF. Leptomeningeal metastasis: MR imaging. Radiology 1987;163(2):449–454.

54. Atlas SW, Grossman RI, Gomori JM, et al. Hemorrhagic intracranial malignant neoplasms: spin-echo MR imaging. Radiology 1987;164(1):71–77.

55. Earnest F 4th, Kelly PJ, Scheithauer BW, et al. Cerebral astrocytomas: histopathologic correlation of MR and CT contrast enhancement with stereotactic biopsy. Radiology 1988;166(3):823–827.

56. Haughton VM, Rimm AA, Czervionke LF, et al. Sensitivity of Gd-DTPA-enhanced MR imaging of benign extraaxial tumors. Radiology 1988;166(3):829–833.

57. Dean BL, Drayer BP, Bird CR, et al. Gliomas: classification with MR imaging. Radiology 1990;174(2):411–415.

58. Tokumaru A, O'uchi T, Eguchi T, et al. Prominent meningeal enhancement adjacent to meningioma on Gd-DTPA-enhanced MR images: histopathologic correlation. Radiology 1990;175(2):431–433.

59. Goldsher D, Litt AW, Pinto RS, Bannon KR, Kricheff II. Dural "tail" associated with meningiomas on Gd-DTPA-enhanced MR images: characteristics, differential diagnostic value, and possible implications for treatment. Radiology 1990;176(2):447–450.

60. Rubin JM, Dohrmann GJ. Intraoperative neurosurgical ultrasound in the localization and characterization of intracranial masses. Radiology 1983;148(2):519–524.

61. McGahan JP, Ellis WG, Budenz RW, Walter JP, Boggan J. Brain gliomas: sonographic characterization. Radiology 1986;159(2):485–492.

62. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 1986;161(2):401–407.

63. Moseley ME, Cohen Y, Kucharczyk J, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990;176(2):439–445.

64. Guo AC, Cummings TJ, Dash RC, Provenzale JM. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. Radiology 2002;224(1):177–183.

65. Moseley ME. Diffusion. J Magn Reson Imaging 1993;3(Suppl 1):24–25.

66. Douek P, Turner R, Pekar J, Patronas N, Le Bihan D. MR color mapping of myelin fiber orientation. J Comput Assist Tomogr 1991;15(6):923–929.

67. Lu S, Ahn D, Johnson G, Law M, Zagzag D, Grossman RI. Diffusion-tensor MR imaging of intracranial neoplasia and associated peritumoral edema: introduction of the tumor infiltration index. Radiology 2004;232(1):221–228.

68. Provenzale JM, McGraw P, Mhatre P, Guo AC, Delong D. Peritumoral brain regions in gliomas and meningiomas: investigation with isotropic diffusion-weighted MR imaging and diffusion-tensor MR imaging. Radiology 2004;232(2):451–460.

69. Goebell E, Paustenbach S, Vaeterlein O, et al. Low-grade and anaplastic gliomas: differences in architecture evaluated with diffusion-tensor MR imaging. Radiology 2006;239(1):217–222.

70. Van Cauter S, Veraart J, Sijbers J, et al. Gliomas: diffusion kurtosis MR imaging in grading. Radiology 2012;263(2):492–501.

71. Axel L. Cerebral blood flow determination by rapid-sequence computed tomography: theoretical analysis. Radiology 1980;137(3):679–686.

72. Edelman RR, Mattle HP, Atkinson DJ, et al. Cerebral blood flow: assessment with dynamic contrast-enhanced T2*-weighted MR imaging at 1.5 T. Radiology 1990;176(1):211–220.

73. Maeda M, Itoh S, Kimura H, et al. Tumor vascularity in the brain: evaluation with dy-

namic susceptibility-contrast MR imaging. Radiology 1993;189(1):233–238.

74. Aronen HJ, Gazit IE, Louis DN, et al. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology 1994;191(1):41–51.

75. Danchaivijitr N, Waldman AD, Tozer DJ, et al. Low-grade gliomas: do changes in rCBV measurements at longitudinal perfusion-weighted MR imaging predict malignant transformation? Radiology 2008;247(1):170–178.

76. Law M, Young RJ, Babb JS, et al. Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology 2008;247(2):490–498.

77. Warmuth C, Gunther M, Zimmer C. Quantification of blood flow in brain tumors: comparison of arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging. Radiology 2003;228(2):523–532.

78. Ng TC, Majors AW, Meany TF. In vivo MR spectroscopy of human subjects with a 1.4-T whole-body MR imager. Radiology 1986;158(2):517–520.

79. Luyten PR, den Hollander JA. Observation of metabolites in the human brain by MR spectroscopy. Radiology 1986;161(3):795–798.

80. Bruhn H, Frahm J, Gyngell ML, et al. Noninvasive differentiation of tumors with use of localized H-1 MR spectroscopy in vivo: initial experience in patients with cerebral tumors. Radiology 1989;172(2):541–548.

81. Fulham MJ, Bizzi A, Dietz MJ, et al. Mapping of brain tumor metabolites with proton MR spectroscopic imaging: clinical relevance. Radiology 1992;185(3):675–686.

82. Bizzi A, Movsas B, Tedeschi G, et al. Response of non-Hodgkin lymphoma to radiation therapy: early and long-term assessment with H-1 MR spectroscopic imaging. Radiology 1995;194(1):271–276.

83. Rabinov JD, Lee PL, Barker FG, et al. In vivo 3-T MR spectroscopy in the distinction of recurrent glioma versus radiation effects: initial experience. Radiology 2002;225(3):871–879.

84. Kim SH, Chang KH, Song IC, et al. Brain abscess and brain tumor: discrimination with in vivo H-1 MR spectroscopy. Radiology 1997;204(1):239–245.

85. Adamson AJ, Rand SD, Prost RW, Kim TA, Schultz C, Haughton VM. Focal brain lesions: effect of single-voxel proton MR spectroscopic findings on treatment decisions. Radiology 1998;209(1):73–78.

86. Law M, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW. High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. Radiology 2002;222(3):715–721.

87. Kovanlikaya A, Panigrahy A, Krieger MD, et al. Untreated pediatric primitive neuroectodermal tumor in vivo: quantitation of taurine with MR spectroscopy. Radiology 2005;236(3):1020–1025.

88. Kallenberg K, Bock HC, Helms G, et al. Untreated glioblastoma multiforme: increased myo-inositol and glutamine levels in the contralateral cerebral hemisphere at proton MR spectroscopy. Radiology 2009;253(3):805–812.

89. Converting Energy to Medical Progress. Vital Legacy of BER Medical Sciences. 50-Year Commitment to Improved Healthcare through Nuclear Medicine. http://www.doemedicalsciences.org/pubs/sc0033/vital.shtml. Published April 2001. Accessed February 25, 2014.

90. Di Chiro G, Hatazawa J, Katz DA, Rizzoli HV, De Michele DJ. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. Radiology 1987;164(2):521–526.

91. Pruim J, Willemsen AT, Molenaar WM, et al. Brain tumors: L-[1-C-11]tyrosine PET for visualization and quantification of protein synthesis rate. Radiology 1995;197(1):221–226.

92. Ogawa T, Shishido F, Kanno I, et al. Cerebral glioma: evaluation with methionine PET. Radiology 1993;186(1):45–53.

93. Kwee SA, Ko JP, Jiang CS, Watters MR, Coel MN. Solitary brain lesions enhancing at MR imaging: evaluation with fluorine 18 fluorocholine PET. Radiology 2007;244(2):557–565.

94. Achten E, Jackson GD, Cameron JA, Abbott DF, Stella DL, Fabinyi GC. Presurgical evaluation of the motor hand area with functional MR imaging in patients with tumors and dysplastic lesions. Radiology 1999;210(2):529–538.

95. Petrella JR, Shah LM, Harris KM, et al. Preoperative functional MR imaging localization of language and motor areas: effect on therapeutic decision making in patients with potentially resectable brain tumors. Radiology 2006;240(3):793–802.

96. Schwartz RB, Hsu L, Wong TZ, et al. Intraoperative MR imaging guidance for intracranial neurosurgery: experience with the first 200 cases. Radiology 1999;211(2):477–488.

97. Martin AJ, Hall WA, Liu H, et al. Brain tumor resection: intraoperative monitoring with high-field-strength MR imaging-initial results. Radiology 2000;215(1):221–228.

98. Pope WB, Chen JH, Dong J, et al. Relationship between gene expression and enhancement in glioblastoma multiforme: exploratory DNA microarray analysis. Radiology 2008;249(1):268–277.

99. Barajas RF Jr, Hodgson JG, Chang JS, et al. Glioblastoma multiforme regional genetic and cellular expression patterns: influence on anatomic and physiologic MR imaging. Radiology 2010;254(2):564–576.

100. Gutman DA, Cooper LA, Hwang SN, et al. MR imaging predictors of molecular profile and survival: multi-institutional study of the TCGA glioblastoma data set. Radiology 2013;267(2):560–569.

101. Schmieder AH, Winter PM, Williams TA, et al. Molecular MR imaging of neovascular progression in the Vx2 tumor with αvβ3-targeted paramagnetic nanoparticles. Radiology 2013;268(2):470–480.

102. Christoforidis GA, Yang M, Abduljalil A, et al. "Tumoral pseudoblush" identified within gliomas at high-spatial-resolution ultrahigh-field-strength gradient-echo MR imaging corresponds to microvascularity at stereotactic biopsy. Radiology 2012;264(1):210–217.

103. Jamshidi N, Diehn M, Bredel M, Kuo MD. Illuminating radiogenomic characteristics of glioblastoma multiforme through integration of MR imaging, messenger RNA expression, and DNA copy number variation. Radiology 2014;270(1):1–2.