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Intraoperative MR Imaging: Making an Impact on Outcomes for Patients with Brain Tumors

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Thromboembolic Events during Endovascular Coil Occlusion of Cerebral Aneurysms

In this issue of the *AJNR*, Rordorf et al (page 5) report their experience with the use of diffusion-weighted MR imaging in detecting clinically silent thromboembolic events that occurred during endovascular coil occlusion of unruptured aneurysms. In a recent issue of the *AJNR*, Biondi et al (1) reported their experience using diffusion-weighted imaging after endovascular coil occlusion of both ruptured and unruptured aneurysms. Rordorf's group imaged 14 patients within 48 hours after elective Gugliemli detachable coil (GDC) occlusion of their unruptured aneurysms. Small diffusion-weighted imaging abnormalities, suspected to represent embolic infarctions, were noted in eight (57%) patients. Six patients had multiple diffusion-weighted imaging abnormalities. All patients were clinically asymptomatic, except for one in whom there was coil stretching and herniation into the parent vessel, resulting in a symptomatic infarct. Biondi's group imaged 20 patients before, 2 to 4 hours after, and 48 hours after GDC occlusion of their aneurysms, 11 of which were ruptured. Diffusion-weighted imaging abnormalities were seen after treatment in only two patients (10%), both of whom were asymptomatic. Clinical management was not altered by the imaging findings in either series.

As is the situation with clinically evident thromboembolic events, which are reported in the literature to range from 2.5% to 28% of cases (2, 3), we are once again left with a discrepancy in the frequency of clinically silent thromboembolic events associated with the GDC treatment of aneurysms. Many interacting variables may account for the disparities in the reported frequency of both clinically evident and silent thromboembolic events. These include, but are not limited to, the anticoagulation regimen before, during, and after treatment; aneurysm location, size, and neck morphology; number of guiding catheters and microcatheters; clinical status of the patient; and skill and experience of the operator. On the basis of these variables, two differences between the Rordorf and Biondi series deserve mention. In Rodorf's series, intravenous heparin was administered to prolong the activated clotting time to greater than 2.5 times baseline. In Biondi's series, the target activated clotting time was five times baseline. In addition, Biondi's series included intravenous aspirin administration during the procedure in selected patients. There was also a notable difference in the degree of final aneurysm occlusion between the two series. Rodorf et al reported only three (21%) patients with complete occlusion and five (36%) patients with residual aneurysm filling, whereas Biondi reported aneurysm occlusion in 18 (90%) patients and small neck remnants in two (10%) patients. The numbers are small, but it is reasonable to postulate that differences in the anticoagulation regimen and degree of aneurysm occlusion may at least partially account for the difference between the two series in the percentage of new diffusion-weighted imaging abnormalities seen after treatment.

What is there to be learned from these two series? First, it is unlikely that routinely obtaining diffusion-weighted images after endovascular treatment of cerebral aneurysms is going to be cost-effective in significantly impacting subsequent patient management. Combining the two series, the diffusion-weighted imaging abnormalities in nine of the ten patients were ''clinically silent,'' and did not prompt a change in the posttreatment care in any of the patients. The remaining patient had a clinically evident infarct, which was probably known before posttreatment imaging was performed. Nonetheless, it is apparent that diffusion-weighted imaging will be a very important tool to help us understand and prevent future complications. Diffusion-weighted imaging provides us with a very sensitive and objective measure of thromboembolic events that occur during treatment. Much uncertainty currently exists regarding the optimal anticoagulation regimen that should be employed for the endovascular treatment of both ruptured and unruptured aneurysms. Investigators should be encouraged to seek funding that will allow routine diffusion-weighted imaging after endovascular treatment of aneurysms, which I hope will result in objective data regarding optimal anticoagulation regimens.

Finally, I agree with Rordorf et al that it is unlikely that the new diffusion-weighted imaging abnormalities revealed in their patients would cause abnormalities detectable on neuropsychological testing. It must be remembered, however, that the unexpectedly high rate of measurable cognitive impairment after surgical clipping of unruptured cerebral aneurysms was unsuspected prior to the publication of the results of The International Study of Unruptured Intracranial Aneurysms (4), primarily because cognition in postoperative patients had not been previously evaluated in a scientific and systematic fashion. In the continuing process of evaluating endovascular treatment versus surgical treatment for cerebral aneurysms, we need to document in a fashion that is undeniable to the skeptics that cognition is not significantly impaired after endovascular treatment.

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Intraoperative MR Imaging: Making an Impact on Outcomes for Patients with Brain Tumors

There is little question that the extent of tumor removal significantly impacts outcome for the majority of patients with brain tumors, especially gliomas. Notwithstanding, it is still a considerable feat to achieve a complete (100%) or radical (> 95%) radiographic tumor resection despite the advances that have been made in the surgeon's armamentarium. Two articles in this issue of the *AJNR* bring us closer to achieving the desired surgical result, thanks to advances with intraoperative MR (iMR) imaging.

The study by Schneider et al (page 89), describes the utility of a 0.5-T vertical ''doughnut'' configuration magnet; the surgeon stands within a 58-cm space between the magnets. The main advantage of this system is that the operating table is stationary, and does not require movement into the magnet. Likewise, the magnet does not have to move into the physical space of the patient. As with any iMR imaging system, requirements for a successful procedure include MR-compatible surgical and anesthetic equipment, proper room shielding, and suitable head coils. This iMR imaging system also uses the technique of interactive, image-guided surgery to allow surgical navigation during the procedure with the Flashpoint Position Encoder and the MR Track Pointer. The disadvantages of this intraoperative imaging system include a small space to work in, a relatively long image acquisition time, and a magnetic field strength that makes intraoperative functional or metabolic imaging difficult, at best.

Despite the potential limitations, Schneider et al achieved complete, or nearly complete, resection of low-grade gliomas in 11 of 12 patients by use of the feedback they received as intraoperative images were obtained. Although this is a spectacular result, one large caveat remains; namely, the inability to avoid surgical morbidity with anatomic images alone. In other words, the use of direct physiological stimulation mapping of functional (eg, motor, sensory, language) pathways cannot be replaced with iMR imaging. iMR imaging must be used in conjunction with the fundamental principles of functional brain mapping in order to achieve radical resections with the least morbidity. Assessing intraoperative complications, such as swelling or bleeding, is also critical in achieving the best outcome possible for patients with brain tumors.

Although surgeons recognize the value iMR imaging adds to the surgical procedure, a potentially dangerous problem exists with spurious contrast enhancement leaking into the resection margin. This has made it difficult to assess adequately the true extent of resection in lesions that preoperatively enhance with contrast agents. In the study by Knauth et al (page 99), the authors report the novel use of monocrystalline iron oxide nanoparticles, or MIONs, to bypass this problem. MIONs are stored within glioma cells for longer periods than they circulate in the blood. This creates a window of opportunity to avoid surgically induced leakage of contrast enhancement. The result of this finding, as elegantly described by the investigators, is that intracellular storage of MIONs may yield an excellent means by which a tumor can be enhanced on preoperative imaging and at the time of surgical resection without causing false leakage during intraoperative imaging. The latter could result in unnecessary resection of tissue that does not contain tumor. Thus, MIONs may be the ideal contrast agent for high-grade gliomas. As the authors readily admit, a limitation to imaging low-grade gliomas may exist, and it is not known whether these tumors will be able to undergo endocytosis of MION particles. Because a disrupted blood-brain barrier is not essential to MION-induced enhancement of tumors, this strategy could solve the problem of spurious intraoperative MR signals simulating residual tumor caused by edema or microhemorrhage within the resection margin.

It certainly appears that iMR imaging is here to stay and will make a significant impact on patient outcome. Nonetheless, a number of issues must be resolved, including the type of magnet system (ie, low vs high field strength), ease of imaging during a complicated operative procedure, and the need to generate intraoperative functional and metabolic data. Neurosurgeons must realize that input from neuroradiologists will be as important intraoperatively for interpreting these findings as it is extraoperatively. One thing is certain—excitement and widespread optimism have been created by knowing that iMR imaging is now a reality.

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Detection of Lymph Node Metastases in the Neck: Radiologic Criteria

Regional metastasis is one of the most important factors in the prognosis and treatment of patients with head and neck squamous cell cancer. In addition, because lymphatic metastasis is a frequent event that impacts prognosis, a decision to treat the lymph nodes in the neck has to be made in almost all patients, even if metastases are not apparent clinically. It is therefore important to assess as reliably as possible whether a patient has regional lymph node metastases.

It is well known that palpation is an inaccurate technique to stage cancer in the neck. In a recent decision-analysis study, a risk of occult neck metastases (in a palpatory-negative neck) above 20% was found to be indicative for elective neck treatment, either radiation therapy or surgery. This risk of occult metastasis, which can occur in both sides of the neck, is determined by characteristics of the primary tumor such as size, site, and several biological criteria (1). Because of the increased risk of nodal metastases, even in clinically negative necks, most patients with tumors staged as T2 or larger undergo some form of elective neck treatment. The disadvantage of this policy is that the majority of patients do not harbor metastases and, therefore, will be subjected to the morbidity of unnecessary treatment. By detecting some otherwise clinically occult adenopathy, modern imaging techniques may have increased sensitivity for detecting positive nodes, and consequently, may decrease the risk of occult metastasis to below 20%. If this can be accomplished, the clinician may refrain from a neck dissection or radiation, and adapt a wait-and-see policy with careful follow-up to detect a neck metastasis as early as possible (2).

Imaging techniques like CT, MR, and sonography are more accurate than palpation. Most clinicians have maintained, however, that the accuracy of these techniques is not high enough to justify a change of policy. Indeed, in 25% of pathologically verified tumor-positive neck dissections, only micrometastases smaller than 3 mm, which are undetectable by most techniques, are present (3). Lymph nodes 2–3 mm in size can be seen as nodules on CT and MR images, and may even be better seen with high-resolution scanners. Nonetheless, differentiation between benign and malignant metastatic disease still remains a problem. Recently, other techniques such as radioimmunoscintigraphy (4) and positron emission tomography (5) have been explored, but these expensive techniques still have to prove their value in clinical practice.

Sonographic criteria, such as nodal size and configuration of the lesion, and Doppler sonographic criteria have been studied extensively for their value in differentiating between benign and malignant lymphatic disease in the neck. The minimal axial diameter appears to be the most accurate size criterion, compared to the maximal axial diameter and the longitudinal diameter (6, 7). Regarding the aspect of lymph nodes on sonograms, the echogenic hilus appears to be a reliable parameter (7). The configuration (shape) of the node might be important, but some authors doubt its value (8). Sonography-guided fine-needle aspiration cytology (FNAC) has been shown to be very accurate in the evaluation of regional metastatic disease. It combines the high sensitivity of sonography with the excellent specificity of FNAC. The reported sensitivity of sonography-guided FNAC in the N0 neck ranges from 48% to 73% (6, 9, 10), whereas the reported specificity is 100% (11). In the United States, this technique has received less acceptance because it is labor-intensive and operator-dependent. False-negative results may be the result of sampling the wrong node or the wrong part of the correct node. Furthermore, the cytopathologist may overlook small nests or single tumor cells.

The potential value of Doppler sonographic criteria (avascular pattern, scattered pattern, peripheral vascularity) as an adjunct to differentiate between benign and metastatic lymph nodes has been the topic of various reports. Because gray-scale criteria are not very accurate, there is a great need for additional criteria for small lymph nodes. In this issue of the *AJNR,* Yonetsu et al (page 163) report on the Doppler sonographic findings in 338 lymph nodes from 73 patients with head and neck cancer in an effort to improve the accuracy of conventional sonography. The authors were able to define a new, more accurate combination of size and Doppler criteria. They report that the combined use of short-axis diameter and Doppler blood flow pattern (the absence or presence of ''normal'' hilar flow) increased the diagnostic accuracy compared to the use of short axis diameter alone. These combined criteria yield a very high sensitivity ($>$ 89%) and specificity ($>$ 94%). The authors performed a histologically verified study in which they analyzed criteria for metastatic lymphadenopathy. Although the authors performed a large study and were able to improve the results of conventional sonography significantly, the article raises some methodological questions. To allow comparison of results of different authors, the reporting of the results should be as uniform as possible. For neck imaging, the sensitivity and specificity per neck side should be reported, ideally for the clinically N0 neck separately, as this is the most clinically relevant. The size criteria used should be defined, as well as the histopathologic techniques used to assess the specimen. If the neck is categorized into different levels, the definition of the levels as proposed by the American Academy of Otolaryngology should be used. Yonetsu et al compared sonographic-histopathologic findings per node, and correlated the nodes on the sonogram and in the surgical specimen on the basis of relation to surrounding struc-

tures and size of the nodes. This method may cause false sonographic-histopathologic correlations, however, especially in the case of small nodes. Because only a limited number of nodes per neck side were correlated, there might have been small metastatic nodes in the specimen that were not seen on sonograms and thus not included in the study. The authors introduced a new classification of neck levels without indicating how it differed from the internationally accepted classification. Furthermore, the authors defined their short-axis diameter as ''the greatest diameter on the maximum axial cross-sectional area of a node.'' Actually, this appears to be the maximum axial diameter. The paramount question is what value can be assigned to these findings for making treatment decisions in patients with head and neck cancer?

First, the predictive value of power Doppler parameters, such as hilar blood flow, remains controversial. In the March 2000 issue of the *AJNR*, this same group compared in a multivariate study the gray-scale and power Doppler parameters (7). In contrast to their current article, they reported that Doppler features did not add significant predictive value to gray-scale criteria in differentiating metastatic from reactive nodes.

Second, clinicians are especially interested in the accuracy of modern imaging techniques for staging of the N0 neck. The high sensitivity and specificity reported in this article only have a limited clinical value as they were calculated per lymph node, and probably a majority of the metastatic lymph nodes were palpable. As a consequence, the sensitivity would have been lower if the study had been limited to an N0-neck population.

Third, clinicians are more interested in the status of the entire neck than in the presence or absence of metastatic disease in lymph nodes separately. Thus, after having defined the optimal criteria in single nodes, it would have been very interesting to see if these new criteria were advantageous for the entire neck as well.

Yonetsu et al studied the potential of a combination of gray-scale and duplex sonography criteria to discriminate between benign and malignant disease, and found a possibly valuable new combination of criteria. They should be given credit for this observation and report. The clinical value and accuracy of this new combination of criteria will have to be assessed in a population of patients with cancer and stage N0 (clinically nonpalpable) neck disease. If the duplex criteria are accurate in very small lymph nodes, there might be an important impact on clinical decision making. On the other hand, a combination of gray-scale and duplex sonography criteria may also be helpful in selecting nodes for sonography-guided FNAC. The use of contrast-enhanced Doppler sonography may also further increase the reliability and accuracy of duplex criteria in small lymph nodes.

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