AJNR

Representation of the ASNR in the AMA House of Delegates at Risk

Arliss Pollack and Pat Turski

AJNR Am J Neuroradiol 2006, 27 (2) 239-240
http://www.ajnr.org/content/27/2/239

COMMENTARY

Representation of the ASNR in the AMA House of Delegates at Risk

Beginning in 1993, the ASNR worked aggressively to gain a seat in the AMA House of Delegates. The process was arduous and was only successful after 3 years of data collection, reapplications, membership recruitment, and debate. Fortunately, persistence was rewarded and in 1996 the ASNR gained a seat in the AMA House of Delegates and access to several key committees of the AMA such as the Current Procedural Terminology editorial panel (CPT), the Practice Expense Advisory Committee (PEAC), and the Resource-based Relative Value System Update Committee (RUC). Over the years access to these committees has allowed the ASNR to comment on CMS decisions, advocate for new CPT codes, develop and participate in RUC surveys, and testify at RUC committee deliberations.

In many instances, this advocacy has resulted in a positive outcome. For example, when the MRA head and neck codes were revised, the ASNR played a key role in the development of the codes, conducted surveys, and represented neuroradiology during the deliberations at the RUC committee. When confronted with the requirement to divide this code into 6 codes, we faced the possibility of having the one code for head and neck simply divided by 6 to satisfy the CMS goal of revenue neutrality. This would have devastated reimbursement for MRA, and we fought vigorously to get it classified as new work so it would not have to be revenue neutral. In another instance when the MR codes were divided into without, with, and without/with contrast, society representatives at the RUC worked tirelessly to assure proper valuation. The ASNR contributes to the development of many codes and provides much needed perspective regarding the importance and complexity of imaging procedures. The fMRI codes are currently under development and will be considered at the February 2006 RUC committee. Without the society's input, there is significant risk that new procedures such as fMRI could be undervalued.

In 2006, the ASNR will need to recertify with the AMA to retain its seat in the AMA House of Delegates. One of the key elements in the AMA recertification process is the requirement that 35% of a specialty society's senior members hold membership in the AMA. Currently, only 25% of ASNR senior members are members of the AMA, thus placing the society at significant risk of losing representation on important committees. This is a real threat and at least one society has lost its seat in the last year. There are many specialty societies that would like to have a seat in the AMA House of Delegates and are waiting for an opportunity to fill a vacant seat. The original ASNR approval occurred during a time when the AMA was receptive to expanding seats to accommodate specialty societies—this may not be the case in the future. If the ASNR seat is lost, it will be very difficult, if not impossible, to regain the level of representation and advocacy that we currently have within the large economic landscape of organized medicine. If our representation is lost, who will advocate for new codes that impact the practice of neuroradiology?

The need for representative advocacy has never been greater. A current example is the across-the-board 4.4% reduction in 2006 and a potential 26% reduction over the next 5 years in physician Medicare payments unless new legislation is approved overriding this reduction. The AMA, in concert with state chapters and specialty societies, leads the process and has worked with Congress to introduce new legislation to modify the current law and reduce or eliminate the reduction. The AMA is pursuing a series of regulatory changes that will also reduce the effects of the proposed cuts in physician payments. The AMA is aggressively pressing Congress and the Administration to reduce costly and counterproductive regulatory burdens and halt unfunded mandates. Your membership in the AMA will add support to these important economic initiatives.

Another of the AMA top priorities is medical liability reform. Many states are facing a malpractice crisis and the AMA has worked closely with state chapters to develop a rational approach to medical liability reform. A recent example is the December 1, 2005 meeting of the AMA with the Washington, DC, city council in which testimony clearly showed that the growing medical liability problem threatens patients' access to health care due to the relocation of physicians outside of the city. The AMA assisted local physicians in staging a rally on the steps of the John Wilson Building. Meaningful liability reform will require major effects at the state and national levels. The AMA is the only organization with the resources to advocate for new legislation and change.

The ASNR needs a close relationship with the AMA to maintain socio-economic collaborations. Negotiations regarding codes and relative value units are conducted through AMA committees. Issues of safety, quality, and utilization are now being addressed within the AMA. Without the participation of ASNR representatives there is a risk that neuroradiology procedures will be undervalued, misrepresented, or inappropriately categorized. The AMA is working to enact legislation to promote voluntary reporting systems for improving patient care with effective confidentiality protections. It is also advocating for a fair and balanced framework for implementation of public and private quality improvement initiatives and developing clinical performance measures for treating disease. The ASNR needs to be a part of these discussions and provide leadership in how imaging procedures are integrated into these programs.

Other AMA initiatives include building public support for tax credits and insurance market reforms that move toward a system of personalized health insurance. The AMA has called for a number of managed care reforms to restore balance and fairness to the system, including strengthening state-managed care laws.

The ASNR clinical practice committees are organized to interface with many national initiatives. Committees for Standards and Guidelines, Coding and Reimbursement, Credentials and Contracts, Government Relations, and Utilization have been developed to support the society in socio-economic issues such as quality, safety, and Medicare coverage. Recently, the ASNR established a closer relationship with the ACR Commission for Neuroradiology, thus enhancing access to advocacy activities sponsored by the ACR. The impact of the ASNR

efforts is greatly amplified by collaborations with partners such as the ACR and AMA.

We strongly encourage you to maintain, renew or initiate membership in the AMA to provide the ASNR with the broadest possible options for collaboration and advocacy on socioeconomic issues. For AMA membership information you can go directly to https://membership.ama-assn.org/JoinRenew/ or call 800-262-3211.

Arliss Pollack, MD
Pat Turski, MD
ASNR Clinical Practice Committees

COMMENTARY

Have You Been Smoking Something That Is Biologically Active?

Up in smoke. . . . That's where my money goes.
—Cheech and Chong

Physicians worldwide are currently spending millions of dollars of other people's money for endovascular coils that are commonly called "biologically active." I fear that too few of these physicians have paused to consider what the term "biologically active" actually means and why they are spending so much money for these coils. I therefore suggest that we critically examine the term "biologically active." Let us start with "biologically." After consulting several dictionaries, I propose that we define "biologically" as "in a manner related to a living organism." I will similarly propose that we define "active" as "causing change." Clearly, these terms are extremely broad. When the words are combined to form "biologically active," we are still left with an extremely broad term that might be most simply defined as "causing change in a living organism." That definition would lead me to conclude that an enormous number of objects in the universe are biologically active, ranging from my college roommate's stash, a Grateful Dead song, the sun, a cup of coffee, and the journal you are reading to any material implanted in an animal, plant, fungus, bacteria, or virus. The term "biologic activity" is thus so broad as to be almost useless.

When the term "biologically active" is used in reference to endovascular coils for cerebral aneurysm therapy, I think that it is intended to mean "eliciting more of a tissue response than platinum." Although this definition of biologic activity is a bit less broad, it is still so broad that it is nearly useless as a scientific term. Yet, it appears to be rather useful as a marketing term.

It remains unknown exactly what the tissue response to a biologically active coil should ideally be to make it more efficacious than platinum. It will only be known post hoc—that is, after a device is shown to safely reduce aneurysm recurrence and rehemorrhage, we will know that it generates a favorable tissue response. In the meantime, theoretically beneficial "biologic activities" such as inflammation, fibrosis, neointima formation, and endothelialization are proposed.[1-6]

Detachable platinum coils were certainly a major advance in the treatment of cerebral aneurysms.[7,8] Contrary to popular opinion, platinum coils are "biologically active." When implanted in a biologic system (eg, human cerebral aneurysm), they elicit a tissue response (eg, thrombosis and fibrosis). Platinum coils disturb blood flow within an aneurysm and thereby promote thrombosis. Thrombosis then progresses to fibrosis in many cases. The major weakness of platinum coils is that the rate of aneurysm recurrence is about 14%–21% overall,[9-12] which is about 10 times higher than the recurrence rate following surgical clipping.[13] Theoretically, this recurrence rate may be related to the *relatively* biologically "inert" or "inactive" nature of platinum. This "inactive" nature of platinum made it an attractive material for coil construction during the development of coils for cerebral aneurysm therapy because biologic activities such as thrombosis, fibrosis, and inflammation might lead to clinical complications. This relative biologic inactivity, however, is now hypothesized to be causative of aneurysm recurrences following endovascular coil therapy.[1-3,5,6] The hypothesis is that aneurysm recurrences are due to a failure of platinum coils to induce an adequate biologic response to the coils rather than to a mechanical failure of the coils. The hypothesis leads us logically to theorize that aneurysm recurrences can be reduced by changing the biologic response to the chemistry of the device. Thus, coil modifications have been proposed that are directed at the biologic response to the chemistry of the device rather than the physical properties of the device. This hypothesis is widely discussed and has led to the introduction of multiple devices for aneurysm therapy; however, the hypothesis remains unproved. Indeed, much of the research published in this area would fail to pass the basic standards of a high school science project.

What we seek with biologically active coils is a nearly perfect balance between promotion of an effect that reduces aneurysm rehemorrhage and recurrence—which is primarily how we would measure *efficacy*—and avoidance of negative clinical effects, especially promotion of aneurysm rupture and/or excessive thrombosis—which is primarily how we would measure *safety*. The choice of biologically active materials, however, is as much related to regulatory issues as it is related to biologic issues. The first priority of development of such a device has been to get the device past regulatory hurdles and onto the market, with proof of efficacy of biologic activity as a secondary priority. Before biologic activity is addressed, "regulatory inactivity" is established.

The combination of platinum and polyglycolic acid/polylactic acid (PGLA) polymer in Matrix coils (Boston Scientific, Natick, Mass) proved to be fairly straightforward in terms of passing through the regulatory process at the US Food and Drug Administration (FDA). Platinum coils were already approved by the FDA for treatment of cerebral aneurysms. PGLA polymer has been implanted in millions of humans as Vicryl (Ethicon, Cincinnati, Ohio) suture and is, therefore, well known to have an excellent safety profile in humans. With the help of this historical information, Boston Scientific managed to gain approval for Matrix coils by claiming that this device was "substantially equivalent" to another FDA-approved device (ie, platinum coils). Ironically, however, the market-

Dr. Cloft has received research funding from Cordis and MicroVention.

ing of these coils is based on the coils being substantially *inequivalent* to platinum coils. Whoever said that "you can't have it both ways" clearly did not work for the medical device industry.

"Regulatory inactivity" has continued to have excessive influence on the development of biologically active coils. The Cerecyte coil (Micrus, Sunnyvale, Calif), the Nexus coil (MicroTherapeutics, Irvine, Calif), and the HydroCoil (MicroVention, Aliso Viejo, Calif) were all approved by the FDA on the basis of claims that they are "substantially equivalent" to platinum coils. Cerecyte and Nexus coils are "me-too" products that both deliver PGLA polymer. I am quite certain that they were produced and sold not because the manufacturers thought that they were the best way to reduce aneurysm recurrences. Rather, they were produced and sold because the manufacturers thought physicians would buy them just as they bought Matrix coils—and, of course, because the regulatory process was trivial. This is not "evidence-based" medicine. This is "fad-based" medicine. Other device modifications such as collagen [1,2] and cells on coils [6] might improve the recurrence rate of cerebral aneurysms. The regulatory pathway, however, would be rather difficult for such devices containing biologically derived materials, thus making medical device manufacturers much less interested in pursuing these treatment strategies. Why would a medical device manufacturer want to take a risk on devices that have expensive regulatory pathways when it can readily market the "biologic activity" of coils that have "regulatory inactivity"?

If you are not confused and concerned by inconsistencies in medical device regulation, you are probably not paying attention. Recently, drug-eluting stents have revolutionized the management of coronary artery disease. They, as were the coils containing PGLA, were designed to elicit a different response than bare metal. Because of regulatory inconsistencies, however, the introduction of drug-eluting stents had a very different course than the introduction of biologically active coils. Drug-eluting stents were required to get premarket approval (PMA) from the FDA. PMA of medical devices, in most cases, involves collection of data in prospective, randomized, controlled trials. Are coils that deliver PGLA not drug-eluting coils and therefore worthy of the same level of regulation as drug-eluting stents? These coils deliver a foreign material (ie, PGLA), which then dissolves over several weeks, with the clear intent of that material eliciting a biologic response from the surrounding tissue. Perhaps PGLA attached to coils was not looked at as a drug because of its historical use as a mechanical device (eg, Vicryl suture) rather than as a drug. In my opinion, however, the coils incorporating PGLA should be considered drug-eluting coils.

Few medical devices are truly revolutionary. Rather, most devices offer an incremental improvement in therapy. We need to realize that we rarely succeed with the first iteration of an invention. As a schoolboy, I learned that Thomas Edison's laboratory tested thousands of filaments in the process of inventing the light bulb. With that in mind, doesn't it seem absurd that we would expect the very first iterations of biologically active coils would dramatically reduce cerebral aneurysm recurrences?

It is time for the field of interventional neuroradiology to mature scientifically. Part of that maturation should be the development of a healthy skepticism toward new devices. The only reliable way to prove that an incremental improvement has truly been made is to conduct prospective, randomized, controlled trials that compare a theoretically improved device to the current standard of treatment. Thus far, biologically active coils have only been studied with single-center case series and postmarket registries. These registries are generally initiated, funded, and controlled by the device manufacturers. The device manufacturers have the right to "spin" the data from their own registry and also the right to entirely avoid the peer-reviewed literature process if they wish.[14] Thus, postmarket registry data are potentially very biased. Also, because a postmarket registry lacks a control group other than historical controls from the literature, data interpretation is very limited. Indeed, unless a registry demonstrates an overwhelmingly positive or negative safety or efficacy result, it is impossible to conclude that the device evaluated is truly significantly different from other devices.

One hopes that the completion of the International Subarachnoid Aneurysm Trial (ISAT)[8] marks a major turning point by proving that prospective, randomized, controlled trials of treatment strategies for cerebral aneurysms are quite feasible and tremendously valuable. Indeed, such trials are the primary means by which we can advance the field. ISAT established that endovascular therapy of ruptured cerebral aneurysms was associated with a 7.4% absolute reduction in morbidity and mortality relative to surgical clipping.[8] This demonstration of risk reduction has resulted in a major shift toward the use of endovascular therapy for cerebral aneurysms. It is very encouraging that prospective, randomized, controlled trials to compare safety and efficacy of platinum coils to biologically active coils are underway. The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) and the Ceracyte Coil Trial are prospective, randomized, controlled trials evaluating the safety and efficacy of biologically active coils relative to platinum coils. These are extremely important because they represent an essential maturation of the field of endovascular aneurysm therapy.

Medical device manufacturers are in the business of making money. They make money by selling medical devices. They interface primarily with physicians in making those sales. Physicians have proved to be pretty easy "marks" for marketing and sales personnel from the medical device industry. Under the influence of the medical device industry, physicians have been spent millions of health care dollars for unproven devices. If we buy these devices with little or no proof of superior safety and/or efficacy, we are a major part of the problem. We are then not *leading* the development of devices through science, but rather *following* the development of devices through marketing. The only clear winner here is the medical device industry, which measures its success primarily in terms of financial profits and stock price. As physicians adhering to the Hippocratic Oath, our success is measured in terms of clinical outcomes. We have a responsibility to our patients to conduct clinically relevant, scientific research that proves or disproves the clinical efficacy and safety of the devices that we permanently implant into those patients.

Harry J. Cloft, MD, PhD

References

1. Kallmes DF, Fujiwara NH, Yuen D, et al. **A collagen-based coil for embolization of saccular aneurysms in a New Zealand White rabbit model.** *AJNR Am J Neuroradiol* 2003;24:591–96
2. Dawson RC 3rd, Shengelaia GG, Krisht AF, et al. **Histologic effects of collagen-filled interlocking detachable coils in the ablation of experimental aneurysms in swine.** *AJNR Am J Neuroradiol* 1996;17:853–58
3. Murayama Y, Tateshima S, Gonzalez NR, et al. **Matrix and bioabsorbable polymeric coils accelerate healing of intracranial aneurysms: long-term experimental study.** *Stroke* 2003;34:2031–37
4. Kallmes DF, Fujiwara NH. **New expandable hydrogel-platinum coil hybrid device for aneurysm embolization.** *AJNR Am J Neuroradiol* 2002;23:1580–88
5. Ahuja AA, Hergenrother RW, Strother CM, et al. **Platinum coil coatings to increase thrombogenicity: a preliminary study in rabbits.** *AJNR Am J Neuroradiol* 1993;14:794–98
6. Marx WE, Cloft HJ, Helm GA, et al. **Endovascular treatment of experimental aneurysms by use of biologically modified embolic devices: coil-mediated intraaneurysmal delivery of fibroblast tissue allografts.** *AJNR Am J Neuroradiol* 2001;22:323–33
7. Guglielmi G, Vinuela F, Dion J, et al. **Electrothrombosis of saccular aneurysms via endovascular approach. Part 2. Preliminary clinical experience.** *J Neurosurg* 1991;75:8–14
8. Molyneux AJ, Kerr RS, Yu LM, et al. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion.** *Lancet* 2005;366:809–17
9. Raymond J, Guilbert F, Weill A, et al. **Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils.** *Stroke* 2003;34:1398–403
10. Murayama Y, Nien YL, Duckwiler G, et al. **Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience.** *J Neurosurg* 2003;98:959–66
11. Kuether TA, Nesbit GM, Barnwell SL. **Clinical and angiographic outcomes, with treatment data, for patients with cerebral aneurysms treated with Guglielmi detachable coils: a single-center experience.** *Neurosurgery* 1998;43:1016–25
12. Cognard C, Weill A, Castaings L, et al. **Intracranial berry aneurysms: angiographic and clinical results after endovascular treatment.** *Radiology* 1998;206:499–510
13. David CA, Vishteh AG, Spetzler RF, et al. **Late angiographic follow-up review of surgically treated aneurysms.** *J Neurosurg* 1999;91:396–401
14. Sluzewski M, van Rooij WJ. **Questionable interpretation of results of ACTIVE Study on matrix coils by Boston Scientific.** *AJNR Am J Neuroradiol* 2005;26:2163–64

COMMENTARY

Unruptured Intracranial Aneurysms: A Call for a Randomized Clinical Trial

The devastation caused by subarachnoid hemorrhage, with overall poor results despite advanced care, and the blind faith in progress that characterizes the latter half of the twentieth century have led to aggressive treatment of intracranial aneurysms before they rupture.[1] Clearly, however, the outcome of elective surgery should not be compared with that of patients with intracranial hemorrhage. Prevention offers only potential benefits and targets healthy individuals; it is justified when risks of our actions are low and benefits are supported by valid trials. Although medicine has an obligation of means, prevention has an obligation of results.[2] The conditions for preventive actions in the management of aneurysms have not been met, and, until this is done, screening in general for unruptured aneurysms cannot be recommended.

Confronted with difficult situations in a repetitive fashion, clinicians often develop defense mechanisms such as dogmatic attitudes, arbitrary decision trees, and habits. To question this background of habits is a difficult but necessary duty. We have witnessed a period of glorification of technology and individual skills in which expert recommendations are based on "clinical judgment," often suspect because it leaves little room for insight and humility. The responsibilities of modern medicine include both the need to help patients understand that the uncertainty cannot be simply resolved and the professional requirement that we should not act as if we knew.[3] How, then, should we deal with the uncertainty? We must first have the strength to acknowledge our doubts. For the clinician, uncertainty is painful and sterile; for the scientist, however, repeated uncertainty is an opportunity for knowledge.

Most published series on unruptured aneurysms are retrospective or prospective observational.[1,4] They do not discuss the natural history of the disease, but rather give indications on the clinical effects resulting from a biased decision. For example, ISUIA investigators were quite "good" in excluding from treatment patients who were observed, because the annual risk of bleeding was low.[4] Conversely, iatrogenia was relatively high in the surgical group, but the prognosis of the patients had they been observed remains unknown. Because results of nonrandomized studies cannot be extrapolated out of the original bias, generalization to scientific knowledge that can be used a priori is impossible. There is still no scientific evidence to support treatment of unruptured aneurysms.

Scientific generalizations and care for the individual are often put into opposition, but even the most casuistic clinician must admit that projected risks of a single lesion and presumed benefits of treatment for a particular patient are based on generalizations. The variability encountered in biology and medicine can be addressed only with statistical methods. There is no alternative to clinical trials when confronted with a balance between the risks of treatment against risks of hemorrhage. Resistance to clinical trials is largely responsible for the dead end that faces the management of unruptured aneurysms today. Much of this resistance has to do with discomfort regarding randomization, but the use of human subjects to reach biased conclusions would be unacceptable. Respect for human rights and dignity dictates that clinical research should not be conducted with methods that do not meet standards. Now the golden rule to prevent bias is randomization. Randomized trials are the most effective means of objectively determining the relative efficacy and "toxicity" of new interventions.[5] They have shown their value in the evaluation of surgical techniques that were commonly performed without prior demonstration of their clinical benefit.[6,7] Clinical trials are not meant to substitute for clinical care and results do not apply uniformly. They are, however, powerful tools to provide facts, rather than opinions, as a basis for accurate clinical judgment and actions.

A multicenter randomized trial has shown that endovascular treatment can improve the outcome of patients treated after subarachnoid hemorrhage as compared with surgical clipping.[8] Epidemiologic comparisons also suggest that endovascular treatment of unruptured aneurysms is safer than surgery.[9-12] The clinical efficacy of endovascular treatment of unruptured aneurysms, however, has yet to be demonstrated.[13-16] A randomized comparison between coiling and clipping has been suggested, but both options may not be beneficial to most patients, whereas favorable indications may be complementary.[1,4,14] So far we have attempted to identify individuals in whom a permanent but invasive solution could be

justified on the basis of a long life expectancy and projected additive yearly risks of hemorrhage. The efficacy of clipping was said to be self-evident, whereas a trial designed to show benefits seemed incompatible with the timeframe of a feasible trial.[4] A treatment does not have to be 100% effective to be beneficial however. Endovascular treatment may prove beneficial—or not—within an observation period that is reasonable for a trial. The main goal here is not to compare the efficacy of coiling and clipping, as defined by angiography, but rather to assess whether treatment offers prevention at a reasonable cost in terms of morbidity. Elsewhere we proposed a randomized trial comparing the mortality and morbidity of patients with unruptured aneurysms treated by endovascular coiling or by conservative management.[15-16] We estimate that recruitment of a population of 2000 patients during a 3-year period in 60 centers, followed for 5−10 years, can provide answers to 2 important questions: Is endovascular treatment effective in the prevention of intracranial hemorrhage? Is the clinical outcome improved as compared with deferred treatment? Randomization will also offer more accurate estimates of the natural history and a more realistic portrait of iatrogenia than current observational and single-center experiences.

A randomized trial can reconcile the introduction of a "new" treatment with the necessity to acknowledge uncertainties, assess potential benefits scientifically, and assist individuals, alerted by our technical advances of an ominous condition, in a controlled environment that respects and promotes their autonomy.

References

1. Weir B. **Unruptured Intracranial Aneurysms: A Review.** *J Neurosurg* 2002;96: 3–42
2. Tubiana M. *Histoire de la pensée médicale; les chemins d'Esculape.* Collection Champs 384. Paris: Flammarion;1995
3. Cadoré B. L'éthique clinique comme philosophie contextuelle. Fidès Montreal; 1997
4. Wiebers DO, Whisnant JP, Huston J, et al. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10
5. Cleophas GC, Cleophas TJ. **Clinical trials in jeopardy.** *Int J Clin Pharmacol Ther* 2003;41:51–55
6. EC/IC Bypass Study Group. **Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial: the EC/IC bypass study group.** *N Engl J Med* 1985;313:1191–200
7. Barnett HJM, Taylor DW, Eliasziw M, et al. **The North American Symptomatic Carotid Endarterectomy Trial Collaborators: benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis.** *N Engl J Med* 1998;339:1415–25
8. Molyneux A, Kerr R, Stratton I, et al. **International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.** *Lancet* 2002;360:1267–74
9. Johnston SC, Wilson CB, Halbach VV, et al. **Endovascular and surgical treatment of unruptured cerebral aneurysms: comparison of risks.** *Ann Neurol* 2000;48:11–19
10. Johnston SC, Dudley RA, Gress DR, et al. **Surgical and endovascular treatment of unruptured cerebral aneurysms at university hospitals.** *Neurology* 1999;52: 1799–805
11. Johnston SC, Zhao S, Dudley RA, et al. **Unruptured aneurysm treatment in California: surgery and endovascular therapy.** *J Neurosurg* 2001;94:188A
12. Johnston SC, Zhao S, Dudley RA, et al. **Treatment of unruptured cerebral aneurysms in California.** *Stroke* 2001;32:597–605
13. Raymond J, Guilbert F, Georganos SA, et al. **Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils.** *Stroke* 2003;34:421–27
14. Bederson JB, Awad IA, Wiebers DO, et al. **Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association.** *Stroke* 2000;31:2742–50
15. Raymond J, Chagnon M, Collet JP, et al. **A randomized trial on safety and efficacy of endovascular treatment of unruptured intracranial aneurysms is feasible.** *Intervent Neuroradiol* 2004;10:103–12
16. Roy D, Milot G, Raymond J. **Endovascular treatment of unruptured aneurysms.** *Stroke* 2001;32:1998–2004

Jean Raymond, MD, Francois Guilbert, MD, Alain Weill, MD, and Daniel Roy, MD

COMMENTARY

Controversies: Is There a Role for Positron-Emission Tomographic CT in the Initial Staging of Head and Neck Squamous Cell Carcinoma?

Positron-emission tomographic CT (PET-CT) is gaining greater acceptance in a wide variety of oncologic indications in numerous organ systems (head and neck, central nervous system, breast, gynecologic, pulmonary, lymphoma). The dual-technique capability of PET-CT, which permits direct image fusion and improves the ability to anatomically localize foci of fluorodeoxyglucose (FDG) uptake, is replacing stand-alone PET systems. There are numerous potential clinical applications for PET-CT to evaluate malignancies of the head and neck, specifically squamous cell carcinoma (HNSCCA). Potential clinical applications include pretreatment staging, treatment monitoring and evaluation of the previously treated patients.

The current literature suggests that most primary site HNSCCA with volumes >1 mL will be FDG avid. These correspond to lesions that are moderately sized T1 or greater. Tumors with volumes <1 mL may be detected with FDG, however, the sensitivity decreases with decreasing size. PET also has the ability to detect metastatic cervical lymph nodes, which may be both clinically occult and not detected by CT or MR. In light of these potential benefits, there is debate as to how to use PET-CT for the initial staging of HNSCCA. The current consensus does not support the use of CT-PET for routine staging of all newly diagnosed squamous cell carcinomas. The intent of this manuscript is to propose potential indications for performing PET-CT for initial staging of HNSCCA before treatment.

One potential application is to perform PET-CT in advanced stage HNSCCA to evaluate for occult distant metastases to the lungs or bones. The presence of pulmonary metastases upstages a patient from M0 to M1 and alters treatment intent (Fig 1). The likelihood of pulmonary metastases is low in patients with early-stage disease and the routine imaging work-up for pulmonary metastases is conventional radiography of the chest at most institutions. An argument can be made to perform chest CT in all patients with advanced stage disease; however, if a solitary nodule is identified, it is often unclear whether this is metastasis or a granuloma. PET may help in this evaluation as a FDG-positive nodule will likely require biopsy, whereas an FDG-negative nodule (>8 mm) likely indicates a granuloma, and a biopsy may be avoided.

Various studies have been performed to evaluate the diagnostic accuracy of PET-FDG for detecting metastatic cervical lymph nodes. The consensus of the current literature suggests that sensitivity ranges of 70%–90%, whereas the specificity is

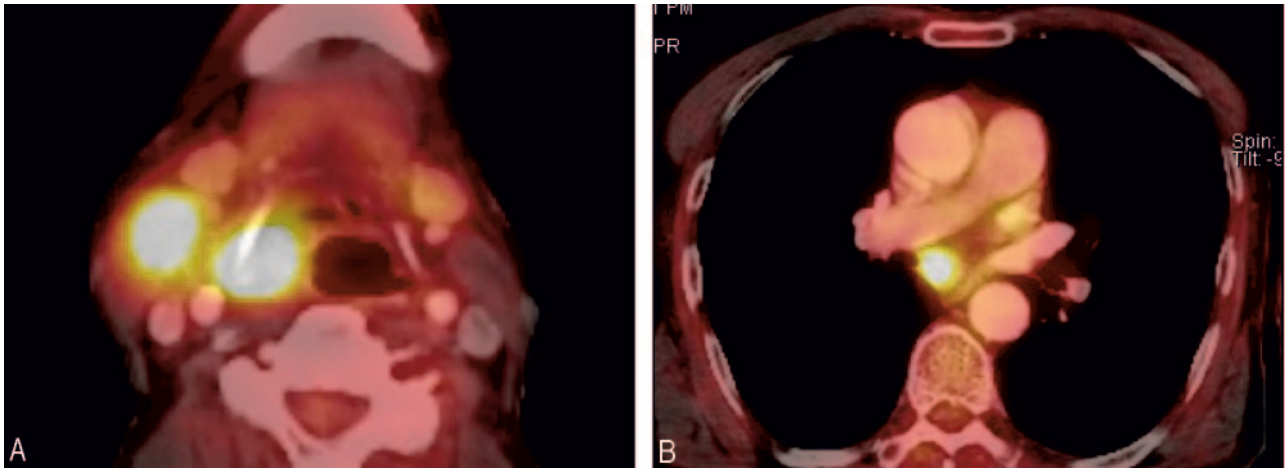

Fig 1. T3N2 pyriform sinus carcinoma.

A, Axial PET-CT demonstrates avid FDG uptake in a right pyriform sinus carcinoma and a metastatic right cervical lymph node.

B, PET-CT of the chest shows a mediastinal mass with focal increased uptake. This was not detected on conventional radiography of the chest.

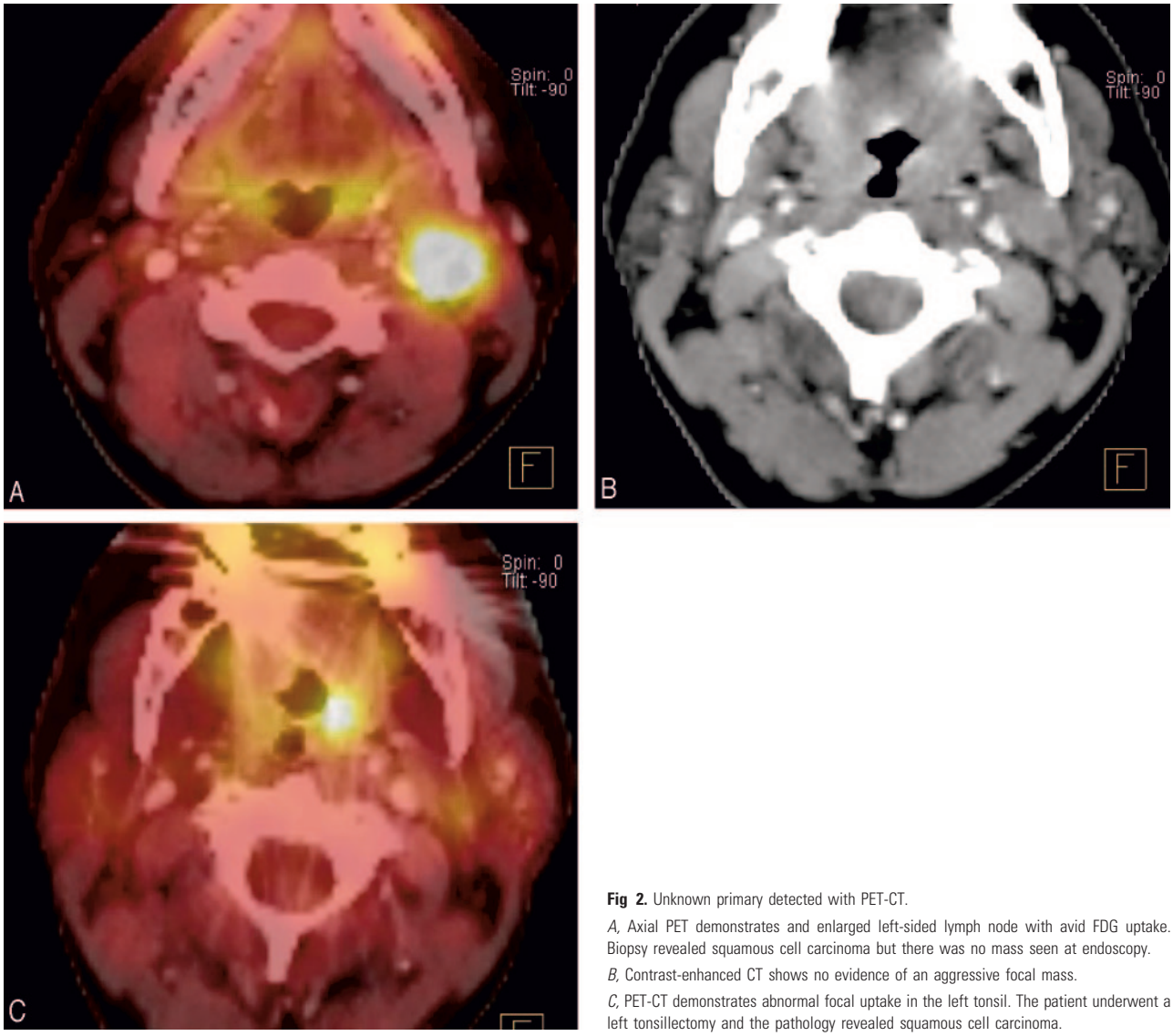

Fig 2. Unknown primary detected with PET-CT.

A, Axial PET demonstrates and enlarged left-sided lymph node with avid FDG uptake. Biopsy revealed squamous cell carcinoma but there was no mass seen at endoscopy.

B, Contrast-enhanced CT shows no evidence of an aggressive focal mass.

C, PET-CT demonstrates abnormal focal uptake in the left tonsil. The patient underwent a left tonsillectomy and the pathology revealed squamous cell carcinoma.

slightly higher (80%–95%). The negative predictive value (NPV) is approximately 90%. This is because >40% of metastatic lymph nodes are <7 mm in diameter. As a result, PET-CT has not gained widespread acceptance to be used to exclude the presence of metastases in the clinically N0 neck. In fact, there is currently no imaging study that has a negative predictive value that has been shown to be consistently >95%. It is conceivable that future advances in CT detector technology in PET-CT units will permit diagnostic CT (<2.5 mm and gantry angulation) to be performed. If so, PET-CT may have greater impact on management of the N0 neck as the NPV of this technique will increase if both studies (PET and CT) are of diagnostic quality and both yield normal results.

Numerous investigators have documented the ability of PET-CT to detect unknown primary tumors of the upper arodigestive tract. The current literature suggests that PET can detect HNSCCA in 30%–50% of patients presenting with an unknown primary tumor (Fig 2). At most institutions, PET-CT is performed after confirming the presence of metastatic HNSCCA and following a negative endoscopy. PET is usually performed before endoscopic biopsies to help improve the yield of the speculative tissue sampling. The diagnostic yield will likely increase with PET-CT because this technique improves accurate anatomic localization of areas of abnormal FDG uptake.

An area of potential utilization of PET-CT currently under investigation is in determining response to nonsurgical treatment modalities, either chemotherapy and/or radiation. Comparison of pretreatment standard uptake values to SUVs 2 weeks into treatment can allow measurement of the speed of response and the sensitivity of the tumor to the treatment technique. Poorly responsive tumors can then be treated to higher effective tumor doses of radiation, for example, or surgery can be performed. Furthermore, initial results suggest that PET-CT can be used to assist in defining primary site and nodal tumor targets for intensity-modulated radiation therapy approaches.

There are numerous professional and financial issues surrounding PET-CT that will require further discussion. Important topics that will need to be addressed include

1. Who should interpret PET-CT? Should these be interpreted by a nuclear medicine physician (PET-CT), the subspecialist who would usually interpret the CT (CT-PET), or some form of joint interpretation?

2. Should intravenous contrast routinely be given for the CT portion of the CT-PET?

3. How should the CT component of the PET be interpreted? Will this only be used as an "anatomic localizer," or will all PET-CT studies need to be interpreted for unsuspected findings, which would be akin to "screening CT"?

4. How will we bill for PET-CT? The CT technology of earlier versions of CT-PET consisted of 2 or 4 detector rows, which were unable to obtain images to obtain thin sections (<5 mm). Newer versions of PET-CT now integrate state-of-the-art CT 16- and 64-row detector configurations, so it is possible that the PET-CT will provide diagnostic quality CT studies. Will we have one code for a combined PET-CT study; will we bill for a PET study with a modifier for the CT component, or will we independently bill for both the CT and PET components? How will this affect states that have certificate of need requirements that regulate the number of CT scanners that an institution may have at any one time?

At our institution, we are now routinely administering intravenous contrast for all PET-CT performed of the extracranial head and neck. The studies are jointly interpreted by faculty members of the divisions of neuroradiology and nuclear medicine. It is our belief that PET-CT is a useful adjunct to initial clinical staging of HNSCCA for specific indications and utilization of pretreatment PET-CT will continue to increase with advances in PET-CT technology.

Suresh K. Mukherji and Carol R. Bradford

References

1. Bruschini P, Giorgetti A, Bruschini L, et al. **Positron emission tomography (PET) in the staging of head neck cancer: comparison between PET and CT.** *Acta Otorhinolaryngol Ital* 2003;23:446–53
2. McGuirt WF, Greven K, Williams D 3rd, Keyes JW Jr, et al. **PET scanning in head and neck oncology: a review.** *Head Neck* 1998;20:208–15
3. Di Martino E, Nowak B, Hassan HA, et al. **Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings.** *Arch Otolaryngol Head Neck Surg* 2000;126:1457–61
4. Benchaou M, Lehmann W, Slosman DO, et al. **The role of FDG-PET in the preoperative assessment of N-staging in head and neck cancer.** *Acta Otolaryngol* 1996;116:332–35
5. Hubner KF, Thie JA, Smith GT, et al. **Clinical utility of FDG-PET in detecting head and neck tumors: a comparison of diagnostic methods and modalities.** *Clin Positron Imaging* 2000;3:7–16
6. Dammann F, Horger M, Mueller-Berg M, et al. **Rational diagnosis of squamous cell carcinoma of the head and neck region: comparative evaluation of CT, MRI, and 18FDG PET.** *AJR Am J Roentgenol* 2005;184:1326–31
7. Halfpenny W, Hain SF, Biassoni L, et al. **FDG-PET: a possible prognostic factor in head and neck cancer.** *Br J Cancer* 2002;86:512–16
8. Haberkorn U, Strauss LG, Dimitrakopoulou A, et al. **Fluorodeoxyglucose imaging of advanced head and neck cancer after chemotherapy.** *J Nucl Med* 1993; 34:12–17
9. Mukherji SK, Drane WE, Mancuso AA, et al. **Occult primary tumors of the head and neck: detection with 2-[F-18] fluoro-2-deoxy-D-glucose SPECT.** *Radiology* 1996;199:761–66
10. Bruschini P, Giorgetti A, Bruschini L, et al. **Positron emission tomography (PET) in the staging of head neck cancer: comparison between PET and CT.** *Acta Otorhinolaryngol Ital* 2003;23:446–53
11. Wong WL, Chevretton EB, McGurk M, et al. **A prospective study of PET-FDG imaging for the assessment of head and neck squamous cell carcinoma.** *Clin Otolaryngol Allied Sci* 1997;22:209–14
12. Lowe VJ, Dunphy FR, Varvares M, et al. **Evaluation of chemotherapy response in patients with advanced head and neck cancer using [F-18]fluorodeoxyglucose positron emission tomography.** *Head Neck* 1997;19:666–74
13. Delgado-Bolton RC, Fernandez-Perez C, Gonzalez-Mate A, et al. **Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors.** *J Nucl Med* 2003;44:1301–14
14. Sheikholeslam-Zadeh R, Choufani G, Goldman S, et al. **Unknown primary detected by FDG-PET: a review of the present indications of FDG-PET in head and neck cancers.** *Acta Otorhinolaryngol Belg* 2002;56:77–82
15. Paulino AC, Koshy M, Howell R, et al. **Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated radiotherapy for head-and-neck cancer.** *Int J Radiat Oncol Biol Phys* 2005;61:1385–92
16. Schwartz DL, Rajendran J, Yueh B, et al. **FDG-PET prediction of head and neck squamous cell cancer outcomes.** *Arch Otolaryngol Head Neck Surg* 2004;130: 1361–67
17. Yao M, Buatti JM, Dornfeld KJ, et al. **Can post-RT FDG PET accurately predict the pathologic status in neck dissection after radiation for locally advanced head and neck cancer? In regard to Rogers, et al.** *Int J Radiat Oncol Biol Phys* 2004;58:694–97; *Int J Radiat Oncol Biol Phys* 2005;61:306–307; author reply 307
18. Koshy M, Paulino AC, Howell R, et al. **F-18 FDG PET-CT fusion in radiotherapy treatment planning for head and neck cancer.** *Head Neck* 2005;27:494–502
19. Nishiyama Y, Yamamoto Y, Yokoe K, et al. **FDG PET as a procedure for detecting simultaneous tumours in head and neck cancer patients.** *Nucl Med Commun* 2005;26:239–44
20. Branstetter BF 4th, Blodgett TM, Zimmer LA, et al. **Head and neck malignancy: is PET/CT more accurate than PET or CT alone?** *Radiology* 2005;235:580–86
21. Gutzeit A, Antoch G, Kuhl H, et al. **Unknown primary tumors: detection with dual-modality PET/CT: initial experience.** *Radiology* 2005;234:227–34