



ASNR Career Center

The Go-To Job Site for Neuroradiology Employers and Job Seekers
Start here: careers.asnr.org

AJNR

Have You Been Smoking Something That Is Biologically Active?

Harry J. Cloft

AJNR Am J Neuroradiol 2006, 27 (2) 240-242

<http://www.ajnr.org/content/27/2/240>

This information is current as of September 26, 2023.

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/poly-lactic 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 coils⁶ 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

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 aerodigestive 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, Chevetton 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