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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.

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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