Editorial

Proton beam for arteriovenous malformations

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Deconstruction of the extensive experience of Dr. Raymond Kjellberg with arteriovenous malformations (AVMs) at the Harvard-affiliated Cambridge Proton Facility and Massachusetts General Hospital is probably easier than its reconstruction. Dr. Kjellberg began his experience in the management of AVMs in the 1960s. At that time, the Cambridge Proton Facility, initially funded by the Navy, represented an enormously valuable potential application of radiation technology to clinical needs. The result of surgical extirpation of large-volume AVMs was (and still is) inadequate. Although each generation of neurosurgeons, and more recently endovascular surgeons, attempt to reexplore the potential role of single or multimodality therapy of such large AVMs, enthusiasm generally wanes as the practicing surgeon’s experience builds and his or her age increases. Lars Leksell, practicing in the same era as Kjellberg, was convinced that minimally invasive or alternative treatment strategies needed to be applied for AVMs. This goal arose from his experience of soliciting intraoperative blood transfusions from patients’ relatives during the surgical reign of Herbert Olivecrona in Stockholm. Similarly, Kjellberg began to apply the proton therapy to an increasingly large group of patients who had virtually no other therapeutic options for their AVMs.

During a visit with Kjellberg in 1981, I was impressed with his unique facility and technique. After regional infiltration of anesthetic agents administered by an onsite anesthesiologist, Kjellberg applied a specially designed stereotactic frame to the maxillary bone after drilling small holes in the anterior maxillary sinus. I was equally amazed by the imaging technique, which consisted of anteroposterior and lateral conventional x-ray films obtained after frame application on the day of the procedure. At the time of these conventional skull x-ray studies, a small strip of beads of graduated sizes was placed over the patient’s head; these served as a magnification reference landmark. On these intraoperative images, Kjellberg sketched a freehand estimate of the AVM as he reviewed preoperative angiographic images obtained several days in advance at the Massachusetts General Hospital. Most of the patients were seen as outpatients by Dr. Raymond Adams for neurological consultation. In the absence of many therapeutic options, a large national and international referral base developed for this innovative single-fraction irradiation of large AVMs by using particle beams. Kjellberg, himself, was extremely reluctant to apply the term “radiosurgery” to his technique, preferring the term “stereotactic Bragg peak proton therapy” (personal communication, 1981).

Kjellberg maintained a large, privately held database, which has been tapped by Barker, et al., in order to analyze on a long-term basis the risk ratio of Bragg peak proton beam radiation. Using a complex statistical methodology, the authors have derived a risk (not a benefit) analysis of adverse events and have related it to dose and volume data. The authors are to be congratulated for this long-term analysis of a technique that (to modern eyes) is of great historical interest, but of little current clinical value. Kjellberg’s patients had large AVMs, often in deep-seated locations. I have serious concerns related to his patient selection, the technical delivery of the dose, and the methodology that he developed to reduce complications.

Kjellberg’s isoeffective risk centile curves have a certain metaphysical aspect. The actual data were derived from a relatively small initial patient experience. For small target volumes, the patient data were supplemented by primate data. His early recognition of an unacceptable (to him) rate of complications led him to develop a strategy of low-dose delivery of Bragg peak proton beam radiation. He hypothesized that AVM obliteration was not a necessary goal. Instead, Kjellberg postulated that radiation increased the stability of the blood vessel walls, possibly by hyalinization, and thereby reduced the risk of delayed hemorrhage. It was unnecessary in his view to obliterate the AVM; one had only to stabilize it by the application of radiation. The subsequent lifetime risk of a hemorrhage from the AVM was reduced. There was, of course, no control group, and his estimation of effectiveness was derived from a comparison with life-table survival curves obtained from the insurance industry. Based on these comparisons (which one could surmise provided at best the lowest level of statistical reliability), he predicted that the hemorrhage and death rates in patients treated with Bragg peak proton beam radiation were less than what would be predicted by the life-table analysis. To his credit, despite the challenges that he and his patients faced, Kjellberg maintained this database. He frequently presented and published his efforts. Kjellberg’s technique
did not really evolve during his more than 20 years of experience; doses were simply kept low to minimize risks.

Barker, et al., describe the complication rates, which are, as expected, related to dose, volume, and perhaps location. They have also wisely dropped the concept of superiority of proton beam radiation in terms of radiobiological effect compared with photon radiation techniques. The AVM volumes in this series are stupendous. Based on current knowledge, we doubt that any very effective therapy exists for the management of such large-volume AVMs. In fact, any treatment of such AVMs, especially in asymptomatic patients, may pose a greater risk than the natural history of the lesion.

At the University of Pittsburgh we have cautiously evaluated the staged treatment of larger-volume AVMs to see whether we may be able to enhance total obliteration rates. We firmly believe that total obliteration (plus neurological preservation) remains the outcome goal, because there is no significant evidence to substantiate the belief that radiation therapy reduces the rate of hemorrhage in incompletely obliterated AVMs. Based on this, as well as on three-dimensional magnetic resonance imaging and angiographic data, we can estimate the size of an AVM preoperatively. In advance, we describe to the patient and family the possible need for a staged approach to increase the oblitative response.

We have found that if all AVMs could be given a minimum 25-Gy dose of radiation that tightly conforms to the AVM volume, the total obliteration rate after a single treatment might be as high as 95%. As volume increases, our ability to deliver such doses safely is greatly reduced. Factors that reduce the success rate for AVM obliteration include lesion size and location, patient age, and preoperative embolization. In small-volume AVMs preoperative embolization may reduce flow, does not decrease the target volume, and may lead to dose/volume mismatch. I consider staged treatment for AVMs when the volumes are greater than 15 cm³. Almost all of the volumes of AVMs treated in Kjellberg’s series were much larger than this. Some “treated” volumes are almost “holoencephalic.” The presence or absence of prior hemorrhages, prior embolization, and radiation sensitivity of individual patients are also possible effects and factors.

Dr. Barker and his colleagues are to be congratulated for putting together this significant, long-term report. Its major weakness is its reliance on questionnaires and oral reports from patients; reporting bias may occur if some happy patients attempt to please their doctors by hiding complications or some unhappy patients exaggerate their difficulties. If patients were seen and examined, and if imaging studies were available for review in conjunction with this report these issues would diminish.

It is likely that efforts similar to Kjellberg’s will be impossible in the current era, especially with oversight from increasingly complex, highly motivated, and vigorous institutional review boards. Of the greatest concern, however, is the application of the Health Insurance Portability and Accountability Act (HIPAA) promulgated by the federal government. Surely, our legislators clearly could not have meant to destroy totally long-term outcomes research? It is fortunate that Barker, et al., were able to complete their study and its report prior to the April 15, 2003 deadline for HIPAA compliance. Records of patients with AVMs must be maintained in a database. How else can we do outcomes research unless we match new data with each patient? Can we really be expected to go back 15 years and contact all of these patients to obtain their informed consent for their records to be maintained in a retrospective database? How will anybody perform outcomes-based clinical research derived from historical series in the future? Such studies are extremely valuable: there is scant evidence that our much-touted randomized prospective trials have significantly contradicted the experience obtained in less statistically sound retrospective trials. The neurosurgical community needs to wake up, and act conclusively as a whole to urge revision of the HIPAA menace. Otherwise, long-term outcome studies such as this analysis of Kjellberg’s experience will never appear in the future.

References


RESPONSE: We thank Dr. Lunsford for his wide-ranging and thought-provoking commentary. As he points out, Dr. Kjellberg’s treatments took place in a technological and societal context that we will never revisit, and many of his methods now seem antiquated. That this occurred almost within a single professional lifetime reflects the rapid acceptance and advancement of stereotactically guided radiosurgery by both neurosurgeons and radiation oncologists since Kjellberg and others began their pioneering work. We should all hope that our own research interests will prosper in the same way.

We think Kjellberg’s complication data do have value for current clinical practice. Neither the physics of proton radi-
ation nor the intrinsic radiosensitivity of brain tissue have changed since Kjellberg’s day, nor is this likely. For a given AVM, Kjellberg’s techniques resulted in larger doses to surrounding normal brain tissue than would modern conformal proton or photon dose planning and delivery. In earlier work, however, it has been suggested that the conformity of an AVM treatment plan is not as strongly related to the complication risk as are dose and volume (whether the treated volume contains AVM or brain tissue), and, to a lesser degree, the eloquence of neighboring brain (which influences the chance that a given physical change in treated tissue will correspond to a symptomatic neurological deficit). Because conformity and mistargeting appear to be secondary issues in risk prediction for AVM treatments, the risk associated with modern treatment with a given dose-volume-location combination is likely to be similar to the risk associated with the same dose-volume-location combination in Kjellberg’s hands.

We lay no claim to understanding the rationale behind HIPAA or its concrete implications for ongoing clinical databases. Perhaps there is a need to protect our patients from being “injured” through their participation in retrospective reviews. It seems more likely that the additional hindrance to research will be harmful in ways that will be difficult to prove to busy legislators—until they find that the diseases afflicting their constituents, their families, and themselves are no longer being actively studied.

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