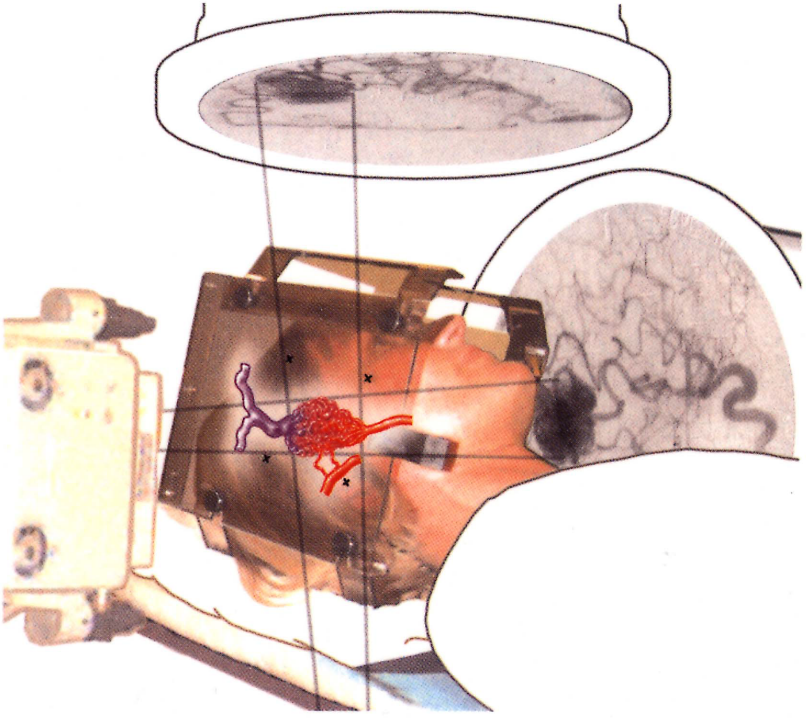
VOLUME DETERMINATION AND PREDICTIVE MODELS IN THE MANAGEMENT OF CEREBRAL ARTERIOVENOUS MALFORMATIONS

BY

MICHAEL SÖDERMAN



KONGL CAROLINSKA MEDICO CHIRURGISKA INSTITUTET

STOCKHOLM 2000

BICÊTRE

Volume determination and predictive models in the management of cerebral arteriovenous malformations

*Se non è vero, è molto ben trovato.**

Giordano (Filippo) Bruno (1548–1600)

* If not the truth, it is very well made up.

Michael Söderman

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STOCKHOLM 2000

Omslagsbild: Ville Stråat
Omslag & Formgivning: ElHå
Typsnitt: New Baskerville 11/13
Tryck: Larserics Digital Print AB, Bromma 2000
ISBN 91-628-4136-X

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Michael Söderman, MD

ABSTRACT

Cerebral arteriovenous malformations (AVMs) entail a high cumulative risk of severe neurological symptoms and are usually treated with surgery, radiosurgery, embolisation or combinations thereof. There are well supported models to predict the outcome of radiosurgery, but similar models do not exist for surgery or embolisation. The aim of this work was to improve the models and implement them in the general management of AVM patients, notably those treated by embolisation.

Aims of the present investigation.
1) To improve predictive models for radiosurgery and adapt them to use without dose planning. 2) To create a method for uncomplicated measurement of AVM volume from angiography. 3) To devise a method to correct for the geometric distortion in digital subtraction angiography. 4) To make a hypothetical comparison of two major management strategies, using the methods and models as reference standard.

Materials and methods.
1) Roughly 1500 patients treated with Gamma Knife radiosurgery for AVM during the period 1970–1993 were retrospectively studied. 2) The "intersecting cone model" for AVM measurement was created and validated. 3) Qualitative and quantitative aspects of the geometric distortion were investigated and corrected for with a calibration-correction scheme. 4) A prospective study of 88 consecutive patients was done during 1997–1999. AVM volumes and clinical information were recorded before the first and after the last embolisation.

Results and conclusions.
1) The obliteration rate depended only on the minimum dose to the periphery of the AVM. The complication rate depended also on AVM volume, location and patient history. The risk for haemorrhage in the latency period after radiosurgery depended on the minimum dose to the AVM, patient age and AVM volume. 2) "The intersecting cone model" can be used instead of volume data from the dose planning system. 3) Geometric distortion may affect high precision stereotaxy but its impact on volume measurement is limited. It can be corrected. 4) For AVM>10ml the outcome models are not very well substantiated. However, embolisation had comparative advantages. For AVM≤10ml the hypothetical outcome of combined treatment with embolisation and radiosurgery was equal to that of radiosurgery alone.

Outcome models from radiosurgery can be used in clinical practise as a reference standard in the management of AVM. However, further studies are necessary to identify specific patient and AVM subgroups amenable to each treatment.

Key words:
Cerebral arteriovenous malformation, Radiosurgery, Embolisation, therapeutic, Outcome assessment.

ISBN 91-628-4136-x Stockholm 2000

DEDICATION

To
Lotta
Pehr
Cecilia
Gabriella
and
Amanda

ACKNOWLEDGEMENTS

No man is an island, and this is perhaps particulary true of the man who is writing his thesis. My apprenticeship has been long and I owe a great debt to many people. In particular I wish to express my sincere gratitude to:

Professor *Kaj Ericson*, chief advisor, for teaching in many matters of stereotaxy and radiosurgery as well as for constructive criticism and generous sharing of ideas.

Bengt Karlsson, MD, PhD, friend and co-advisor, for fruitful discussions and the sharing of unique data, and for all the efforts put into teaching me the art of radiosurgery and the use of predictive models. Without him this work would not have existed.

Professor *Pierre Lasjaunias*, co-advisor and brilliant teacher in interventional neuroradiology, for generously sharing the data from l'hôpital de Bicêtre, for constructive criticism, support and good discussions.

Ass. Prof. *Olof Flodmark*, Head of the Department of Neuroradiology, for continuous and generous support throughout the whole research project.

Georges Rodesch, friend and co-author, for teaching in the art of embolisation, for strenuously collecting data and last but not least for many a cheerful time in Paris, particularly an evening at Disneyland that never will be forgotten.

Ingmar Lax, Björn Thuresson, Catherine Picard, Laurent Launnay and *Christer Lindquist* who have all contributed as co-authors.

Ass. Prof. *Tomas Hindmarsh*, who generously spent time in correcting manuscripts.

All my colleagues and friends at the Departments of Neuroradiology and Neurosurgery at Karolinska hospital. Particular and sincere thanks to my roommate *Pernille Skejø*, always supportive and encouraging. She is present in this thesis as the cover picture.

The staff at Hôpital de Bicêtre, assisting in so many ways, particularly with "les images avec la boîte". Particular thanks to *Hortensia Alvarez*, MD.

My brother *Erik*, for patiently explaining some intricacies of the world of mathematics to me.

My old friend *Leonard Hagberg*, VDM, whom helped in design and printing matters.

Karolinska Institutet that gave me a year to work in peace.

General Electric Medical Systems that supported the software development.

ABBREVIATIONS

ARE	Adverse radiation effect
AVM	Cerebral arteriovenous malformation
C.I.	Confidence interval
CT	Computerised tomography
D_{ave20}	Average radiation dose in a volume of 20ml containing the AVM
D_{ave}	Average radiation dose to the AVM
D_{max}	Maximum radiation dose to the AVM
D_{min}	Minimum radiation dose to around 90% of the prescription volume
DSA	Digital subtraction angiography
GKRS	Gamma Knife radiosurgery
Gy	Gray
ICM	Intersecting cone model
I/I	Image intensifier
LGP	Leksell GammaPlan®
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
NBCA	N-butyl-2-cyanoacrylate (Histoacryl®, a liquid tissue adhesive)
PA	Posteroanterior
P_{compl}	Probability of complication after GKRS
P_{hem}	Probability of haemorrhage in the two years latency period after GKRS
P_{obl}	Probability of obliteration after GKRS
ROI	Region of interest
v	AVM volume (the volume within the best fit isodose line).
VOI	Volume of interest

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I

Karlsson B, Lax I, Söderman M (1999): *Can the probability for obliteration of arteriovenous malformations after radiosurgery be accurately predicted?* Int J Rad Onc Biol Phys 43(2): 313–319

II

Karlsson B, Lax I, Söderman M (1997): *Factors influencing the risk for complications following Gamma Knife radiosurgery of cerebral arteriovenous malformations.* Radiotherapy & Oncology 43: 275–280

III

Karlsson B, Lax I, Söderman M (Submitted): *Risk for haemorrhage during the two years latency period following Gamma Knife radiosurgery for arteriovenous malformations.* Submitted to Int J Rad Onc Biol Phys.

IV

Ericson K, Söderman M, Karlsson B, Lindquist C (1996): *Volume determination of intracranial arteriovenous malformations prior to stereotactic radiosurgical treatment.* Interventional Neuroradiology 2: 271–275

V

Söderman M, Picard C, Ericson K (1998): *An algorithm for the correction of distortion in stereotaxic digital subtraction angiography.* Neuroradiology; 40: 277–82

VI

Söderman M, Karlsson B, Launnay L, Thuresson B, Ericson K: *Volume measurement of cerebral arteriovenous malformations from angiography.* Accepted for publication in Neuroradiology.

VII

Söderman M, Rodesch G, Karlsson B, Lax I, Lasjaunias P: *Gamma Knife outcome models in the embolisation of cerebral arteriovenous malformations.* In manuscript.

INTRODUCTION

Cerebral arteriovenous malformations (AVM) have occasionally been diagnosed in the neonate but never in the foetus (93). The rarity of this malformation in the paediatric population suggests that it may not exist at birth, at least as a mature entity, but develops or expresses itself later in life (96, 203)

The term malformation means that something has developed incorrectly and thus implies that we know the origin of the lesion. It has been proposed that the development of an AVM might be the effect of triggers on a genetic defect of the post-capillary endothelium (96). Other intracerebral vascular lesions, such as cavernomas (18, 29) and pial arterio-venous shunts in Rendu-Osler-Webers disease (126, 168) are known to be associated with genetic defects. Collagen type III mutation causes fragile cerebral arteries in Ehlers-Danlos syndrome type IV (151) that predisposes for direct arterio-venous fistulae. Thus some cerebral vascular diseases, with and without arteriovenous shunts, are associated with genetic disorders. However no genetic linkage has as yet been found for AVM, nor have they been shown to be familial (94), with rare exceptions (3, 10, 11, 91).

Other authors suggest that the origin of an AVM might be a pathologic haemodynamic response to exogenous factors such as trauma (177, 178).

In this text an AVM is defined as a localised subpial arteriovenous shunt consisting of a tangle of capillaries and veins with fibrointimal thickening and elastic tissue destruction (120). It is a dynamic lesion; it evolves (120, 147) and may appear, increase in size, regress or disappear spontaneously (77, 90, 110, 132, 171, 172, 191, 203). There are subgroups of arteriovenous shunts with distinctly different morphological and clinical characteristics, such as the Wyburn-Mason syndrome (199) and the proliferative angiopathy (97), indicating that the AVM is a heterogeneous entity composed by different diseases, different expressions of the same disease or both.

Arteriovenous shunt or anastomosis is a more generic description than AVM, advocated by some as a more adequate term (96, 177). However, in this text the term AVM has been used, since it is internationally established.

Although the malformation is clinically silent until the equilibrium between

the patient and the AVM is upset, it will then cause symptoms such as headache, seizure or neurological deficit. This may be considered as an expression of evolution of the lesion or of "the weakness of the host".

45–70% of patients with an AVM present with acute intracranial haemorrhage, in the vast majority of cases the most dreaded event (15, 19, 50, 66, 83, 95, 137). The yearly risk for haemorrhage increases with age (19, 83). Due to the accumulated risk, most patients experience their first haemorrhage when they are 20-40 years of age. In the 30-year old patient the risk for haemorrhage over a period of 10 years is 30–40% while the accumulated risk over a lifetime is well above 80% (83, 137). The rates of mortality and permanent morbidity after an AVM haemorrhage are still not clear. Most investigators have found that a symptomatic AVM haemorrhage has a combined severe morbidity and mortality of 20–40% (14, 19, 50, 62, 137, 141). Others have argued that the risk for impairment or death from a haemorrhage is less than generally believed (58, 153, 183). Nevertheless, the life span of an untreated patient harbouring an AVM is shortened - in Ondra's material it was 51 years for the total AVM population and 44 years for those who died from an intracranial haemorrhage (137).

Most AVM patients are subject to treatment, unless it is felt that the risk inflicted by the remedy itself cannot be justified. In the absence of knowledge and tools for a proper assessment of the risk this judgement tends to be subjective, and in addition biased towards treatments available "in-house".

> The goal of the treatment is that the patient will be able to live a normal life. If possible the risk for neurological deterioration is eliminated by excluding the AVM from the blood circulation. Other objectives may be to reduce the risk for haemorrhage or to alleviate symptoms such as seizure or headache by partial obliteration of the AVM.

Today there are four management options: surgery, ionising radiation, embolisation and no treatment. Treatments are often combined in various ways. Each has specific advantages and disadvantages and the choice has to be tailored to meet the requirements of the individual patient and AVM. In this context it would be advantageous to be able to predict the outcome of a treatment, before its application. For this purpose an outcome model is needed, a mathematical description of the impact of AVM, patient and treatment parameters on the outcome. The effects of an adjustment of the treatment parameters can also be predicted in such a model. It can thus be used as a tool to optimise the treatment it concerns, combinations of treatments and in addition to compare the actual outcome of one remedy to the predicted outcome of another.

This work was done with the intent to improve outcome models for Gamma Knife radiosurgery (GKRS) for AVM and to apply these models to patients treated with embolisation for the same disease.

Three methods have been developed:

CORRECTION OF THE GEOMETRIC DISTORTION in digital subtraction angiography (DSA).

The method was developed to make possible stereotactic angiography with DSA. The study also provided valuable insight into the problem of the geometric distortion in the imaging chain and its possible impact on volume measurement from angiography.

PRELIMINARY DOSE PLANNING of an AVM from diagnostic angiography.

The method was developed to allow for accurate prediction of the outcome of radiosurgery from the diagnostic angiography.

VOLUME MEASUREMENT OF an AVM from angiography.

The method was developed to facilitate volume measurement of an AVM from angiography. It is also the basis for the clinical use of the outcome models, at institutions without easy access to dose planning.

HISTORICAL NOTES

Introduction

Extracranial arteriovenous malformations were known in ancient Egypt (Papyrus Ebers 1500, ca 1500 BC) (87) and over the centuries there have been numerous descriptions. The works upon the blood circulation by Harvey (63) and Willis (198) in the 17th century laid the foundation for the understanding of the arteriovenous shunt, while the concept itself originates from Hunter (71, 72).

In 1826 Bell (4) in his textbook "The principles of surgery" provided us with a modern description of an arteriovenous malformation and Virchow proposed that they represented congenital lesions rather than neoplasias (188–190). Cerebral arteriovenous malformations were recognised as a clinical entity in the late 19th century (144, 152).

There is an excellent chapter upon the history of the diagnosis and treatment of cerebral AVMs in "Microneurosurgery IIIA" by Yasargil (204).

Surgery

The first successful extirpation of an AVM was made in 1899 by Péan (139), who wrote:

> "Le malade, âgé de quinze ans, etait affecté d'accès d'épilepsie partielle localisés au membre supérieur gauche, accompagnés de contractions spasmodique des muscles du pharynx, et d'une douleur violente au sommet de la tète, a droite de la ligne médiane, au niveau de l'angle antéro-supérieur du pariétal droit
>
> Nous pratiquâmes l'opération en mai 1889 avec le concours de MM. Ballet et Gelineau, suivant les règles que nous avons déjà communiquées à l'Académie.
>
> Au cours de l'opération, nous nous trouvâmes en présence d'un angio-

me des méninges en communication avec le sinus longitudinal supérieur.

Malgré sa richesse vasculaire, malgré son étendue, la tumeur put être enlevée en totalité, sans perte de sang, grâce au pincement temporaire et définitif des vaisseaux variqueux, dilatés, érectiles, dont elle était composée."[1]

Surgical results were however generally poor and the opinion of the leading neurosurgeons at the time, such as Dandy or Cushing (20) was that AVM surgery was exceedingly dangerous. Olivecrona had the same cautious attitude towards AVM found unexpectedly at surgery. Nevertheless, by 1936 he had attempted to remove an AVM in 16 cases (5), and by 1954 he had removed 81 AVM with for the time exceptional results (135).

Continuous development of the surgical technique, particularly the introduction of microneurosurgery by Yasargil in the 1970s (204) together with improvements in neuroradiology and anaesthesiology, has brought neurosurgery to a high standard. Today, in the best centres, surgery for cortical AVM<3cm is performed with a cure rate of 100% and a morbidity of 1-15%. Larger and deeply located AVM have higher surgical morbidity/mortality and lower rate of total resection. (61, 64, 138) Neurocognitive assessment by independent neurologists points at the fact that these patients sometimes have important postoperative deficits that are not diagnosed at routine follow up (49, 119, 176).

Diagnostic neuroradiology

Neuroradiology in its modern sense began with the introduction of contrast medium. Reynier and Glover described ventriculography in 1897 (154), but it was the surgeon Dandy who developed it into a clinical method (22). His papers on ventriculography in 1918 and on encephalography in 1919 further developed by Lysholm and Lindgren are milestones in diagnostic neuroradiology (22, 23, 107, 115). The technique was, however, not suitable for AVM diagnosis and the breakthrough in this field was the work on cerebral angiography by the Portuguese neurologist Moniz in 1927 (131). Lindgren and his school at Serafimerlasarettet in Stockholm developed angiography into a routine method (106, 108). The excellent article by Lindgren in "Radiology of the skull and brain", editors Newton and Potts (109) is recommended for a more complete review of the early history of neuroradiology.

1. "The patient, 15 years old, had attacks of partial seizures of the left upper limb, accompanied by spasmodic contractions of the muscles of the pharynx, and a severe pain of the top of the head, to the right of the midline, in line with the straight antero-superior parietal gyrus …

We performed the operation in May 1889 with the help of Mr Ballet and Mr Gelineau, according to the guidelines already communicated to the Academy. During the operation we found the presence of a meningeal angioma communicating with the superior sagittal sinus. Despite its rich vascularity and with difficulties, the tumor was totally removed, without loss of blood, thanks to temporary and permanent clips on its varicose, dilated and distended vessels."

In the beginning, catheterisation required surgical exposure of the vessel and an incision made for the catheter. An important technical shortcoming was that the catheter, without a guide wire, was introduced through a large bore needle. When Seldinger (166) introduced his technique for percutaneous angiography it was a major achievement, since it permitted the use of coaxial systems and easy exchange of guide wires and catheters during the procedure, a prerequisite for interventional neuroradiology. Cerebral angiography was performed by direct puncture of the carotid or vertebral arteries until 1956 when catheterisation of the vertebral artery from the femoral artery was reported (108). Angiography of all cerebral arteries from the groin was first performed in 1964 at Ullevål Hospital in Oslo by Amundsen (1).

The imaging tools of the neuroradiologist have gone through a tremendous evolution since the first angiography in 1927. Sjögren and Fredzell first introduced a serial film changer suitable for cerebral angiography in 1953 (170). Improvements in computer technology have made possible a number of imaging applications such as DSA, now indispensable in diagnostic and interventional neuroradiology.

Computerised tomography (CT), for which Hounsfield and Cormack received the Nobel Prize in 1979, was a revolution in neuroimaging, that greatly facilitated AVM diagnosis and treatment follow up. Magnetic resonance imaging (MRI) has today in many aspects replaced CT and is a most important tool in the management of AVM patients.

Other methods to display angiographic or flow images, such as magnetic resonance angiography (MRA), CT angiography and digital rotational and 3D-angiography have also been developed. Nevertheless, DSA remains the "gold standard" for AVM diagnosis and treatment, the exception being stereotactic applications, where the inherent geometric image distortion impairs accuracy.

Positron emission tomography is used mostly as a research tool and not in the management of AVM.

Interventional neuroradiology

Embolisation or endovascular treatment of an AVM was the second treatment option, after surgery, to emerge. It relied on the advances in catheterisation and fluoroscopy from diagnostic neuroradiology. The technique itself was pioneered by Luessenhop (112) in 1960:

"With the patient under local anaesthesia the left common carotid bifurcation was exposed. Four spherical emboli, made of methyl methacrylate, were introduced at intervals of about 15 minutes. They measured successively about 2.5, 3.0, 4.0 and 4.2 mm in maximum diameter. After introduction of each embolus, strength of the right arm and speech were tested and x-rays were taken to determine the site of arrest. Immediately after introduction of the fourth embolus the patient became drowsy and showed increasing weakness of the

right hand, but no alteration of speech ... The malformation was reduced to a slight stain, and for the first time normal filling of the anterior and middle cerebral arteries was evident."

Newton performed the first spinal embolisation (134) – with lead pellets and muscle – shortly followed by the French neurologist Djindjian (70), who also pioneered embolisation of intracranial dural arteriovenous fistulae and extracranial AVM, using particles and gelfoam (25, 26).

The notion of the shunting zone itself as the primary target for the treatment of an extracranial arteriovenous fistula was put forward by Brooks as early as 1930. He advocated surgical extirpation of the shunt itself, and strongly advised against proximal ligation (12). The concept of the nidus as the target for endovascular treatment of an AVM was proposed by Doppmann (27). In 1971 he published experimental results from transcatheter embolisation with silicone rubber and proposed to use the material to fill the vascular bed of a spinal AVM (28).

The balloon catheter for extraction of arterial emboli and thrombi was invented by Fogarty (40). It was further developed into a tool for catetherisation and occlusion of cerebral vessels by Serbinenko (105) who began his work in 1963. This was largely unnoticed in the western world until his presentation at the Symposium Neuroradiologicum in Punta del Este and his article in the Journal of Neurosurgery, both in 1974 (167). However, being in effect a feeder ligature – a concept now abandoned in AVM treatment – balloon occlusion was seldom successful.

As important as the technical innovations is the work on functional vascular anatomy and haemodynamics from the French school of interventional neuroradiology, beginning in the early 1960s. The most important pioneers were the neurologists Djindjian (25, 26) and Picard (145), followed by the anatomist Lasjaunias (98), all of whom became neuroradiologists.

Catheters and guide wires have been improved, through the calibrated leak balloon catheter (86) to the progressive suppleness Pursil catheter (24) and further to today's more sophisticated material. The goal has been better and safer access to the nidus to allow the proper deposit of an embolic agent, such as tissue adhesives that were proposed for AVM treatment in 1972 (205) (Fig. 1).

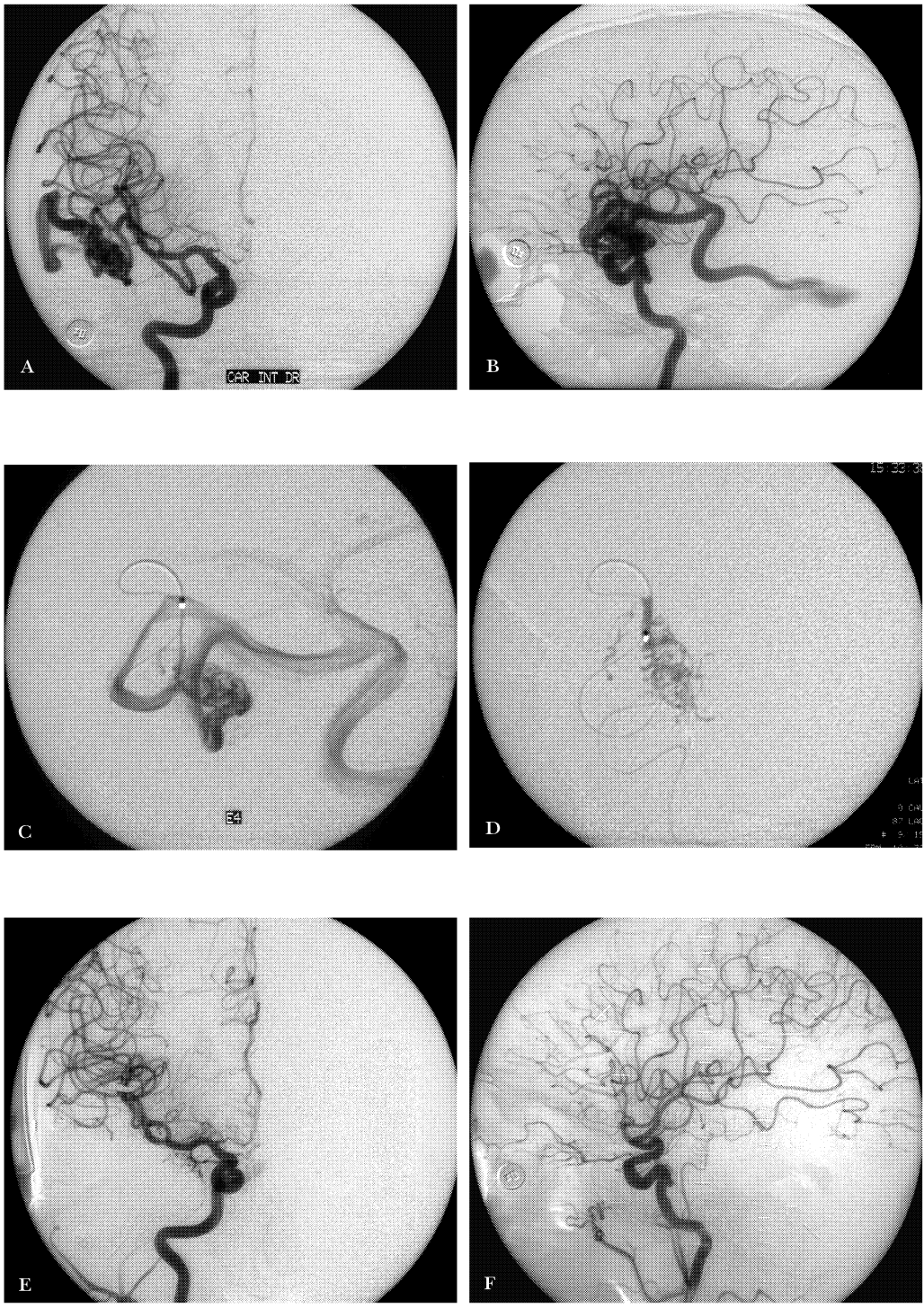
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Fig. 1 A–F. Embolisation of a cortical AVM with NBCA in a 60 year old male. The patient had experienced a single seizure from a temporal haemorrhage.

A) Angiography before embolisation. Injection into the right internal carotid artery (ICA), PA view. Medial temporal nidus draining into two Sylvian veins that converge into a superficial temporal vein.

B) Same as A. but lateral view.

C) Superselective angiography through microcatheter before NBCA injection. Lateral view, higher magnification. Note single arterial supply to compartments with separate venous exits.

D) One of five NBCA injections. Note glue deposition in nidus.

E) Angiography with injection into the right internal carotid artery (ICA) four months after the embolisation, PA view. There is no remaining AV shunt, and there was no supply from the external carotid artery. Note thrombosis of the large temporal arterial branch. The angiography was performed in stereotactic conditions to allow radiosurgery in the same session.

F) Same as E. but lateral view. The patient was asymptomatic.

Stereotaxy

The surgical difficulties and the delicacy of the brain called for minimally invasive techniques. Stereotaxy was therefore a logical invention, with the aim to localise a target and allow a surgical procedure with a minimum of damage to the surrounding brain tissue. The stereotactic method to define the position of a point in a Carthesian co-ordinate system by means of intersecting X-rays was described by Mackenzie Davidson as early as 1898 (116). He also designed a stereotactic instrument for intracranial interventions (117) using a design similar to that of Ironside Bruce in 1915 (74). Another contribution from the United Kingdom came from Horsley and Clarke, who in 1908 developed a stereotactic instrument (68), as a tool for neuroexperimental purposes. It seems, however, that the stereotactic method was not used in neurosurgical practise until 1947 when Spiegel published his work on an apparatus for operations on the human brain (175), shortly followed by Leksell (100).

Localisation of the target is made with neuroradiology and may be direct or indirect. Indirect localisation employs specific anatomical landmarks and an anatomic brain atlas to define the co-ordinates of the structure in question. Direct visualisation with CT, MRI or angiography is today the routine method to define the target.

CT was an immediate revolution in stereotaxy (6). MRI in the beginning had significant geometric distortion and was not used for stereotaxy until 1987 (161). DSA likewise suffers from geometric distortion (16, 159) and in 1998 a method to correct for this became commercially available (V).

Radiation treatment

The third method to treat an AVM, ionising radiation, was occasionally tried in the beginning of the 20th century. Interestingly enough, the first record of successful treatment of an AVM with ionising radiation is that of Cushing (20) in 1928:

"On January 17, 1924, a left osteoplastic exploration which proved to be a most desperate procedure was made. The astonishing lesion consisted of a tangle of small thin-walled actively pulsating arterioles. The Sylvian vessels were greatly dilated and a large pulsating vein evidently containing arterial blood passed up around the posterior margin of the lesion. The tumour itself felt firm in consistency and was fairly well circumscribed, but it was inconceivable that it could be attacked without fatal haemorrhage."

A series of deep x-ray treatments were performed and the patient was operated a second time in 1927:

"The reopening of the dura disclosed a most unexpected condition. The lesion proved to be of stony hardness. The tangle of pulsating vessels previously encountered was largely thrombosed and transformed into a multitude of small bloodless shreds. It was found that the central lesion could be easily separated from the adjacent normal-looking cortex."

X-ray irradiation of AVM was, however, not advocated by Cushing and never gained general acceptance.

Radiosurgery

In Berkeley, California, stereotactic irradiation with heavy-charged-particles was begun in the 1950s and was first utilised in "Irradiation hypophysectomy" (185) for advanced metastatic carcinoma of the breast. In 1965, Kjellberg at Harvard University treated the first patient with an AVM with proton beam radiotherapy. However, it was Steiner et al. who in 1972 published the first results from a – successful – treatment of an AVM with radiosurgery (182), performed with the Gamma Knife.

Leksell defined the concept of radiosurgery as "The delivery of single high dose of radiation to a small and critically located intracranial volume through the intact skull" (101). To fulfil the specification two things are needed, an accurate localisation system and an apparatus to irradiate a small volume inside the skull with sufficient precision and dose rate.

Leksell already had a stereotactic system suitable for biopsies and minimally invasive functional neurosurgery (100). Initially he added an X-ray tube that could be moved around the head of the patient in arcs, always aimed at the same spot (101, 103). The radiation was focussed to one small volume, while surrounding structures were spared. The first patient was a woman who was treated with bilateral anterior capsulotomy (103) for schizophrenia – in effect a radiosurgical lobotomy.

Neither heavy-charged particles nor X-rays was at the time a practical solution to the problem of delivering a high dose of radiation to a small well-defined intracranial volume. In collaboration with the team at Gustaf Werner institute in Uppsala, notably Larsson and Sarby, Leksell constructed a device intended for hospital based stereotactic irradiation. (21, 92, 102). It was placed in Sophiahemmet in Stockholm. Later named the "Gamma Knife 1", it contained 179 Cobalt^{60} gamma sources distributed within a spherical sector of 70 degrees times 160 degrees. Precisely focussed in one point they provided high radiophysical and mechanical stability as well as reproducibility (Fig. 2 and 3).

Neuroradiology was obviously necessary to define the target for the treatment. Initially this was done with plain film, air ventriculography and encephalography or with intrathecal positive contrast medium. Conventional angiography was utilised for vascular structures.

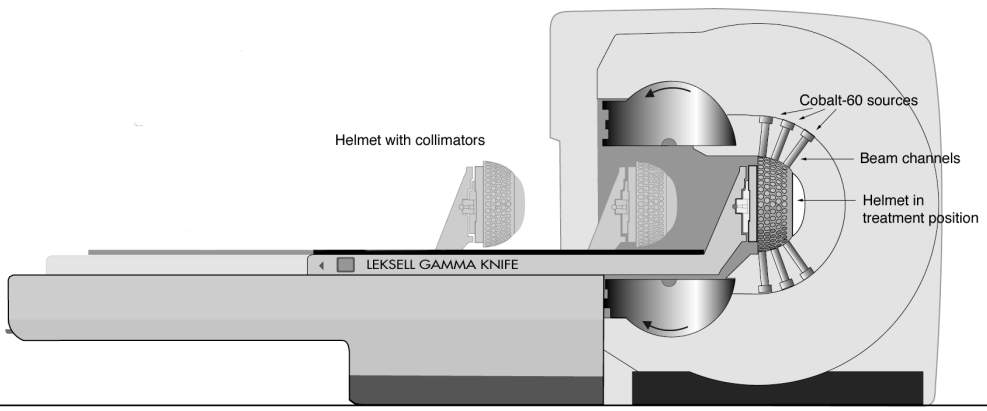

Fig. 2. The principle of the Gamma Knife (type C). 201 Cobalt^{60} sources are focussed in one point. The irradiation device is stationary and the patient on the couch is moved into position for the treatment (Courtesy Elekta, Sweden).

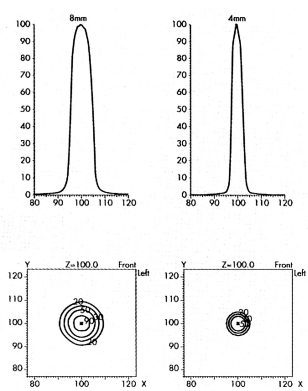

Fig. 3. Dose gradients for 4 and 8 mm collimators. The steep dose gradient illustrates the rapid fall-off of the radiation that permits single session high dose irradiation of a small volume. It is also the basis for the high targeting precision of the Gamma Knife.

The first three AVM patients were subjected to feeder irradiation. Doses were decided upon on the basis of a report by Marcial-Rojas on vessel rupture after irradiation of head-and-neck cancer (123). Two AVM were patent at control angiography. When it was found that the third AVM (Fig. 4) had obliterated, additional patients were treated.

The practice of feeder irradiation was founded on concepts that had evolved when treating meningeomas, and also as a necessity because of the collimator system of the Gamma Knife, which was designed for small, disc shaped lesions suitable for functional radiosurgery. Feeder irradiation was however only practised systematically during the first years, and it was soon clear that irradiating the nidus was a superior method, now routine.

Initially Leksell's spiral diagram was used for the stereotactic localisation of the AVM. Since it presupposed fixed geometry in the angiographic system, a special apparatus with rather primitive X-ray equipment was used, most often at the treatment locus. It provided one image in AP and one in lateral view, both in arterial phase. Bergström's introduction of an uncomplicated graphic method for localisation of the target (7) changed the routine so that the stereotactic angiography was performed at the department of neuroradiology, with much better facilities and image quality. The graphic localisation method had, however, unbeknownst to Bergström, been described previously by Watson Alberts (193).

Dose planning was primitive in the beginning, and it was not until the introduction of the KULA (ELEKTA, Sweden) dose planning system in 1987 that the radiation doses of several isocentres could effectively be added. Dose/volume histograms could not be obtained until the latest dose planning software (Leksell GammaPlan®, Elekta, Sweden) was introduced in 1993. In the meantime, radiation doses were reduced when the first cases of radionecrosis appeared, and a routine of reducing dose in large AVM came into existence.

For delineation of the target in radiosurgery for AVM (53), angiography remains the gold standard, supplemented by MRI, particularly in large irregular AVM or those located close to the brain stem or cranial nerves (55).

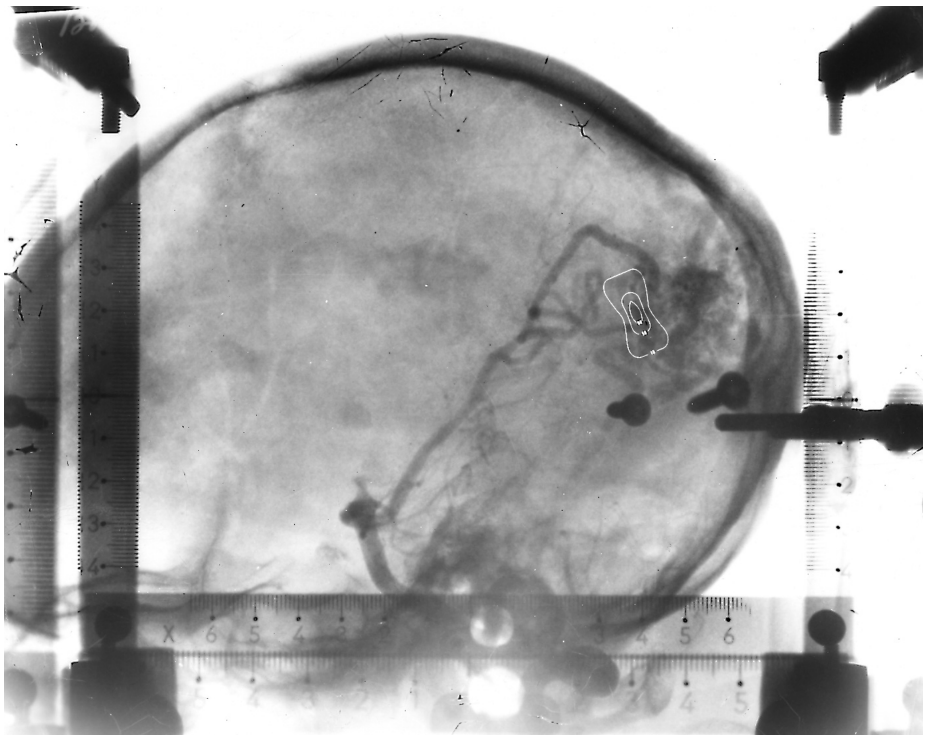

Fig. 4. The first successful Gamma Knife treatment of an AVM. The feeding arteries from the posterior cerebral artery were irradiated, while the occipital nidus was outside the prescription volume.

Predictive models

An essential part of health care is to analyse the consequences of management decisions. Initially this was done as personal collections of cases, but as experience and treatment possibilities increased there emerged a need to be able to predict the outcome of a particular patient in a particular treatment situation.

Luessenhop in 1965 proposed a classification for the prediction of the outcome of embolisation of AVM based on the localisation and feeder system of the lesion (111). It was never generally accepted. Neither was another system, proposed by Richling in 1994 (WIN-94, Val d'Isère, France).

The first predictive model for the surgical management of AVM patients, taking AVM, patient and treatment parameters into consideration, was that of Pellettieri in 1979 (140). Several grading systems and models have been proposed. Today the most widely used grading system for predicting the risk of AVM surgery is the one proposed by Spetzler and Martin (173) in 1986. It takes into consideration AVM parameters only, while patient and treatment parameters are not included.

Radiosurgery is – contrary to embolisation and neurosurgery – to a large extent a reproducible procedure, an important prerequisite for a predictive model. Apart from Kjellberg's early experiences (89), the first risk estimation model based on dose/volume analysis was presented by Karlsson at a meeting in Charlottesville in 1989. At the same time Flickinger published his first model, which, however, was only partly based on a clinical material (35). Today there are well supported models to predict the obliteration rate and risk of complication after radiosurgery as well as the risk of haemorrhage in the two years latency period following the treatment (I, II, III, VI and VII). These models, based on experience from more than 1500 AVM treatments, are used in clinical routine in the Karolinska hospital.

NATURAL HISTORY

Origin of AVM

As discussed in the introduction, there is no evidence of AVM being congenital in the sense that they are present at birth. On the contrary, cultured endothelial cells that originate from peripheral arteriovenous malformations have defective growth regulation (194) indicating an ongoing dysplastic vascular remodelling, which may be part of a process of AVM evolution. There are also indications that vascular endothelial growth factor (VEGF) may be important in the origin or recurrence of an AVM (171). Nevertheless, the emergence of a new AVM has only been documented in a few cases in children (77, 90, 110, 203) and is a very rare finding indeed in the adult (48, 65, 110).

Prevalence and incidence

In the Western population, the prevalence of AVM has been estimated in autopsy series to be 0.06% and 0.11% (76, 79) and the incidence to be between 0.01% and 0,001% (19, 137, 197). If the global risk for haemorrhage is 4%/year and 50% of the AVMs reveal themselves with haemorrhage, a prevalence of 0.1% implies that in Sweden (9 million inhabitants) the yearly incidence should be 360 AVM, out of which 180 present with haemorrhage. The AVM incidence in Sweden, however, appears to be less than that (data from unofficial queries among university clinics).

Evolution of AVM

The AVM is a dynamic lesion and causes progressive vessel change that has also been demonstrated experimentally. Tears in the internal elastic lamina of the artery afferent to an experimental AVS appear after 2 to 5 days (51, 52). Further changes involve all layers of the vessels and may progress to a point where the layers are destroyed and the vessel is actually unidentifiable as being artery or

vein (177). Localised fibrointimal thickening is present, together with uneven stretching and distension that progresses over time, creating wall thinning and aneurysms (120). The histopathologic changes in the AVM nidus and its afferent and efferent vessels have been proposed to be secondary to the high flow (120, 147, 177) and increased shear stress. However, the afferent vessels adapt to the flow demand by widening, and at rest shear stress is not significantly higher than in arteries supplying normal brain tissue (158). Thus, additional factors such as lack of autoregulation with augmented flow changes during normal blood pressure variations or disturbed laminar flow may interact with the endothelium and promote vascular remodelling.

AVMs have been reported to increase in volume because of actual AVM "growth", but more commonly because of flow changes, vessel dilatation and angiogenesis, sprouting and non-sprouting. They can also spontaneously regress or disappear; the mechanism for this is unknown, but spontaneous thrombosis has been suggested (73, 110, 172, 191, 203).

Revealing event

When the host cannot compensate for the stresses caused by the AVM symptoms become evident. In the neonate, cardiac failure – similar to that associated with the vein of Galen malformation – is the most common revealing event (157). Progressive brain destruction may affect the neonate, whereas haemorrhage with neurological deficit is less common. In the infant and later in life, seizures, headache and neurological deficits because of haemorrhage dominate the clinical picture (15, 19, 83, 137, 141, 157).

Risk to present with haemorrhage

45–70% of patients with an AVM present with acute intracranial haemorrhage (15, 19, 50, 66, 83, 95, 122, 137). The remaining patients that present with another clinical picture, or have their AVM discovered incidentally, might be accessible for a study with the aim to determine the risk to bleed for the first time. However, all studies in which this information might be available have an inclusion bias because of the referral pattern or because treatment was considered to be too risky. (13, 14, 19, 43, 50, 75, 83, 137, 141, 183). In addition, the understanding that the natural course of the disease is less favourable than once believed (83, 137), together with the increasingly good treatment results, have contributed to a situation where the vast majority of patients are treated. In most cases treatment is commenced soon after the AVM has been discovered. It is therefore unlikely that a large cohort of untreated patients will ever be followed for many years in an unbiased prospective study.

Another approach to the problem is that of Karlsson in his study of 2262 pati-

ents sent for GK radiosurgery (83). It differs from other studies in that it is based on the assumption that the AVM is present at birth and thus the time at risk is equal to the age at the first haemorrhage. It was demonstrated that the risk for a haemorrhage increases with patient age and increasing AVM volume and is relatively higher for AVM with central location and for females of fertile age (83). Due to the accumulated risk for neurological symptoms the appearance of an AVM after the age of 40 was rare in this study. Nevertheless, Crawford in his study found 11 patients over 60 years of age at time of diagnosis (19). Eight of those bled during the follow up period of 9 years, giving a risk for haemorrhage of 11%/year in that age group, similar to the numbers reported by Karlsson.

The observation that the risk to present with haemorrhage is less in small AVM has been made previously (150). Others have proposed that the risk for haemorrhage is higher in small AVM (174). Several authors have proposed that that central location of the AVM or central venous drainage may be a risk factor for haemorrhage (31, 83, 122, 124, 133). The largest and most important study of AVM angioarchitecture did not support a correlation between associated aneurysms and risk to present with haemorrhage but found that venous stenosis and central location were risk factors (122).

Pregnancy has been proposed to be a risk factor for AVM haemorrhage by several authors (19, 44, 83, 130, 156), while a few has proposed the opposite (69).

Risk for rehaemorrhage

Ondra and Karlsson (83, 137) could not find any proof that AVM haemorrhage is more common in those who had suffered previous haemorrhage. Others (19, 43, 62, 125) have found that the risk for haemorrhage increases if there has been a previous bleed.

Morbidity and mortality of AVM haemorrhage

The rate of mortality and permanent morbidity after an AVM haemorrhage is a matter of debate (14, 19, 50, 58, 62, 137, 141, 183). However, in Ondra's material the average life span was 44 years for those who died from an AVM haemorrhage and remarkably only 59 years for those who died from other causes (137). Pollock (148) reported in 1996 on 295 patients subjected to GKRS for AVM out of whom 21 bled from the AVM during follow up. Seven (33%) of those died and 6 developed new neurological deficits. Equal mortality and morbidity was reported by Karlsson (84).

Conversely, in the study by Prayer et al, 20% of the patients without any history of haemorrhage had haemosiderin deposits suggesting haemorrhage prior to one month before the clinical presentation (153). Guo et al. found in their pro-

spective study of 136 patients following GKRS a 17% incidence of asymptomatic petechial haemorrhage with a 2.3% annual incidence of symptomatic haemorrhage (58). In Hartmann's series (62) 27 patients experienced AVM rehaemorrhage. Since 20 were not disabled and there was no mortality, it was suggested that AVM haemorrhage might be more benign than previously believed.

Summary

It is possible to find support in the literature for almost any opinion concerning the natural course of AVM. Nevertheless, several important studies support the following conclusions.

The risk for haemorrhage increases with age; in the 30-40 year old patient it is about 4% per year.

Pregnancy is most probably a risk factor for haemorrhage.

Centrally located AVM have a higher risk for of rupturing than peripherally located AVM.

Venous stenosis is a risk factor in centrally located AVM, while associated aneurysms are not a risk factor for the presentation with haemorrhage.

The risk for haemorrhage increases with AVM volume.

The combined mortality and morbidity of an AVM haemorrhage is not clear. It is as low as 5% in some studies and as high as 50% other.

CURRENT TREATMENT OPTIONS

Introduction

In order to assess the efficacy of a treatment, its aim and measurable outcome parameters must be defined. All treatments have similar aims: a patient able to live a normal life. However, this may be accomplished with different means, where radiosurgery and surgery are alike in that the endpoint usually is obliteration or removal of the AVM from the blood circulation. Embolisation is different in that most AVM are only partially treated and supplementary treatment with surgery or radiosurgery is often required for obliteration. Sometimes because of the size and location of the lesion no cure is possible, and the treatment is palliative and aimed at reduction of the risk for haemorrhage or alleviation of symptoms.

We have in our studies recorded rate of obliteration of the AVM, gross neurological complication rate and severity (cf. complications) and presence of haemorrhages during the management period (II, III and VII). We did not investigate quality of life, intellectual performance or cognitive and behavioural aspects – important but rarely regarded outcome parameters.

Cognitive and behavioural outcome

Waltimo examined 40 AVM patients prior to treatment and found normal intelligence and cognitive functions (192), whereas Mahalick found neuropsychological impairment in all his 24 patients prior to surgical treatment (118), both ipsi- and contralaterally to the AVM. Fourteen of these were investigated again after surgery, and roughly 50% had improved (119).

Gómez-Tortosa studied 10 patients that had been subject to "high-risk" AVM surgery in the dominant hemisphere and found postoperative neurological or cognitive defects of varying severity in 9 of them. Six of the ten were living a "normal life" (49). Actually only one of their patients had no cognitive defect post haemorrhage and surgery.

On the other hand Yamada et al. claimed regression of behavioural changes

after surgery in 22 patients out of 56 operated for AVM in "functional areas" but do not mention how this was assessed (200). This material is amazing in that before surgery 53 out of 56 patients had symptomatology that precluded regular employment or satisfactory performance of household duties. 55 out of these 56 patients resumed their original occupations after surgery. The largest AVM was reported to be 317 ml, which is roughly 50% of the volume of a cerebral hemisphere (35, 200).

Stabell and Nornes in the most comprehensive study done to date performed neuropsychological testing before and after surgery in 31 consecutive patients and found some deterioration post surgery with recuperation to approximately pre-surgery level after a year (176).

Blonder et al. examined 10 patients with a battery of neuropsychological tests before and 11 months after GK treatment and found no significant difference (8). The patients were slightly impaired relative to normal controls. In 1997 Riva et al. (155), reported 8 patients, some of whom were children, to be normal at neurobehavioural follow up at an average of 6 years post radiosurgery for AVM. In a study of 79 AVM patients Wenz et al. (195) found marked negative deviations from the normal population regarding intelligence, attention and memory functions before treatment. There was slight improvement at 6-12 months follow up after GK radiosurgery.

There is no published study of the cognitive or behavioural outcome of embolisation of AVM. However, there is ongoing research in at least in London (NHNN, personal comm., Dr W. Taylor) and Gothenburg (Sahlgrenska hospital, oral comm., NFNR conference 1999).

Thus it is clear that the higher functions of the brain may be impaired in the patient harbouring an AVM, with or without haemorrhage or treatment, and in one report even contralaterally to the lesion.

No treatment

The decision not to treat is to take the standpoint that it is better for the patient to be exposed to the natural course of the disease than to the remedy.

In view of the risk for neurological sequelae (83, 137, 157), an unacceptable treatment risk is the only rationale not to treat (2). The exceptions are the patients who refuse treatment or whose medical condition does not permit intervention. Patients with symptoms like headache and seizures can often be helped by medical treatment, even if no cure is possible.

Interventional neuroradiology

Large studies of the outcome of embolisation are few. The best published results are those by Valavanis, who had a 40% obliteration rate from embolisation

alone, with a mortality of 1.3% and a morbidity of 1.3%, in his study of 387 consecutive patients (187). Wikholm et al investigated 150 consecutive patients and found an obliteration rate of 13%, with a mortality of 1.3% and a morbidity of 33%. Fournier et al. in their study of 49 patients had similar obliteration and mortality rates but with a permanent morbidity of 8% (45).

Recently, it was demonstrated that partial or targeted embolisation with NBCA reduced the risk for haemorrhage by 24–78% (129) as compared to the natural history of Crawford (19).

The widely diverging results from embolisation may reflect methodological problems. The aim of the treatment may differ, patient materials may not be comparable and the technical evolution in the field has been tremendous. In addition, patient outcome has in some studies been very thoroughly assessed by an independent neurologist, in other studies by the physician who performed the treatment. As pointed out by Wikholm (197) it is amazing that so many microcatheters for AVM embolisation are purchased and so few results are published.

Radiosurgery

Radiosurgery is fundamentally different from embolisation and surgery in that the results of the treatment are largely predictable and thus suitable as a basis for accurate outcome models (I, II, III, VI and VII). The impacts of patient, AVM and treatment parameters on the outcome are discussed in the appropriate chapters (cf.)

Surgery

A distinct advantage of surgery is that after complete removal of an AVM in one session, the patient is exposed only to the perioperative risk. The best results from surgery of cortical AVM<3 cm in diameter show morphological cure in 100% with no mortality and a permanent complication rate of 0% (61, 146, 169). The inclusion bias makes evaluation of the results difficult, and for example Hamilton only published the cases where total resection had been possible (61). For larger and deeply located lesions results are less good (61, 138). Surgical removal of the AVM has not been investigated in this study and will only be mentioned occasionally.

Permanency of obliteration

Recurrence or appearance of new AVM has occasionally been reported after surgery or radiosurgery with angiographically proven obliteration, almost exclusively in children (48, 65, 77, 90, 110, 203). No such reappearance after emboli-

sation has been demonstrated, but it seems unlikely that NBCA has protective effects in areas not embolised. This does not contradict the conclusion of Wikholm that the properly embolised part remains closed (196).

Recurrence or appearance of a new AVM is most likely very unusual, and therefore it seems unreasonable to propose late follow up angiography, even for patients < 15 years of age and regardless of mode of treatment.

AIMS OF THE STUDY

The overall aim of this work was to create methods to implement outcome models from GKRS of AVM onto the general management of the same disease, particularly combined treatment, i.e. embolisation and GKRS. This was to be accomplished in several steps, that may be summarised as:

- To improve outcome models in Gamma Knife radiosurgery for AVM.
- To develop a method for prediction of the outcome of radiosurgery from diagnostic angiography.
- To develop a method for correction of the geometric distortion in DSA.
- To develop a method for uncomplicated volume determination of an AVM. from diagnostic angiography, useful as a substitute for dose planning in prediction of the outcome of Gamma Knife radiosurgery for AVM.
- To implement the methods and models onto a clinical material of patients treated with embolisation for AVM and make a hypothetical comparison between management strategies.

STATISTICAL METHODS

To compare nominal data, the chi-square test or Fisher's exact test was used. The Mann-Whitney U-test was used to compare nominal with continuous data. The Wilcoxon two-sample test was used to compare continuous data. Dunn's method (30) was used for determining the intraclass correlation coefficient.

DISCUSSION OF THE INDIVIDUAL PAPERS

Definitions of complications

In this text the event of a complication in general is defined as:

New or aggravated neurological symptoms or signs, transitory or permanent, occurring together with or associated to the treatment.

The temporal aspect of the appearance of a complication is defined as:

1. Immediate – in conjunction with the procedure
2. Early – within 0–3 days
3. Intermediate – within 3–30 days
4. Late – within 30 days to two years
5. Very late – after two years

The morbidity of a complication is defined as:

1. Transient – no remaining neurological symptoms after 30 days
2. Insignificant, permanent – 30 days post ictus there are remaining neurological symptoms that do not interfere with normal life
3. Significant, permanent – 30 days post ictus there are remaining neurological symptoms that interfere with normal life
4. Death

Since the brain can recuperate over a long time, function that was lost at the 30-day deadline may be regained later. This was not accounted for in the direct comparison of treatment modalities (VII).

The event of haemorrhage was regarded as related to the treatment if it occurred during the first 30 days after the procedure.

In the Gamma Knife outcome model a complication was defined as "radiation-induced new or aggravated neurological symptoms or signs, transitory or permanent, occurring together with radiological evidence of oedema or radionecrosis". In practise this applies only to the late reactions (59). Radiation

damage to the cranial nerves and very late complications are not included and has to be accounted for separately (184, 201).

Embolisation has a procedure-related mortality of 1-2% (45, 187, 197). Deaths from radiosurgery for AVM, because of uncontrollable oedema in sensitive structures, have been reported but are very rare (2 out of 1255 treatments reported by Flickinger et al) (38).

Prediction of the obliteration rate

Previous investigations

Obliteration is the morphological goal of radiosurgery, only limited by the risk for complications. In most centres the urge to avoid radiation necrosis has prompted prescription of doses incurring a predicted risk of <3%, based on Kjellberg's experiences from 1983 with Bragg peak proton beam therapy (89) and later the integrated logistic formula presented by Flickinger (35). Effectively, this meant that radiation doses were reduced as the treatment volume increased. It was not clear whether the obliteration rates was an effect of the dose, the volume or both. This is important since volume is an AVM parameter and therefore cannot be modified at the time of the irradiation, while treatment parameters may be adjusted. In this study three previously published models for prediction of the obliteration rate in GKRS for AVM were investigated together with the novel Karlsson-Lax model.

THE FLICKINGER MODEL (36) is a logistic regression analysis of 197 patients out of a total of 316. In this study the notion of "in-field obliteration" was created, meaning that a treatment was successful if the irradiated part of the nidus had obliterated, regardless of AVM remaining. In addition, subtotally obliterated AVM were included among the successful treatments and angiography three years after the irradiation was defined the endpoint. The minimum dose to the AVM was the only independent variable with effect on the "in-field obliteration" rate. When AVM with remaining nidus were classed as failures, volume became the only significant independent variable.

THE SCHWARTZ MODEL (165) was based on the assumption that larger AVM need a higher minimum dose for obliteration. The equation was based on 42 patients with angiographic follow up three years after the irradiation, out of which 28 AVM had obliterated. It was tested on a cohort of 394 patients. The AVM size was defined as the largest diameter measured on the stereotactic angiography corrected for the magnification.

THE K-INDEX (85) model was founded on the assumption that large AVM need a lower minimum dose for obliteration. AVM volume was defined by the best-fit isodose technique (85) and an index based on minimum dose to 90% of the prescription volume (D_{min}) and the third root of the AVM volume was created. The material comprised 1319 patients treated during 1970–1990 at four different centres. After exclusion of patients with additional irradiation, deaths

and lack of follow up, 930 patients with 945 AVM remained that had completed two-year follow-up angiography. 43 patients were examined with MRI only, showing remaining AVM two years after the treatment, and were included as treatment failures.

Current investigation

The material investigated consisted of 1006 patients with 1033 AVM treated with GKRS at the Karolinska hospital during the period 1970-1993. Two hundred and three did not undergo conclusive angiogram. Eight were examined with MRI only, revealing patent AVM in six cases and not in two cases. These were included in the study that thus comprised 838 (81%) AVM with known outcome. AVM volume was defined by the best-fit isodose technique (85).

The Karlsson-Lax model was based on the observation from reference (85) that a logarithmic function almost perfectly (R^2=0.99) describes the empirically found relation between D_{min} and P_{obl} (85) (Fig 5):

$$P_{obl}=36*\ln(D_{min})-40 \quad ; 0\leq P_{obl}\leq 100 \qquad \text{Eq.1}$$

where P_{obl} = Probability of obliteration

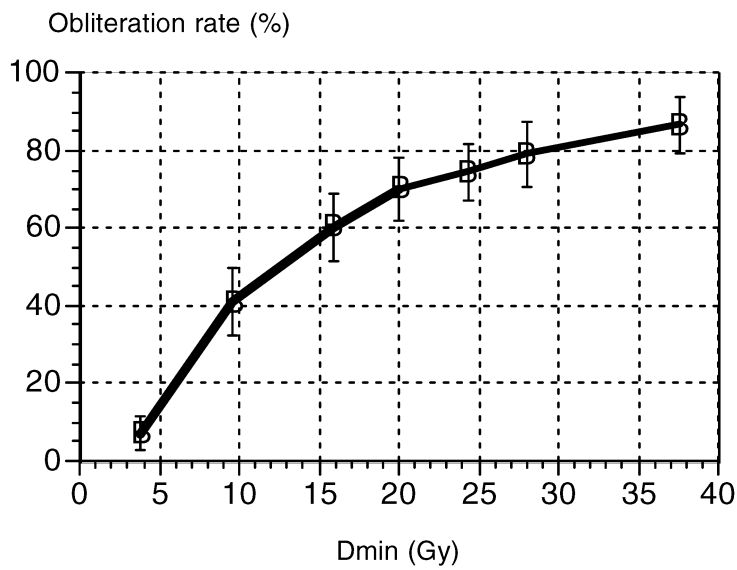

Fig. 5. Obliteration rate plotted against D_{min}. The bars represent the 95% confidence interval.

The accuracy of the methods was investigated. The patient material was divided into groups based on parameters that may have impact on the treatment results (Table 1). For each of the continuous parameters the material was divided at the median into two groups and the probability for obliteration was calculated for each patient. In each group of AVM defined by the nominal or continuous parameters, probabilities for obliteration were added and compared to the number of observed obliterations in the same group (Table 1).

THE FLICKINGER MODEL was volume and dose dependent in that it predicted significantly too few obliterations for $D_{min} \leq 22$Gy and too many for $D_{min} > 22$Gy or AVM volume<2ml (Table 1).

THE SCHWARTZ MODEL predicted a significantly smaller number of obliterations than observed in the total material (Table 1). It was also volume and D_{min} dependent.

THE K-INDEX, when applied to our material, was volume and D_{min} dependent in that it underestimated the obliteration rate for AVM<2ml and $D_{min} \leq 20$Gy while it overestimated the obliteration rate for AVM≥2ml (Table 1).

None of the three models were thus accurate.

THE KARLSSON-LAX MODEL accurately predicted the outcome in all subgroups (Table 1).

	N	Pred obl	Obs obl	Δ	95% C.I.	Significance
K index						
All patients	814	527	503	−24	475–530	N.S.
AVMvol<2 ccm	420	292	317	25	299–334	S
AVMvol≥2 ccm	394	236	186	−50	167–206	S
Dmin≤ 20 Gy	411	215	188	−27	168–208	S
Dmin> 20 Gy	403	312	315	3	299–331	N.S.
Karlsson-Lax model						
All patients	814	505	503	−2	476–530	N.S.
Age ≤ 29 yrs	417	260	258	−2	238–277	N.S.
Age > 29 yrs	397	245	245	0	226–264	N.S.
Male	399	247	245	−2	226–264	N.S.
Female	415	258	258	0	239–278	N.S.
AVMvol<2 ccm	420	307	317	10	300–337	N.S.
AVMvol≥2 ccm	394	198	186	−12	167–206	N.S.
Dmax≤ 44 Gy	411	252	255	3	236–274	N.S.
Dmax> 44 Gy	403	253	248	−5	229–267	N.S.
Dmin≤ 20 Gy	411	190	188	−2	168–208	N.S.
Dmin> 20 Gy	403	315	315	0	299–331	N.S.
Daver≤ 33 Gy	405	221	218	−3	198–238	N.S.
Daver> 33 Gy	409	284	285	1	267–303	N.S.
Cerebellar	51	35	32	−3	25–39	N.S.
Central	387	243	260	17	242–278	N.S.
Peripheral	376	227	211	−16	192–230	N.S.
Hemorrhage	630	401	412	11	389–435	N.S.
No hemorrhage	173	98	87	−11	86–98	N.S.
Prev surg or embo	161	95	95	0	81–105	N.S.
No prev surg or embo	653	410	408	−2	386–434	N.S.
Schwartz model						
All patients	814	473	503	30	476–530	S
AVMvol<2 ccm	420	336	317	−19	301–333	S
AVMvol≥2 ccm	394	137	186	49	167–206	S
Dmin≤ 20 Gy	411	141	188	47	168–208	S
Dmin> 20 Gy	403	332	315	−17	299–331	S
Flickinger model						
All patients	704	516	493	−23	469–517	N.S.
AVMvol<2 ccm	408	340	316	−24	299–333	S
AVMvol≥2 ccm	296	176	177	1	160–194	N.S.
8≤Dmin≤ 22 Gy	344	182	208	26	190–226	S
Dmin> 22 Gy	360	334	285	−49	270–300	S

The predicted and observed numbers are compared for different subgroups of the total patient population, and the 95% confidence interval for the observed numbers given.

Table 1 (From (I) with permission). Comparison between the total number of predicted obliterations and the observed numbers for the four different models analysed.

Discussion

For 19% of the patients there was no conclusive angiographic or MRI follow up. This is not surprising, since before the widespread use of radiosurgery many patients came from abroad, and there were thus logistic problems in the follow up routine.

It might be proposed that those patients had remaining AVM on MRI or CT and therefore were not referred for conclusive angiography, or that a fair number of them have died from haemorrhage and the material may not be representative. However, Sweden has a strict social security and medical care system and routines for follow up with angiography were rigid until the beginning of the 90s. Therefore the subgroup of Swedish patients has a follow up rate of >90%. This group does not differ from the total material (unpublished data), which speaks against the existence of an inclusion bias.

If a predictive model is accurate it has the power to predict the outcome in every AVM subgroup regardless of how the subgroup is defined. The method used for the analysis eliminates the influence of D_{min} and thus allows separate analysis of the other parameters. No other parameter had independent impact on the $p<0.05$ level. However, there was a trend that centrally located AVM had a higher obliteration rate than predicted (260 (242-278) observed, 243 predicted), and the opposite for peripheral AVM (211(192-230) observed, 227 predicted). This agrees with the findings of Meder et al. (127) in their analysis of 102 patients treated with radiosurgery for AVM. A possible explanation is that the venous pressure is slightly higher in central structures, with a lower pressure gradient than in peripherally located AVM.

Previous surgery or embolisation had no impact on the obliteration rate. Since AVMs that have been reduced in volume respond equally to other AVMs this does not support the notion that there is "radiation resistance factor" (149) of large AVMs. It is interesting that neither alleged difficulty in delineating the AVM nor possible late reperfusion after surgery or embolisation decreased the obliteration rate. Could a favourable change in angioarchitecture by the embolisation (60, 127) might possibly have counteracted these effects?

There are very few reports on the impact of angioarchitecture on the response to radiosurgery. However, Meder in 1997 (127) suggested that AVM with plexiform nidus had a higher obliteration rate and faster obliteration than fistulous AVM. The findings are in line with the investigations by Petereit et al. (142) and may correspond to the need for a more pronounced wall thickening to occlude the larger lumen of a fistula (162).

How is it that other groups have reported a correlation between AVM volume and obliteration rate (46, 85, 127, 165) in contradiction to the results of Flickinger (36) and the findings in paper I? There may be several reasons.

First, there is the confounding effect of the dose reduction customary in large AVM, which prompted the reasoning in some studies (85, 114, 165). This confounding effect is neutralised with the present study design.

Second, in a large AVM it is more difficult to delineate the AVM from angio-

graphy as well as to shape the dose plan to conform to the AVM (55). The importance of correct delineation was illustrated by Flickinger (36), who found a strong relation between D_{min} and P_{obl}, if patients with "in-field obliteration" and remaining nidus outside were included as successful treatments. If included as treatment failures there was a correlation between AVM volume and P_{obl}, but none between D_{min} and P_{obl}. In ref. (127) all treatments were made with linear accelerator to a D_{min} of 25 Gy and the dose-obliteration relation therefore can only be calculated for one D_{min}. In their material large AVM obliterated significantly less often than small, which could thus be an effect of inaccuracy.

Third, the definition of AVM volume from treatment parameters, regardless of conformation to anatomical structures, introduces an error. This is particularly important in linear accelerator radiosurgery where few isocentres are used.

Are the findings reasonable? If the response of an AVM is analogous to that of a tumour, an increase in dose to induce obliteration would be anticipated as the volume increases. This was not the case, which may be because it is not necessary to affect every segment of every vessel in the AVM to cause obliteration. Another explanation could be that due to difficulties in appreciating the true shape of the nidus, too much tissue was included in the irradiated volume, and thus the true D_{min} was higher than believed (9, 55). In addition thrombosis can be self-promoting, due to local inflammatory response and flow decrease, a process that may be more prominent in larger volumes.

Is the study affected by circular evidence? The two models from Karolinska hospital were based on treatments performed at Karolinska hospital and by Steiner during 1970–1990 (85). In the present population all 358 patients (38%) from outside Karolinska hospital were excluded and the treatment results from another 244 patients (29%) were added. The Karlsson-Lax model was accurate when applied on both materials, while the K-index, based on the former material, proved to be inaccurate when applied onto the present material. Circular evidence therefore seems unlikely.

Conclusions

The decisive factor for prediction of the obliteration rate after radiosurgery is the minimum dose to the AVM. No other parameter, including AVM volume and previous treatment, had independent impact. There is a tendency that centrally located AVM have a higher obliteration rate than peripherally located AVM.

Prediction of risk of radiation induced complications

Previous investigations

Obliteration is the morphological goal of radiosurgery to AVM and depends only on D_{min}. However, the radiation dose is limited by the risk of complications.

Radiosurgery is fundamentally different from radiotherapy in that it employs single session therapy with a high dose to small volume. The very heterogeneous dose distribution has posed difficulties in constructing a model that could accurately predict the risk of radiation-induced complications in the central nervous system.

The first model was that of Kjellberg (89). It was based on experiences from 74 patients treated with Bragg peak proton beam therapy, out of whom 8 developed radiation necrosis. From this limited material a dose-volume relationship was suggested. The 99th and first percentile isoeffective doses for inducing radionecrosis of the brain were presented graphically.

Kjellberg's graph and local experience were used for risk prediction until 1989, when Flickinger published the integrated logistic model (35):

$$P(D)=\frac{1}{1+(D_{50}/D)^{k}} \qquad \text{Eq.2}$$

D_{50} is the dose that gives a probability of complication of 50% and k is a constant. D_{50} and k have to be determined from clinical data. The formula was based on Schultheiss' analysis of the results of Berg and Lindgren from split field brain irradiation in rabbits (163) and the 3% complication rate reported by Steiner (181) using a 14mm collimator with 25 Gy to the 50% isodose line in AVM treatment. It was assumed that only the dose to the tissue outside the target has impact on the risk for complication (a standpoint later revised by the same author (39)).

The relationship between the risk for complication and the given treatment (dose-volume) was further investigated in 1996 by Lax and Karlsson (99). Their material consisted of 862 patients subjected to GKRS for supratentorial and brainstem AVM, out of whom 45 experienced complications. Their reasoning was based on the formula for the probability of complication, P, in a volume Δv_i with a heterogeneous dose distribution, given by Schultheiss (164):

$$P(\{D\},v)=1-\prod_{i}[1-P(D_i,1)]^{\Delta v_i} \qquad \text{Eq.3}$$

Where the product is taken over all irradiated volume elements v_i. Each fractional subvolume $\Delta v_i = v_i / V$ is irradiated with dose D_i ,where V is the reference volume of the whole brain. The dose-response function of V is given by P(D,1):

$$P(D,1)=\exp(-N_0 * \exp(-D/D_0)) \qquad \text{Eq.4a}$$

Eq.4a may also be expressed in terms of the parameters D_{50} and γ :

$$P(D,1)=2^{-\exp(e\gamma(1-D/D_{50}))} \qquad \text{Eq.4b}$$

Eq. 4a was reduced to:

$$P(\{D\},v)\approx 1-\exp[(\ln N_0 - D_{ave20}/D_0)v] \qquad \text{Eq.4c}$$

where D_{ave20} is the average dose in v (in this context a volume of 20ml containing the AVM) obtained from an add-on to the dose-planning program. N_0 and D_0 were determined by a fitting procedure of Eq. 3 to the data of the incidence of complications grouped according to average dose (cf Eq. 4c). In this study no parameter but dose distribution had impact on the risk for complications on the P=0.01 level.

Current investigation

All 1112 AVM patients with 1128 AVM treated with GKRS at Karolinska hospital during the period 1970–1993 were included. For all patients observation time was more than 2 years. CT or MRI had been performed either as a matter of routine or when prompted by neurological symptoms. Of the 550 patients treated before 1988, 308 had a CT scan.

The treatment plans of 19 patients could not be evaluated and were set to the predicted average risk of the population studied (5.3%). The 104 patients (9%) subject to previous irradiation were analysed only for that parameter. The impact of the other parameters was analysed in the cohort of 1024 cases that had not received previous irradiation.

The model of Lax was applied to this material, using the values of D_0, N_0, D_{50} and γ from the original model (99). The observed number of complications was compared to the predicted number and related to patient, AVM and treatment parameters (Table 2). In the primary analysis all predicted numbers were within the 95% C.I. of the observed numbers, except peripheral AVM that had significantly fewer complications than predicted.

	N	Predicted	Observed	Diff.	95% C.I.	Sign.
Total	1024	55	52	-3	38-66	N.S
Prev. irrad. (1128 pat)	104	5	12	7	6-19	S.
Age≤15	149	7	7	0	2-12	N.S.
Age>15	875	48	45	-3	32-58	N.S.
Male	513	28	26	-2	16-36	N.S.
Female	511	27	26	-1	16-36	N.S.
Cerebellar	77	N.A.	N.A.	N.A.	N.A.	N.A.
Central	491	25	34	9	23-45	N.S.
Peripheral	456	28	18	-10	10-26	S.
Haemorrhage	787	41	38	-3	26-50	N.S.
No haemorrhage	237	14	13	-1	6-20	N.S.
Prev. surg or embo	228	14	14	0	6-20	N.S.
No prev. surg or embo	796	41	38	-3	26-50	N.S.
Central and haemo	441	22	30	8	19-41	N.S.
Central and no haemo	46	3	3	0	0-6	N.S.
Peripheral and haemo	290	19	8	-11	2-13	S.
Peripheral, no haemo	166	11	10	-1	4-10	N.S.
Central, age≤15	88	4	7	3	2-12	N.S.
Peripheral, age≤15	46	3	0	-3	0-6	N.S.
Central, age >15	403	20	27	7	17-37	N.S.
Peripheral, age >15	410	25	18	-7	10-26	N.S.

Table 2. Predicted numbers of complications using the N_0 and D_0 from ref. (99) in relation to observed numbers. (N.S.= not significant, N.A.= not analysed)

There was a parameter interdependence so that previous haemorrhage was significantly more common in centrally located AVM than in peripherally located ($P<0.0001$). In addition age≤15 years correlated with central location ($P<0.001$).

The impact of haemorrhage and location was studied separately and there was a significant relative reduction of the risk for complications in the group peripheral AVM with haemorrhage (Table 2). Therefore a second fitting procedure to clinical data was done for the three AVM groups centrally located, peripherally located without haemorrhage and peripherally located with haemorrhage (Fig. 6). The determined parameter values were for central all, D_0= 1.80Gy, N_0= 37.3 and D_{50}= 7.17, γ = 1.46; for peripheral without bleeding D_0= 2.29Gy, N_0= 38.8 and D_{50}= 9.22, γ = 1.48; and for peripheral with bleeding D_0= 3.29Gy, N_0= 35.8 and D_{50}= 13.0, γ = 1.45.

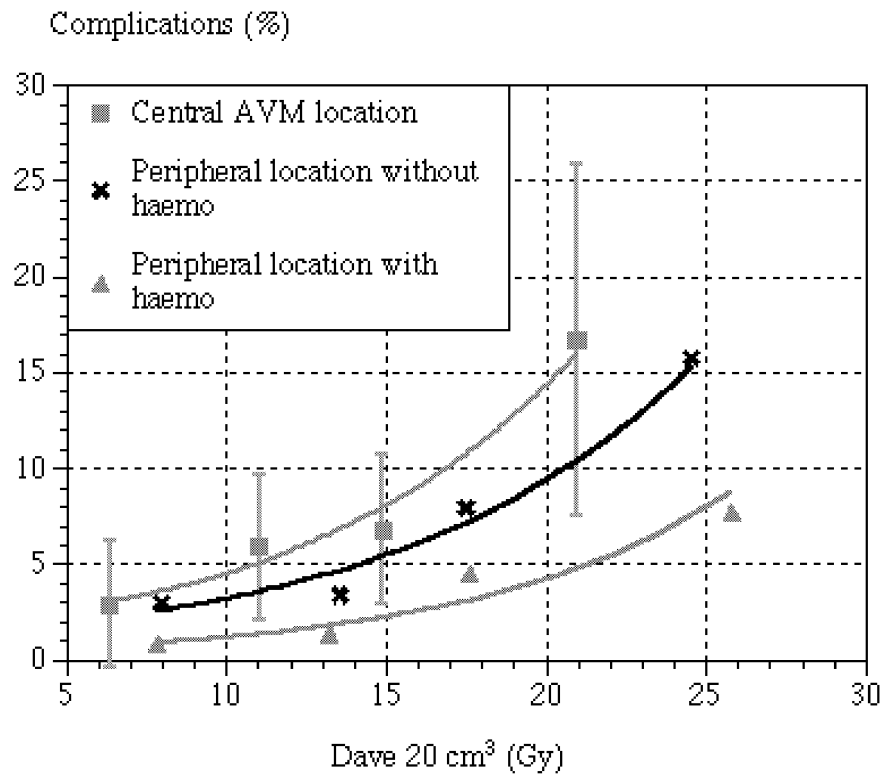

Fig. 6. The incidence of complications is plotted against the average dose in the 20cm³ of tissue that received the highest dose of radiation. The 95% confidence interval is plotted for centrally located AVM only, but are of the same magnitude for the other two groups.

Discussion

In this series there was clinical and radiological follow up with angiography, CT or MRI on 90% of the patients. All patients who reported neurological symptoms were investigated with CT or MRI. The remaining 10% of the patients had mainly been referred from other countries. The follow up rate in Swedish patients was higher; suggesting that geographical and cultural difference may explain the lack of information.

The risk of developing a complication depends on D_{ave20}, AVM location and previous haemorrhage. Flickinger in 1997 correlated the risk to the size of the volume containing tissue irradiated with 12Gy or more (39), which effectively is very close to D_{ave20} and supports the notion that all irradiated tissue, including the AVM, is of importance for the risk to develop adverse radiation effects (ARE).

Centrally located AVM had a relatively high complication rate while peripherally located AVM after haemorrhage had a lower rate. Can the difference be explained by location only? There seems to be no experimental evidence of differences in radiosensitivity between grey and white matter. However, ARE present in central structures may cause clinical symptoms more readily than ARE in "silent" areas of the brain, and thus will prompt a neuroradiological investigation. ARE may disappear within a few months, so chances are it will be missed if it does not cause neurological symptoms (59). Thus the differences in complication rate between centrally and peripherally located lesions might be attributable to the clinical situation and not to actual differences in radiosensitivity. However, other investigators have found that the risk for complications have a strong correlation to location, while the amount of energy delivered to the target has relatively less impact (37).

91% of the patients with centrally located AVM had experienced haemorrhage, so obviously haemorrhage by itself was not a strong enough protective factor to neutralise the impact of location. A possible explanation for the impact of haemorrhage is that an intracerebral haemorrhage from a peripheral AVM may result in an encephalomalacic cavity that contains no tissue that can develop ARE. A haemorrhage of the same size in central structures is much more likely to cause high morbidity and mortality, and the patient never becomes subject to radiosurgery. Other investigators have found that previous haemorrhage has no impact upon the complication rate, and even lessens the recuperation frequency (38).

It should be noted that the definition of complications excludes acute effects on the cranial nerves and late adverse radiation effects (ARE), typically pseudocysts that may be symptomatic (38, 39, 88, 202). In the investigation by Guo 16% (131/816) of patients subject to GKRS for AVM developed ARE (54). Clinically, 39% (51/131) were symptomatic, and 50% of those had remaining symptoms at follow up. Today there are unpublished data suggesting that these figures might be too conservative.

The relation between AVM volume, P_{compl} and D_{min}

In the clinical setting, where dose-planning facilities might not be present, an uncomplicated relation between AVM volume (v) and P_{compl} for different D_{min} would make the outcome model more versatile. To investigate this topic 600 patients subjected to GKRS for AVM with Dmin≤15Gy were extracted from a previous study (84). The original data were recalculated to show the relation between v and D_{ave20} for different Dmin, which was found to be:

$$D_{ave\,20} = a * v^{b} \qquad \text{Eq.5}$$

Where the best fit to empirical data was b=0.483. The constant (a) depends on D_{min} and was 6.49 for 15 Gy, 8.67 for 20 Gy and 10.8 for 25 Gy (Fig. 7).

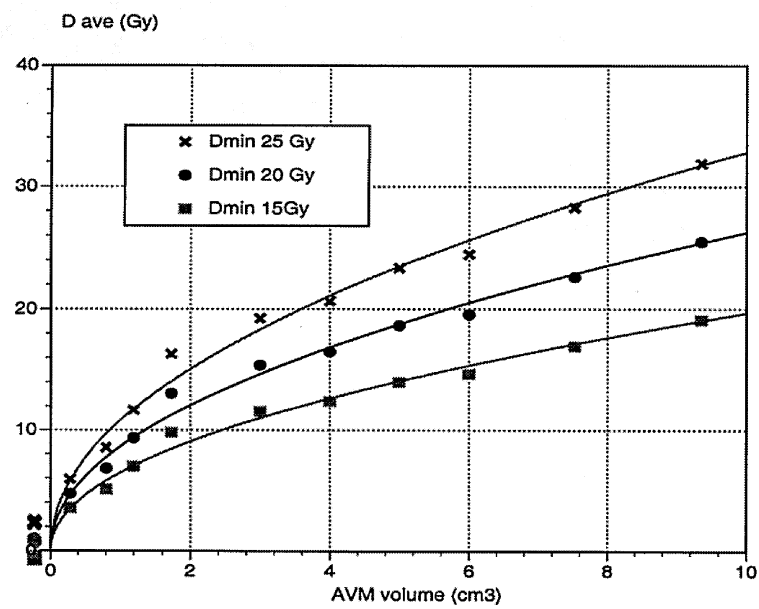

Fig.7. The relation between AVM volume (v) and D_{ave20} for three different D_{min}. (N=600, R^2=0.98).

The relation between D_{ave20} and P_{compl} was calculated for the same 600 patients, using the equation of Schultheiss as suggested by Lax et al. (Fig.8) (99, 164), and the best fit was found to be:

$$P_{compl} = 0.0829 * (D_{ave\,20})^{1.58} \qquad \text{Eq.6}$$

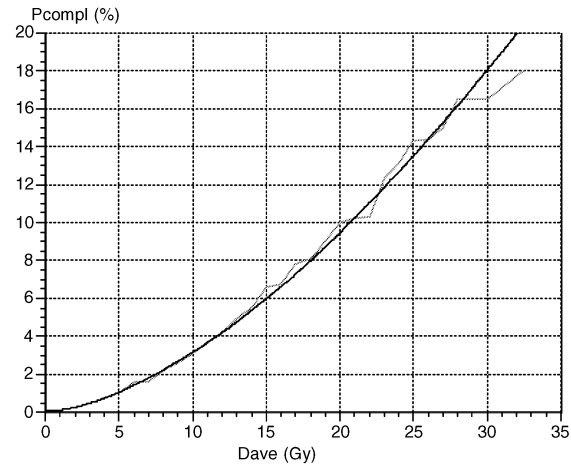

Fig.8. The relation between D_{ave20} and P_{compl}. The light grey curve represents the computed values of discrete groups of treatments, while the black curve is the result of the fitting procedure. (N=600, R^2=1.00).

If D_{ave20} in Eq.6 is substituted with Eq.5, the relation between v and P_{compl} may be expressed as:

$$P_{compl} = d * v^{0.76} \qquad \text{Eq.7}$$

in which d depend on D_{min} and is 1.59 for 15Gy, 2.51 for 20Gy and 3.56 for 25Gy (Fig.9) R^2=0.98. This relation has been used to predict the complication rate in paper VII. The 25Gy curve is almost identical to the 25Gy graph in paper VI. However, it should be borne in mind that for centrally located AVM is P_{compl} higher and lower for peripherally located AVM with haemorrhage.

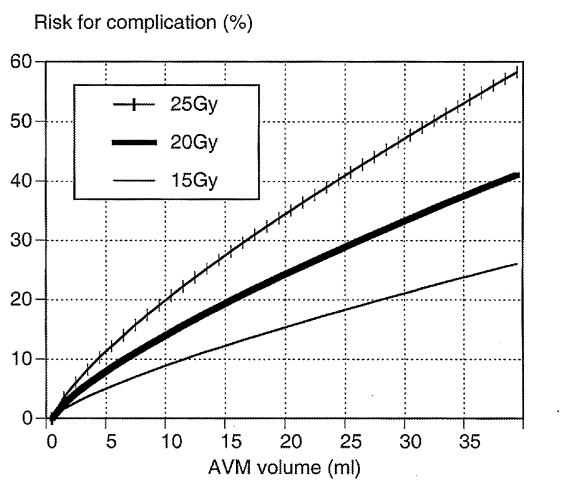

Fig. 9. The relation between AVM volume and P_{compl} for three different D_{min}. The confidence interval is not shown, but is of the same magnitude as in Fig.6. The 25Gy curve closely resembles the 25Gy curve in (VI).

Conclusions

The risk for complication after Gamma Knife radiosurgery is predictable and depends on the amount of radiation delivered to a volume of 20cm^3 containing the AVM (D_{ave20}), which can be expressed with the parameters D_{min} and AVM volume. It also depends on AVM location and patient history, i.e. previous irradiation and haemorrhage.

Prediction of the risk of haemorrhage during the latency period

Previous investigations

A major drawback of GKRS is the risk of haemorrhage during the latency period before the AVM obliterates. Different opinions as to the magnitude of the risk relative to the natural course of the disease have been presented (34, 47, 84, 104, 148, 180). Most likely, the apparent discrepancies reflect differences in natural history, patient materials or treatment parameters and the figures are therefore not directly comparable.

However, it has been shown that an increase in the average dose (D_{ave}) delivered to the AVM volume, entails a decrease in time to obliteration (85). In addition P_{obl} is directly related to D_{min} (36, 82, 85, 165) (I). AVM volume and patient age in themselves have impact upon the risk of haemorrhage, according to the natural course of the condition (84).

The aim of this study was to present a model for prediction of the risk of haemorrhage in the two year latency period after GKRS for AVM (P_{hem}).

Current investigation

The material comprised 1259 patients treated at the Karolinska hospital 1970–1995 and 317 patients treated at the University of Virginia 1989–1990. Eleven patients had multiple AVM and were counted as 28 cases. Thus a total of 1593 cases were included in the study. The time during which a patient was at risk for a haemorrhage was defined as beginning at the time of GKRS and ending after two years or earlier if any of the events retreatment, haemorrhage or death occurred. The total number of risk years was 3123.

Patient parameters investigated included age at the time of GKRS, gender and previous haemorrhage, radiation or embolisation. AVM parameters were volume and location and the treatment parameters were D_{max}, D_{min} and D_{ave}.

Results

During the time at risk 55 haemorrhages were reported, which equals an annual incidence of 1.7%. Of those, 24 (44%) occurred within 6 months after the treatment. In addition 44 haemorrhages occurred more than two years after GKRS, out of which 17 occurred after more than 5 years and 8 after more than 10 years.

Both D_{min} ($P = 0.0003$), and D_{ave} ($P = 0.0005$) were related to the incidence of post treatment haemorrhage, while D_{max} was not ($P = 0.99$). D_{min} and D_{ave}

were strongly related to each other (P<0.0001). The simple four-field table analysis in table 3 disclosed, however, that a low incidence of haemorrhages was more closely related to a high D_{min} than to a high D_{ave}.

	Low D_{min}	**High D_{min}**
Low D_{ave}	6.1%	2.0%
High D_{ave}	4.2%	1.6%

Table 3. The incidence of post treatment haemorrhages grouped according to D_{min}≤20Gy or D_{min}>20Gy and D_{ave}≤30Gy or D_{ave}>30Gy.

Patient age at treatment (P = 0.003) and AVM volume (P < 0.0001) were both related to the incidence of post treatment haemorrhage. Previous radiation treatment (P = 0.85), gender (P = 0.93), central AVM location or noncentral location (P = 0.92), history of haemorrhage prior to GKRS (P = 0.42), and previous embolisation (P = 0.85) were not.

Prediction of the risk of post treatment haemorrhage

The relation between the incidence of post treatment haemorrhage and D_{min} was calculated by defining the best-fit Gaussian function with the general form of:

$$P_{hem} = a * \exp\left(-b * (D_{\min})^2\right) \qquad \text{Eq.8}$$

where P_{hem} = probability for haemorrhage (%). The best fit to empirical data

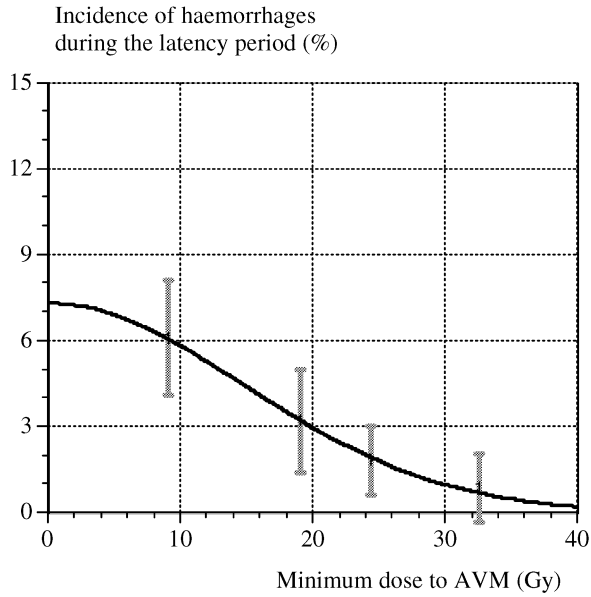

Fig. 10. The relation between D_{min} and the incidence of post treatment haemorrhage during the first two years after GKRS. The error bars represent the 90% C.I.

was found for a=7.29 and b=0.00226, (R^2=1.00) (Fig. 10).
For the 791 AVMs treated with a D_{ave}>30 Gy and the 802 AVM treated with D_{ave}≤30Gy, the observed and predicted number of haemorrhages were equal (table 4), proving that the findings in table 3 were correct, and that Dave had no independent impact on P_{hem} (Eq.8).

Was the relation previously found between AVM volume and incidence of post treatment haemorrhage related to D_{min} only? If so, the quotient between the predicted and the observed number of haemorrhages, Q, should be AVM volume independent. The relation between Q and AVM volume (v) was:

$$Q = 1.28 - 0.204 * \ln(v); v \geq 1 \qquad \text{Eq.9}$$

(R^2=0.99), as illustrated in figure 11. The relative risk of AVM haemorrhage was overestimated (Q > 1) for smaller and underestimated (Q < 1) for larger AVMs. This dose independent relation between the AVM volume and the risk of haemorrhage is in accordance with data from a previously published large study (83). Eq.9 can compensate for the AVM size dependence.

Finally, to take the age dependence of the risk for AVM haemorrhage into consideration, the relation between age and risk for AVM haemorrhage in a previously published study was used (83). An age dependent relative risk factor, f(age), was calculated (Fig.12).

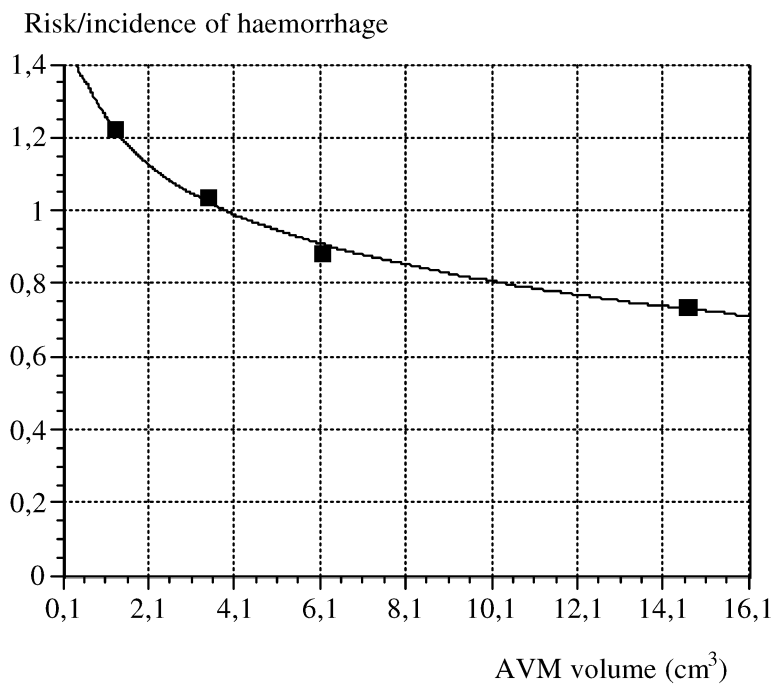

Fig. 11. Graph illustrating the relation between the quotient predicted/observed haemorrhages and AVM volume.

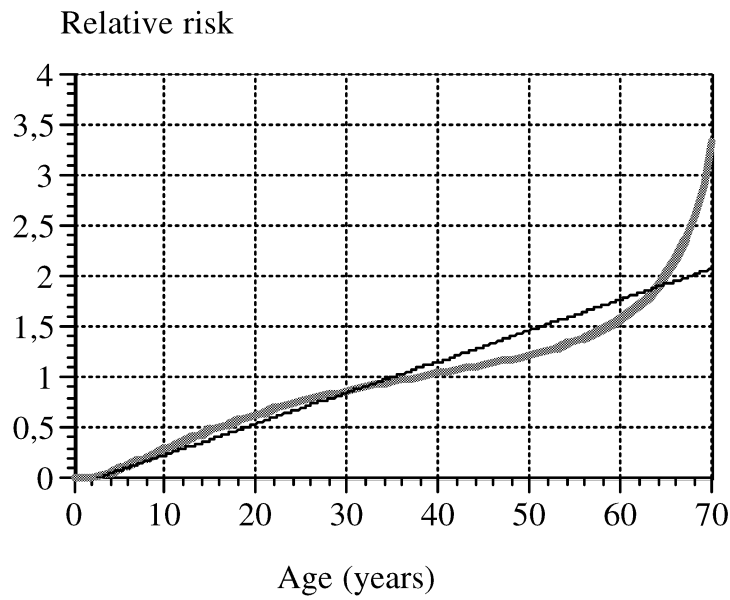

Fig. 12. The age dependent relative risk of AVM rupture in this material. The exact algorithm of the curve can be found in ref. (83). The graph itself can be used for a reasonably accurate value of f (age), to be used in Eq.10. The linear approximation was used in the outcome predictions in paper (VII).

In conclusion, the risk of post treatment haemorrhage could be calculated from the formula:

$$P_{hem} = \frac{7.29 * \exp\left(-0.00226 (D_{\min})^2\right) * f(age)}{1.28 - 0.204 * \ln(v)} \qquad v \geq 1 ml \qquad \text{Eq.10}$$

where f (age) can be extracted from figure 12.The relationship between D_{min}, v and P_{hem} expressed in Eq.10, for f (age)=1 (patient age approximately 38 years), is illustrated in fig. 13. Eq.10 accurately predicted P_{hem} for all subgroups, within the 90% C.I. (Table 4).

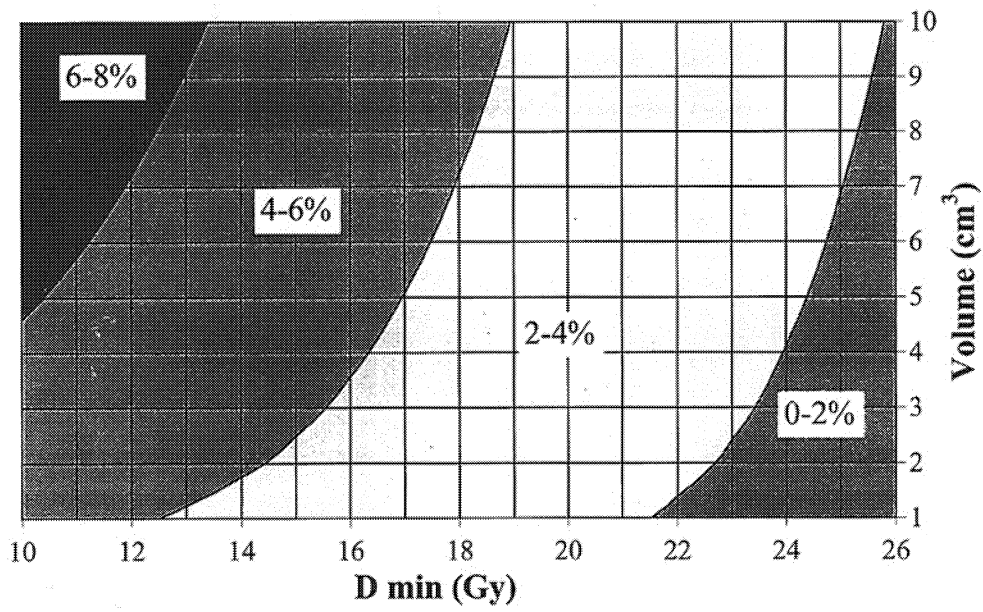

Fig. 13. The relation between D_{min}, AVM volume and the probability of haemorrhage in the latency period for a patient 38 years of age, where f (age) = 1. To calculate the risk of haemorrhage for patients of other ages, the risk numbers in the graph should be multiplied with f (age).

	N	Predicted	Observed	Diff.	90%C.I.	Signific.
Age ≤30 years	781	20	19	-1	12–26	N.S.
Age >30 years	812	35	36	1	26–45	N.S.
AVM vol ≤2.5 ml	890	17	17	0	11–24	N.S.
AVM vol >2.5 ml	703	38	38	0	28–48	N.S.
Central	684	21	24	3	16–32	N.S.
Cerebellar	122	3	4	1	1–7	N.S.
Peripheral	787	31	27	-4	19–35	N.S.
Female	761	26	25	-1	17–33	N.S.
Male	832	29	30	1	21–39	N.S.
D_{max} ≤40Gy	921	34	32	-2	23–41	N.S.
D_{max} >40Gy	672	21	23	2	15–31	N.S.
D_{min} ≤20Gy	919	46	45	-1	34–56	N.S.
D_{min} >20Gy	674	9	10	1	5–16	N.S.
D_{ave} ≤30Gy	802	37	37	0	27–47	N.S.
D_{ave} >30Gy	791	18	18	0	11–25	N.S.
Previous haemo.	1175	36	38	2	28–48	N.S.
P. haemo within 1 year	621	16	16	0	9–22	N.S.
Previous irradiation	134	5	5	0	1–9	N.S.
Previous embolisation	254	12	8	-4	3–13	N.S.

Table 4. For each of the continuous parameters used, the material was divided in two groups, one with a lower and one with a higher value than the median value. P_{hem} was calculated from Eq. 10 for each patient, the probabilities were added and compared to the number of observed haemorrhages in each group. A difference between the predicted and the observed number was considered to be significant if the predicted number of haemorrhages was outside the 90% confidence interval of the observed number of obliterations. As shown, the model predicted the number of haemorrhages accurately for all analysed groups and is thus valid for this material

Discussion

The results from this study are representative only if the vast majority of haemorrhages were reported. In Eq. 10, if we set D_{min}=0, the annual risk for haemorrhage will be 3.6%, which is of the same magnitude as in most studies (14, 19, 83, 137). This is not conclusive evidence but suggests that there was no significant underreporting of haemorrhages.

AVM location had no impact on the risk of haemorrhage, which is surprising, considering the accumulating evidence that AVM with central drainage have a relatively higher risk of bleeding (78, 83, 122). However, the small number of patients with haemorrhage might explain this.

There was a trend (8 (C.I. 3–13) observed, 12 predicted) that previously embolised AVM had a lower risk of haemorrhage. This is in accordance with the findings of Meisel (129) that partial embolisation reduces the risk of haemorrhage.

The model predicted that among the 621 patients who were treated within one year after the first AVM haemorrhage, 16 haemorrhages would occur. If the risk were doubled, 25 haemorrhages would be expected within the period beginning with the GKRS and ending one year after the haemorrhage. The observed number of haemorrhages was 16, which does not support the assumption of a higher risk for AVM rupture during the first year after a haemorrhage.

In view of the number of haemorrhages after the latency period (44), no long-term protection from haemorrhage seems probable for patients with still patent AVM after GKRS.

Conclusions

The risk for haemorrhage in the two years latency period following GKRS is predictable and depends on D_{min}, patient age and AVM volume. There was a trend that previous embolisation decreased the risk. There was no evidence of long term protection from haemorrhage from non-obliterated AVMs.

The complete outcome model

There are different applications for the model.

In the GKRS treatment situation the models are used interactively to predict outcome and adjust treatment parameters. We have at the Karolinska hospital implemented the models onto our dose-planning software and use it routinely to optimise the treatment as shown in figure 14. A proper dose planning is necessary to enable a risk prediction with this degree of accuracy.

Conforming the AVM

Doselevel	50 percent	55.0 - 45.0 percent
Volume:	4.9 cm^3	4.0 - 5.9 cm^3
Mean dose:	34.0 Gy	35.7 - 32.2 Gy
Integraldose:	166.0 mJ	142.6 - 189.6 mJ
Minimum dose:	25.0 Gy	

Location of AVM:	Unspecified
Risk of compl.	7.2 percent (3.6 - 10.9 percent, 95% c.i.)
Risk of hemorrhage.	1.7 percent
Probab. of oblit.	75 percent

Mindose (Gy)	Maxdose (Gy)	P(oblit) (%)	P(compl) (%)	P(bleed) (%)	P(tot) (%)
0.0	0.0	0	0	7	7
6.0	12.0	24	1	7	7
8.0	16.0	35	1	6	7
10.0	20.0	43	2	6	8
12.0	24.0	49	2	5	8
14.0	28.0	55	3	5	8
16.0	32.0	59	4	4	8
18.0	36.0	63	5	3	8
20.0	40.0	67	5	3	8
22.0	44.0	71	6	2	8
24.0	48.0	74	7	2	9
26.0	52.0	77	8	2	9
28.0	56.0	79	8	1	10
30.0	60.0	82	9	1	10

Fig. 14. Printout from the dose-planning computer, giving P_{obl}, P_{compl} and P_{hem} for a 30-year old patient that has not previously been irradiated. Pcompl. is lower than predicted from Eq. 7. This is partly due to the dose plan in this particular case, partly to the fact that because of improved dose planning in general D_{ave20} has decreased over time, for the same v and D_{min} (Wilcoxon's test p<0,0001).

However, for risk assessment in connection to a diagnostic angiography or an embolisation, the model should preferably be uncomplicated. In paper VII we therefore decided not to pay attention to the parameters location and previous haemorrhage, and in addition substitute a linear approximation for f (age):

$$f(age)=0.031x-0.078 \qquad (R^2=0.87) \qquad \text{Eq.11}$$

In the clinical situation the model may thus be used is such a way that the AVM volume is first measured from angiography, using the intersecting cone model (cf.)(53) (VI). By choosing an appropriate D_{min} the obliteration rate may be predicted from Eq.1 or read from the graph (Fig. 5). The risk for radiation induced complications can be predicted from Eq.7 or from the graph (Fig. 9). Finally, the risk for haemorrhage in the two-year latency period may be found in Eq. 10 or the graph (Fig. 13), with adjustment for f (age). The same information can be extracted from figure 15.

Thus the predicted outcome of GKRS may be calculated and compared to the natural course or to the predicted or actual outcome of other treatments.

As can be seen from figure 5, the confidence interval in the obliteration model is narrow. For the models predicting the risk for radiation-induced complications or post treatment haemorrhage the situation is different. The 95% confidence intervals in these two models are larger and the predictions have a higher degree of uncertainty.

It must, however, be emphasised that for AVM volumes of more than 10 ml the GKRS outcome models have not been validated against clinical data. In addition, the complication model is not applicable to volumes larger than the 20ml volume containing the AVM used in the calculation of D_{ave20} and P_{compl}.

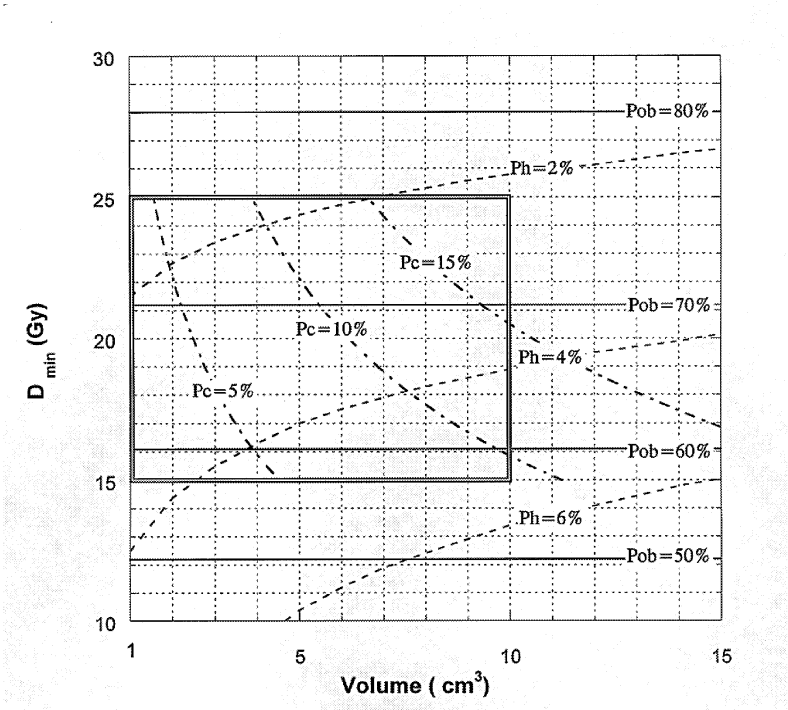

Fig. 15. The relation between AVM volume, D_{min}, P_{compl} and P_{hem}. For a given volume and D_{min} and thus predicted obliteration rate, P_{compl} and P_{hem} can be read directly from the graph.

Volume measurement

Previous investigations

AVM volume, location and patient history are parameters of importance in the management of AVM patients (II, III, VI, VII) (19, 50, 61, 75, 83, 99, 138, 173, 174). Size or volume has been quantified in most studies, but the measurements have generally been inexact, except when radiosurgery was done. Such data are of limited or no value when comparing patient outcome in different centres or between therapeutic alternatives. In an effort to find a solution to this problem, Lui (113) in 1993 utilised simultaneous biplane angiography, presupposing that the object was spherical. The first to propose the use of a stereotactic box for precise measurement of AVM size during diagnostic angiography was Elisevich in 1994 (32, 33). Another approach was that of Foroni (41, 42), who described the three-dimensional reconstruction of the shape and volume of an AVM from biplane stereotaxic angiography as part of radiosurgical treatment planning.

Ericson et al. suggested in 1996 pre-procedure dose planning and outcome prediction of GKRS as a means to improve patient management (IV). In this context reproducibility of measurements and correlation to the prescription

volume in GKRS is important, a consideration which initiated the use of a stereotactic box for precise measurement. The original approach was based on dose planning, which is, however, not available in many centres for endovascular or surgical treatment of AVM. Therefore a technique for uncomplicated volume measurement from angiography and GKRS outcome assessment was developed, named the intersecting cone model (ICM) (VI).

Volume measurement software

Images from angiographic examinations in stereotactic conditions were transferred to a workstation (Advantage windows, General Electric Medical Systems, Buc, France) where the fiducials of the stereotactic box were manually detected and the object to be measured was delineated in posteroanterior (PA) and lateral projection as a region of interest (ROI). The volume of interest (VOI) was limited by the intersection of the X-ray cones defined by each ROI, and was computed voxel by voxel (Fig. 21). Several volumes could be determined and computed separately or added. The VOI was neither modified to fit any fixed shape nor edited in any other way.

Validation of the ICM

Phantoms of different sizes were positioned inside the stereotactic box and a biplane X-ray exposure was made. The object was outlined and its volume was measured with the ICM software. Dose planning and measurement of the volume inside the prescription isodose line was performed with the LGP (Leksell GammaPlan®, Elekta, Sweden) from the same images.

In addition the angiographic examinations of 63 consecutive patients with AVM scheduled for GKRS were used for the evaluation of irregular objects. All images were corrected for geometric distortion (V). The delineation and dose plan used in the original treatment was used. Some of the patients had complicated targets with several subvolumes, both overlapping and separate (Fig. 16). Different shapes were present. With the exception of three patients, all volumes were below 10 cm^3.

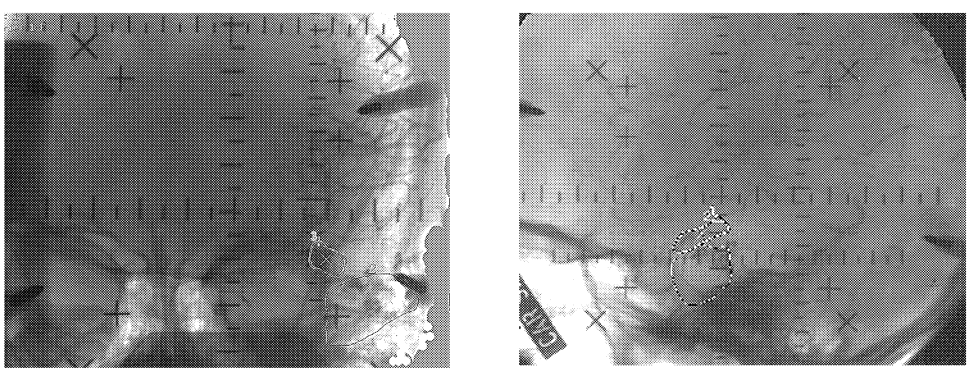

Fig. 16a and b. Unsubtracted PA and lateral images of a temporal AVM, previously embolised, with supply from the internal and external carotid arteries to separate compartments. Volume (ICM)=5.4 cm^3, volume (GammaPlan®)= 5.4 cm^3, P_{obl} = 75 %, P_{compl} = 9,9 % (the patient had not bled).

Correlation between volumes measured with LGP and ICM

The phantom studies disclosed excellent correlation between the two methods.

In the patient study dose plans were remade for 15 patients where prescription volumes initially correlated the least to ICM, i.e. where the quotient LGP/ICM was initially found to be <0,5 or >2. In all 15 cases redefining the dose plan and consequently the prescription volume lessened the disparity between the two methods. This could be explained either by the fact that MRI had been taken into account in the original dose planning and the delineation modified accordingly, or the physician performing the treatment was inexperienced.

For the 63 AVM volumes (after the dose plans had been redefined) data were fitted to a linear regression (Fig. 17):

$$LGP = 0.41 + 0.97 * ICM;\ (R^2 = 0.85,\ SD = 1.2) \qquad \text{Eq. 12}$$

In the 63 AVM patients the mean quotient LGP/ICM was 1.2 with a decrease with increasing nidus volume (Fig. 18). If only volumes in the interval 3–8 cm^3 were included, the quotient was 1.1. This was probably due to limitations in the dose planning, as small irregular targets will include some normal tissue.

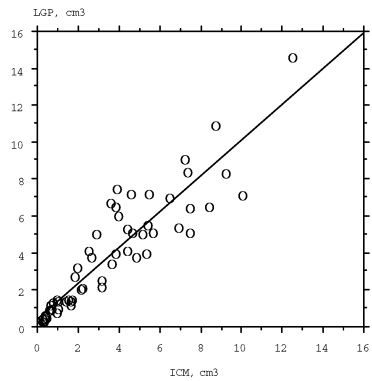

Fig. 17. Regression plot for volume measured with ICM versus the volumes inside the prescription isodose line from the LGP.

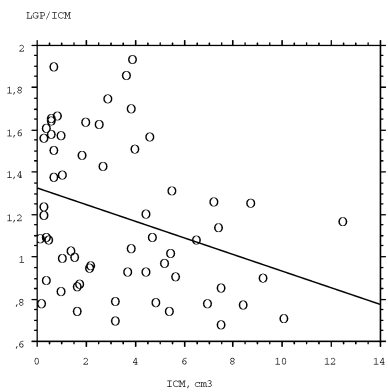

Fig. 18. Regression plot for quotient LGP/ICM versus ICM.

Discussion

The AVM "nidus", without feeders or veins, is measured in currently used predictive models and grading systems (Fig. 25)(81, 138, 173). The Spetzler-Martin AVM classification (174) stratifies the malformation according to its largest diameter, i.e. <3, 3–6 and >6 cm. The middle group may for example contain lesions of a size between 1x1x3 cm up to 6x6x6 cm, corresponding to volumes from 0.5 cm^3 to 113 cm^3. In a radiosurgical outcome model, or for volume comparison in general, a more exact measurement is necessary (II–IV, VI and VII) (83). In GKRS the volume of the AVM has been defined as being the volume within the prescription isodose line, not the same as the "true" nidus, but a reasonable approximation (81).

Pasqualin et al. in a study of 248 patients subjected to microsurgical removal of AVM found that AVM volume >20ml was associated with a significant increase in perioperative problems (138). Patients with AVM volumes >50 ml had a very high rate of perioperative problems and developed new deficits. The difference in diameter is exemplified in figure 19. It was noted that volume was the single most important parameter for the outcome of AVM surgery. A method to measure AVM volume ($r_1 * r_2 * r_3 * 0.52$) was proposed. However, this method assumes that the AVM has an ellipsoid shape, which is sometimes far from true. Nevertheless, in our material, correlation between the method proposed by Pasqualin et al. and the volume within the best fit isodose line was acceptable for volumes ≤6ml, but less good for larger AVM (Fig. 20) (II). In the original paper (138) there was no comparison to volumes from the dose planning software.

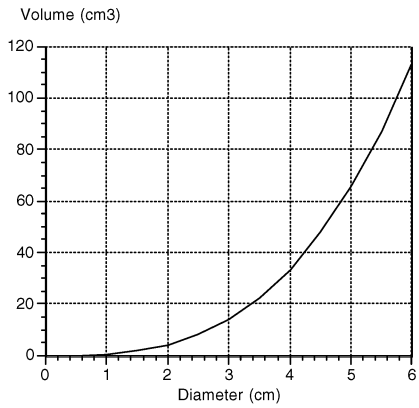

Fig. 19. Diameter versus volume for a sphere. An increase in volume from 20 ml to 50 ml entails an increase in diameter from 3.4 cm to 4.5 cm. A diameter measurement error of ± 10% causes a volume difference of close to 100%, with concordant outcome differences in GKRS.

Virtually all patients with cerebral AVM undergo diagnostic or therapeutic angiography and thus the procedure with the stereotactic box adds no extra risk or cost. In addition, the outcome models of the GK were based on treatments where in a majority of cases the delineation was made on angiographic images alone (81). In the immediate post treatment situation angiography is often more informative than MRI or CT, where oedema, embolisation material and

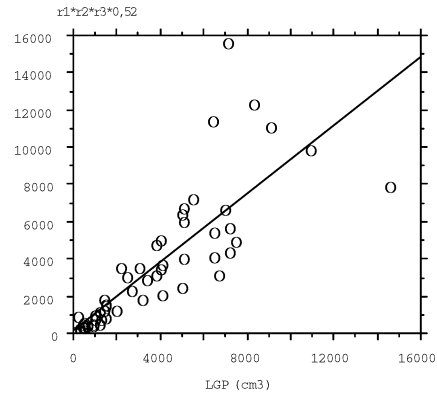

Fig. 20. Comparison between volume measurement by multiplying the product of the three radii of the AVM with 0.52 (138) to volume data from the dose planning system (GammaPlan®). For large irregular volumes the difference between methods is considerable (R^2=0.67).

blood products may cause interpretation problems. It may, however, take as long as 3 months following an embolisation until an AVM is angiographically stable (60) and particularly in large AVM (>10ml), MRI and CT have spatial advantages because of the tomographic capabilities (9, 55).

The AVM rarely has the shape of two intersecting cones. Its volume is therefore in most cases overestimated by the ICM, the amount depending on the shape and orientation of the AVM. In our material of 63 consecutive cases, extreme shapes with oblique orientation were not encountered, however.

Patient examination

During the biplane diagnostic angiography or in connection with an endovascular treatment a localisation box for stereotaxy (Elekta AB, Sweden) was placed over the head of the patient (Fig. 21) (IV, VI, VII). The usual routines for stereotactic angiography were followed (53), with the exception of the lack of fixation of the box in relation to the head of the patient (IV). Images were transferred to a workstation and the AVM volume measured with the ICM as previously discussed.

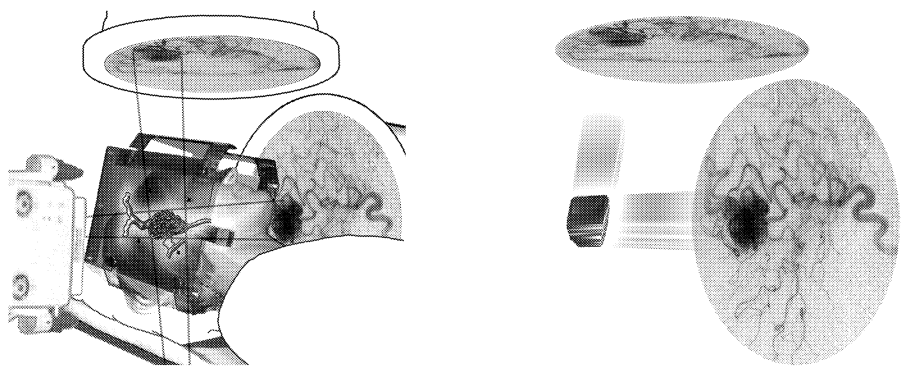

Fig. 21a and b. The artist's impression of the ICM. The volume defined by the intersection of the two X-ray cones is measured.

One limitation is that spatial information from the images can only be added if the head of the patient has not moved relative to the box in between series. When monoplane equipment is used, movement of the head in between AP and lateral projection will therefore render the examination useless for precise volume calculation. Delineations on images from different series can be graphically added if the patient's head in the stereotactic box was in exactly the same position relative to the X-ray equipment during each acquisition (usually, the couch is moved back to its original position).

The exact reposition of the box relative to the X-ray equipment in not necessary for merging or reprojecting volumes once these have been created. The dose planning system can also handle multiple volumes. The geometry of the equipment does not have to be fixed, nor does the X-ray beam have to be perpendicular to the sides of the box (Fig.21).

Conclusions

AVM volume measurement from angiography may be done with the ICM. It is a reasonable approximation of the volume inside the prescription isodose line in Gamma Knife radiosurgery and can be used as a standard method for measurement of AVM volumes less than 10 cm^3 from angiography. In this context GKRS outcome models may be applied, but with restrictions as to the precision.

Geometric distortion

Introduction

In a stereotactic system geometric distortion is important when it affects the relationship between the reference points and the object that is measured and thus impairs accuracy (V). It may affect any part of the DSA imaging chain, but is in practise limited to the image intensifier (I/I) (159). Two main components are discernible, "pin-cushion" distortion and influences of external magnetic fields. There are two interdependent effects: spatial displacement and variations in magnification.

The curvature of the I/I photocathode, or input phosfor, is for electro-optical reasons close to spherical (159). Conversely, to be compatible with the flat input surface of the video device, the output phosfor of the I/I is generally flat. The difference in curvature of the surfaces of the I/I is the cause of the "pin-cushion" distortion (Fig. 22), which becomes less significant the larger the radius of the I/I input phosfor (159) or the smaller the field of view. It is constant and the I/I can be designed to avoid it (159), but this is rarely done. An algorithm that compensates for the curvature has been formulated (16, 159).

External magnetic fields, global and local, (16, 159) are the cause of the S-distortion and other non-constant distortions, which can be avoided or compensated for by careful passive and active shielding (159). The non-constant distortion varies with the position of the I/I in the room and the trajectory taken to get to that position (V).

In our equipment additional shielding was impractical, and therefore the composite distortion is corrected for with a classical calibration-correction scheme for each angiographic series (V). Other investigators have found that in their equipment the non-constant fraction of the distortion was insignificant and have employed a single calibration, regardless of I/I position (17, 143).

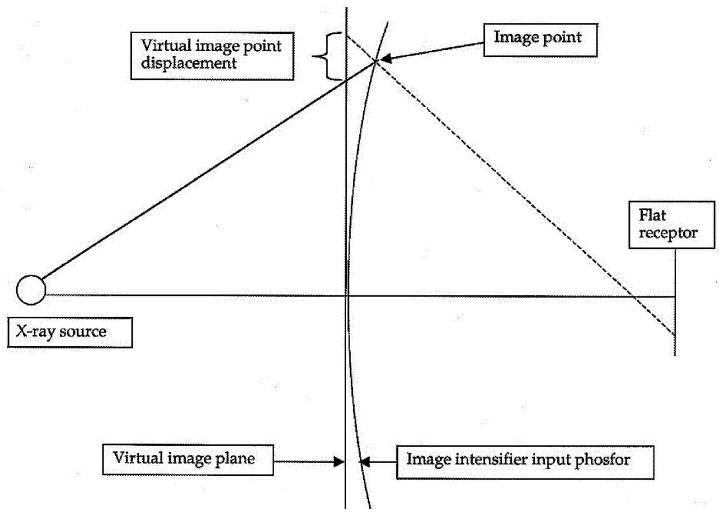

Fig. 22. Schematic view of the pincushion distortion. Its origin is the difference in curvature between the I/I input phosfor screen and the surface of the receptor.

Correction of the distortion

The calibration-correction scheme works as follows. A grid with known properties is inserted in front of the I/I after each patient series. The centre of the grid and each intersection of the lines are identified by the software. The image of the grid is then compared to the image of an ideal grid stored in a separate workstation. The displacement of each line intersection is calculated, and the position of each pixel in between is determined by bilinear interpolation. The resulting "distortion field" is used to move each pixel back into its original position (Fig. 23). The images from the patient series are then corrected with the same distortion field.

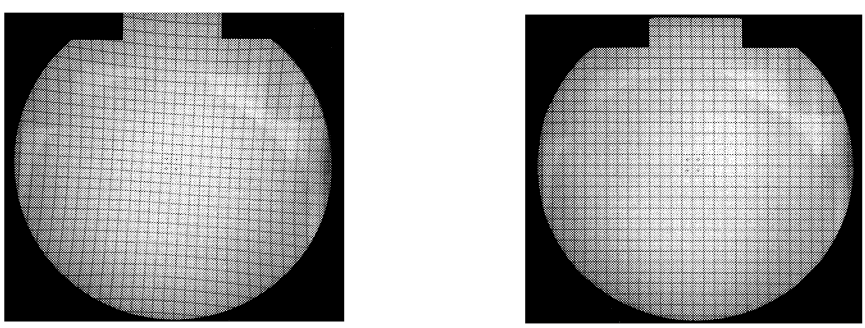

Fig 23a and b. Grid image before and after correction for the geometric distortion. Note uneven square sizes in the uncorrected image.

The need for distortion correction

The targeting precision necessary for successful treatment of an AVM with the GK is unknown. The total geometric uncertainty of the GK treatment system, including MRI examination, is ±1mm (57, 136). A displacement of ±0.5 mm relative to the stereotactic frame was therefore assumed to have no impact on the outcome of GKRS, and was chosen as the limit to the distortion. With our angiographic equipment there was a maximum displacement of the target relative to the box of more than 2mm in the original images (Fig.24a) (V). Therefore correction of the distortion was a prerequisite for high precision stereotactic angiography, regardless of angle of incidence. After correction the geometric distortion could not be measured with the method used.

Does geometric distortion affect volume measurement?

The limited displacement of the object has little impact on volume figures. Due to the positions of the fiducials of the stereotactic box and the curvature of the I/I, there is negative magnification in the centre of the I/I and positive in the periphery. With the present equipment (V) a sphere with a real volume of 5.6ml (Ø=22mm) measured 5.2ml (-7%) in the centre of the image, whereas in the periphery it was magnified to 6.6ml (+15%) (Fig. 24b).

In the investigation in paper VII we did for logistic reasons not apply distortion correction (V). This probably had some impact on the measurements of absolute AVM volumes. It should, however, have little impact on the relative volume reduction.

In the near future flat panel X-ray receptors will most probably supersede the I/I for angiography (160) (Pers. com. Catherine Picard, GEMS), and make distortion correction redundant.

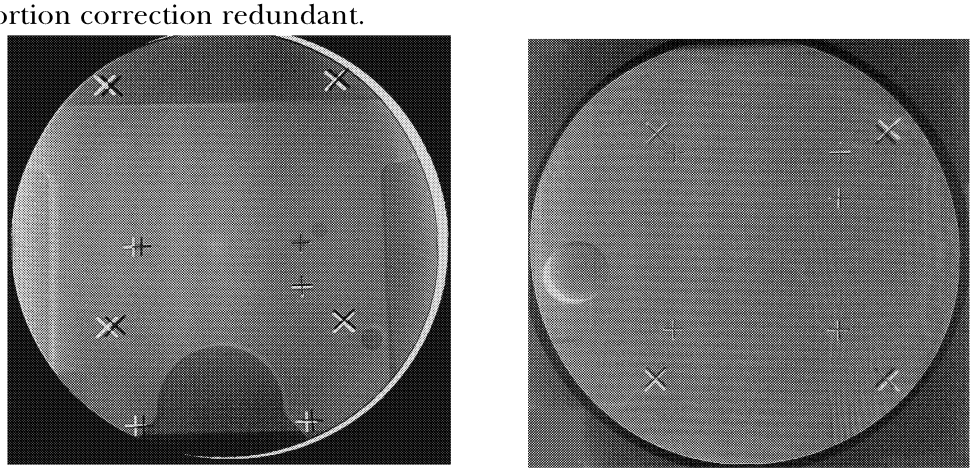

Fig. 24 a. Subtraction between distortion corrected and non-corrected images acquired with a 13 degree caudal X-ray tube incidence. Note displacement of lead fiducials for stereotactic localisation. The horizontal lines are artefacts induced by the raster of the laser film.

Fig. 24 b. Subtraction between distortion corrected and non-corrected images acquired with orthogonal X-rays. Note deformation of the shape of the 5.2mm sphere. The horizontal lines are artefacts induced by raster of the laser film.

Conclusions

I/I distortion may affect the precision in stereotactic angiography with DSA. If considerable it should be corrected for. This can effectively be done with a classical calibration-correction method. The impact on volume measurement is limited in comparison to other sources of errors.

Delineation of the AVM

The nidus

In studies I–IV, VI and VII, AVM delineation was performed according to established routines based on more than 1500 AVM treatments and 20 years of experience (53). The few exceptions are the very early treatments before the nidus concept was thoroughly established. The nidus is identified on images from the arterial phase, just as the draining vein begins to fill (Fig. 25). This can be fairly straightforward on a small compact nidus and very difficult in a previously embolised patient, where different parts of the shunting zone may fill in separate phases. In addition the radiopaque NBCA-Lipiodol®-Mixture can obscure the nidus. Opinions as to what is the nidus proper can also differ considerably (Table 4, patient 9), particularly if it has been embolised. The importance of choosing an image from the proper filling phase is shown in figure 25.

The efficacy of the delineation and the dose planning can only be assessed by the final outcome. The material from Karolinska hospital has an obliteration rate of 75–80% for patients treated with a D_{min} of 25Gy, proving that the nidus concept and the delineation had been correct in most cases. Interestingly, previously embolised or operated AVM have the same obliteration rate, complication rate and risk for haemorrage in the two years latency period as those previously untreated, indicating that the delineation and dose planning is of equal value in these patients.

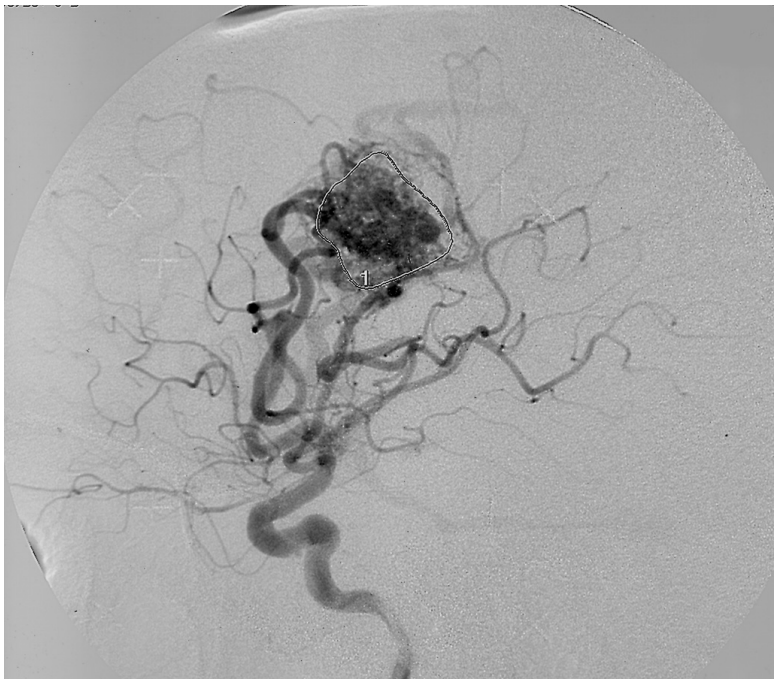

Fig. 25. a) ICA injection, lateral view. "Correct" delineation of the nidus of a frontal cortico-ventricular AVM, in the arterial phase just as vein begin to fill with contrast medium.

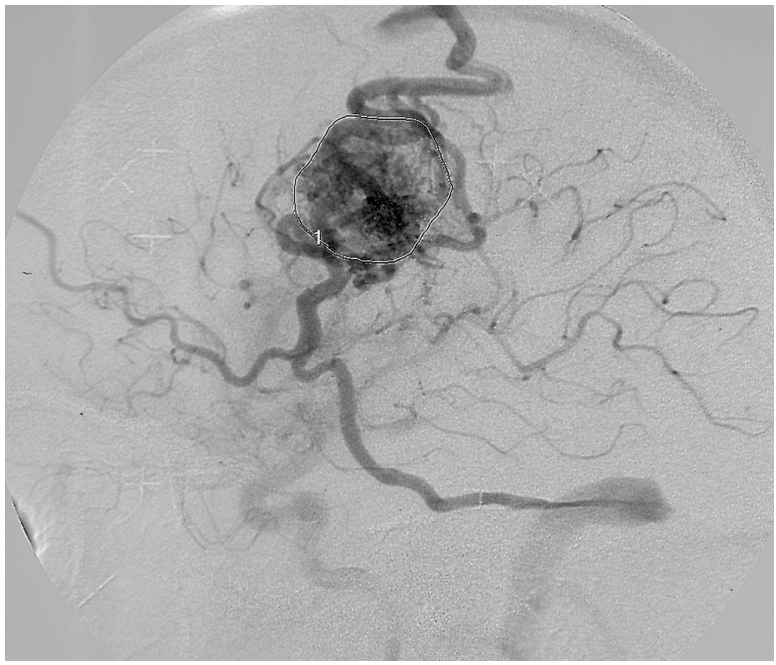

Fig. 25. b) ICA injection, lateral view. Delineation of the nidus in early venous phase of AVM filling cycle. There is an intranidal aneurysm and stenosis of the pial-dural junction of the draining vein.

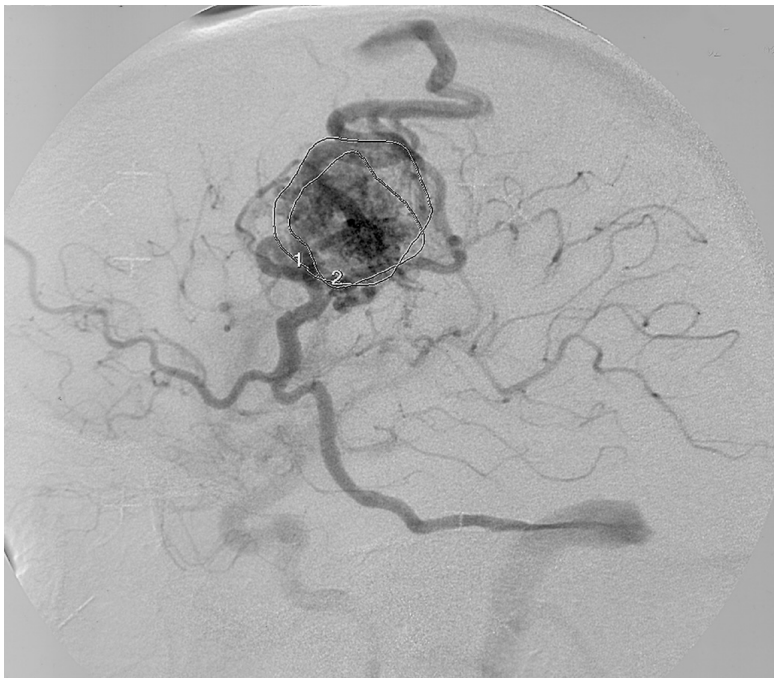

Fig. 25. c) ICA injection, lateral view. Both delineations are superimposed.

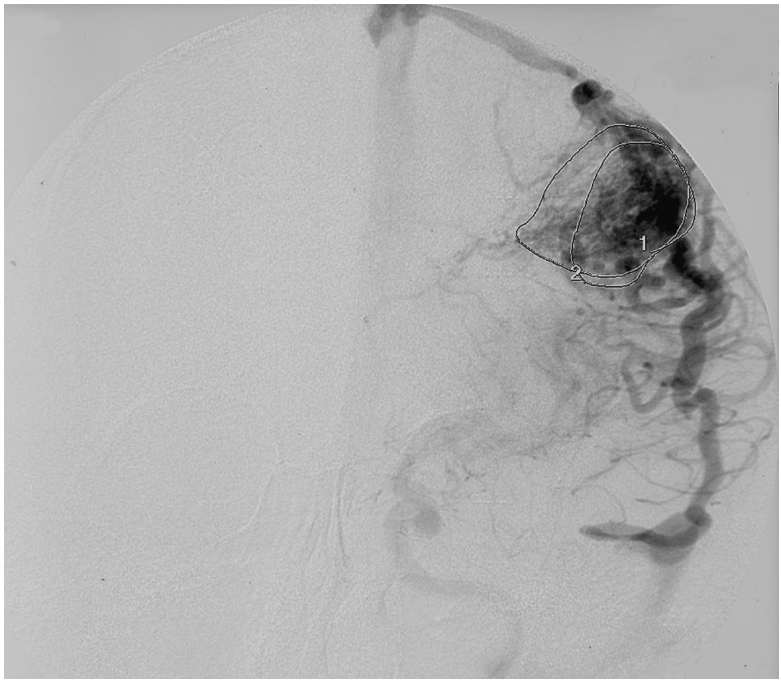

Fig. 25. d) ICA injection, PA view. Both delineations are superimposed. The volume of a) was 8.2 cm³ and of b) was 16.2 cm³. The use of delineation b) instead of a) implies at least a 100% increase in the risk of a complication at the same obliteration rate (Eq. 7).

Intra and interobserver variability

The interobserver variation in delineation was determined in 10 randomly chosen stereotactic angiographies with AVM >1 ml in which three independent examiners delineated the AVM nidus (Table 5). The intraclass correlation coefficient (r), which takes into consideration both the correlation and the systematic error (30), was 0.74, showing a reasonable correlation. Nevertheless, opinions may differ considerably between observers, as seen in patient 9, table 5. Intraobserver variation, another possible source of error, was not systematically investigated.

Pat nr	Exam 1	Exam 2	Exam 3	Comment
1	2.5	2.3	1.6	
2	2.7	1.6	1.1	2 volumes, ICA+vert
3	4.8	3.7	4.7	2 volumes, ICA+vert
4	1.7	1.9	2.6	
5	7.8	6.6	7.8	
6	7.1	4.3	8.8	2 volumes, embolised
7	3.3	3.3	4.4	Embolised
8	2.3	2.5	2.4	Arteriovenous -fistula
9	1.3	4.0	4.5	Embolised by examiner 1
10	3.3	2.3	3.1	Embolised

Table 5. The interobserver variability in the delineation of the AVM nidus. The numbers refer to AVM volumes measured with the ICM.

Stability over time

It is well known that AVM may over time change spontaneously in size (73, 191). A more acute situation is after an embolisation with concurrent reperfusion, sprouting and non-sprouting angiogenesis, collateral development, progressive thrombosis and haemodynamic changes (Fig. 26). Therefore the result cannot be considered stable until after 3 months (60). In the study upon the embolised patients, several experienced progressive thrombosis with obliteration after the termination of the study period (Fig. 26) (VII).

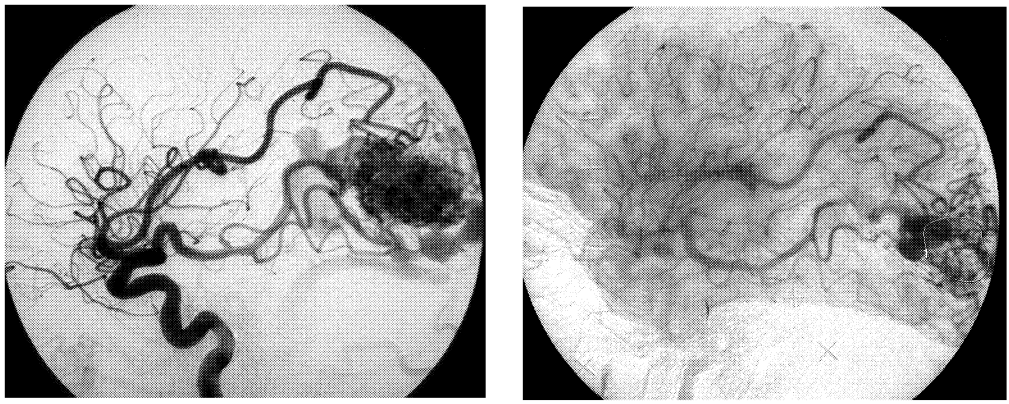

Fig. 26a) Occipital AVM before embolisation. There was also a prominent dural supply. The volume (ICM) was 15.5 cc.

Fig. 26 b) Immediately after the last procedure. The dural supply had been embolised. Because of the slow flow through the nidus, delineation was done on images with some venous filling. The volume was 5.8ml and the patient was accepted for GK radiosurgery. At the time of the intended GK treatment three months later, the AVM had obliterated.

The role of MRI and MRA

In the GKRS treatment situation MRI and MRA are used to better assess the shape of the nidus (60). However, angiography still remains the "gold standard" particularly for patients previously operated or embolised (60). The role of MRI in GKRS at present is to allow modification of the treatment volume, particularly to exclude vulnerable tissue, such as the optic nerves. As exemplified in paper VI a volume may be built from angiography with the ICM, later to be edited with the aid of MRI (Fig. 27). In large AVM the prescription volume may be edited to minimise the volume actually irradiated (56). It is, however, very difficult to evaluate the impact on final outcome from of this modification of routine.

MRI and MRA are not very useful in assessing the remainder of a newly embolised or operated AVM and these techniques were not part of this study.

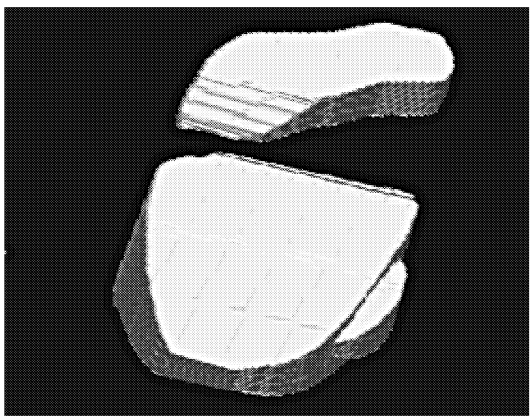

Fig. 27. 3D-reconstruction of AVM from the ICM. Same patient as in figure 16. Two separate AVM volumes remain after the embolisation. View from left craniolateral.

Clinical application of the methods and models

Introduction

The aim of this study was a prospective comparison of two major management strategies for AVM. On the one hand Gamma Knife radiosurgery, with the outcome predicted by the outcome models. On the other hand combined treatment, i.e. embolisation followed by radiosurgery, where outcome data for the embolisation were taken from actual treatments and data for radiosurgery were predicted from the outcome models.

Material and methods

PATIENTS

138 AVMs in 136 patients were subject to treatment attempt by embolisation between January 1, 1997 and December 31, 1999 at l'hôpital de Bicêtre, Paris, France. Inclusion criteria were intent to treat for the first time an AVM by embolisation with NBCA and age ≥10 years at the time of the treatment. Forty-nine patients whose treatment had commenced before January 1, 1997 or who were < 10 years old were excluded, leaving 88 AVMs in 87 patients amenable for and included in the study. Mean age at the time of the first embolisation attempt was 36 years for 37 patients who presented with haemorrhage and 35 years for 51 who had other symptoms (Fig. 28). There were 48 males and 40 females. The distribution according to the Spetzler-Martin grading is shown in figure 29. Localisation was central in 20 patients, peripheral in 60 and cerebellar in 8 (II). All patients were managed by the same team.

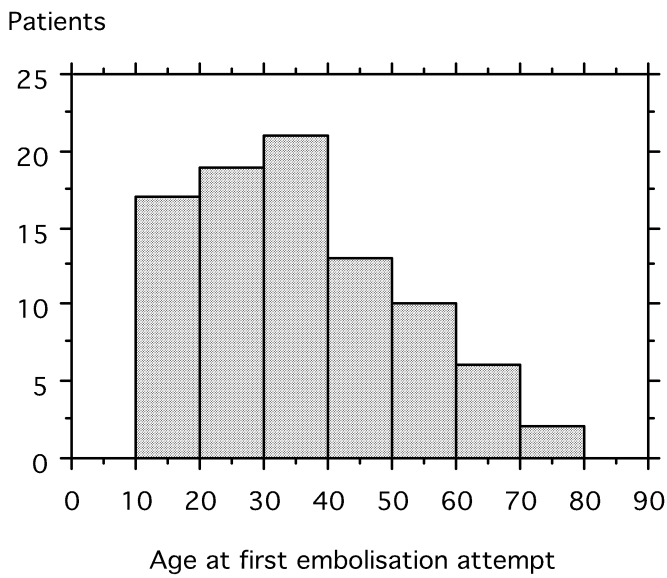

Fig. 28. Age distribution for the 88 patients at the time of the first embolisation attempt.

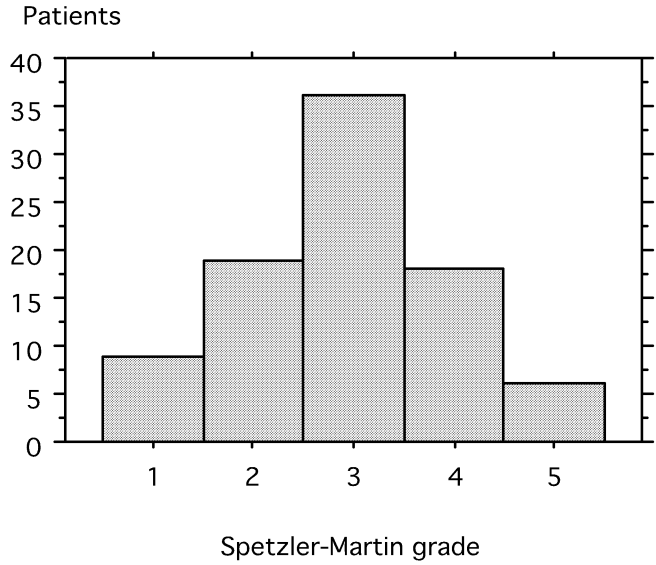

Fig. 29. Distribution according to the Spetzler-Martin grading system for the 88 patients.

VOLUME MEASUREMENTS

The angiogram preceding the embolisation was performed with a stereotactic box in 60 patients and in 18 patients when the endovascular treatment had been completed, while the remaining examinations were performed without a box (IV). To enable AVM volume measurement for the latter cases the fiducials of a stereotactic box were afterwards superimposed onto the angiographic images.

In all patients the AVM nidus was delineated from angiography by one neuroradiologist (MS) and nidus volume was measured with the ICM (VI) before the first embolisation procedure and at the end of the last procedure within the study period.

MANAGEMENT RISK

The management risk following both embolisation and radiosurgery has two components: the risk of complications and the risk of haemorrhage until occlusion of the AVM.

Transient complications from embolisation have no analogue in radiosurgery and were excluded from the analysis. All "permanent" complications were accounted for (see pp. 36-37).

The perioperative risk period was defined as beginning the day of the endovascular procedure and ending 30 days later, regardless of whether the AVM had been excluded from the circulation or not. Any event within this period was assumed to be related to the procedure.

The time at risk begun at the end of the perioperative risk period and conti-

nued until AVM obliteration or until no further embolisation was possible. For patients exposed only to the natural course of the disease and not to any management, time at risk was zero. Waiting time for control angiography or decision upon such is included in time at risk.

The probability of haemorrhage during time at risk was calculated by using the relation between patient age and risk for haemorrhage from a previous paper (83). The linear approximation (Fig.12):

R_{hem}= 0.17*a (R^2=0.92)

where R_{hem} is the annual risk of haemorrhage and a is the age of the patient, was substituted for the iterative curve in the original publication. The risk was also assessed from demographic data originating from the same population group as on which the embolisations were performed (128).

For GKRS the definitions were inappropriate, since the risk of an event was included in the risk of haemorrhage in the two-year latency period after the treatment. The risk of an event outside of these time limits was considered to be related to the disease itself and not to the treatment.

At discharge, every patient was clinically examined of the physician that had performed the embolisation. Follow up information was available on all patients, either collected from the patient himself or from the referring doctor.

Haemorrhage was diagnosed with CT when clinical symptoms had prompted an investigation, but CT was not routinely used in the follow up.

COMPARISON OF THE OUTCOME

The material of 80 patients was split into two groups, AVM ≤10ml and AVM >10ml.

Two alternative strategies were analysed.

The first alternative (group A) was that all patients were subjected to GKRS as the only treatment. For each patient, obliteration rate, complication rate and risk of haemorrhage were predicted using volume data from before the first embolisation (Table 6).

The prerequisites of the second alternative (group B) were that the same patients were first treated with embolisation (with the outcome observed in the present study) and at the end of time at risk with supplementary radiosurgery.

The minimum doses to the periphery of the AVM was chosen to correspond to values reasonably close to those in clinical routine (Table 6). The predicted number of complications and haemorrhages of group A was compared to that of group B, *for the same number of obliterations.*

The analysis was restricted to the hypothetical outcome of the two management strategies during a defined period. Neither the situation when all patients were treated by embolisation to the limits of the method, nor the outcomes of the radiosurgery actually performed were investigated.

Results

PATIENTS

Of the 88 patients, 80 were actually embolised. Two patients were considered to suffer from proliferative angiopathy (94) and were left untreated. In 6 additional patients no satisfactory position of the microcatheter could be reached and they were all referred for radiosurgery.

By the end of the study period no further embolisation attempt was planned for 55 out of the 88 patients (63%). Treatment with radiosurgery was intended or had already been executed in 39 patients (44%). In 19 patients control angiography or clinical control was planned either because obliteration was expected or because it was unclear whether further embolisation was possible. 15 patients either had AVM obliteration proven on control angiography, did not accept further treatment or were not expected to benefit from any treatment. Additional embolisation was planned in 14 patients, and one patient had further treatment in another centre.

In the 54 patients embolised for an AVM ≤10ml, 160 NBCA injections were performed during 89 procedures. In the 26 patients embolised for an AVM >10ml, 170 NBCA injections were done during 60 procedures.

CLINICAL RESULTS FROM EMBOLISATION

61 patients had an AVM ≤10 ml before embolisation. 54 of those were actually treated, and all four immediate obliterations were in this group. One insignificant and two significant permanent complications were recorded (Table 6). One late post procedure haemorrhage resulted in a neurological deficit and is included among the complications.

27 patients had an AVM >10ml before embolisation, 26 of these were actually treated. One insignificant and four significant permanent complications were recorded in this group (Table 6). Two patients with perioperative haemorrhage suffered neurological deficits and are included among the complications.

	Dmin (Gy)	AVM vol. (ml)	N	Mean vol. (ml)	Oblit.	Compl.	Haemo
Group A	25	≤10	54	3.9	41	6	1
Radiosurg.	20	>10	26	19.2	17	6	1
Group B		≤10	54	3.9	4	1 insign/2 sign	0
Embol.		>10	26	19.2	0	1 insign/4 sign	0
Radiosurg.	22	≤10	54	2.3	37	3	1
	20	>10	26	13	17	4	1

Table 6. The material was divided into groups according to treatment strategy (A and B), and volume (AVM ≤10ml and AVM >10ml). Predicted outcome for the cohort of 80 patients if subjected to GKRS is shown in the uppermost rows. Actual outcome data from embolisation of the same cohort of 80 patients are shown in the middle. Predicted outcome for the cohort of 80 patients if subjected to GKRS after the embolisation is shown at the bottom. For patients with AVM ≤10ml the minimum dose to the periphery was reduced with the intent to reach the same number of predicted obliterations with both treatment strategies. The risks for complications and haemorrhages during the two years latency period were predicted for each group and rounded to the nearest integer.

In the 80 patients who were actually embolised, mean AVM volume before embolisation was 8.9ml (Fig. 30) and after embolisation 5.8ml, a reduction by 35%. There was no relation between volume before embolisation and relative volume reduction (Fig. 31). Obviously, the absolute volume reduction was most prominent in larger AVMs.

In the 61 patients with AVM volume ≤10ml before embolisation, the mean volume was 3.8 ml and after embolisation 2.3 ml, a reduction by 40%. By the end of the study period 19 of these patients were awaiting control angiography or further embolisation. There were no haemorrhages during time at risk.

Because of the limited follow up time, the final outcome was unknown in the majority of the 39 patients referred for primary or supplementary radiosurgery. The majority had, however, been irradiated by the end of the study period and a few had angiographically proven obliteration. No complications had been reported.

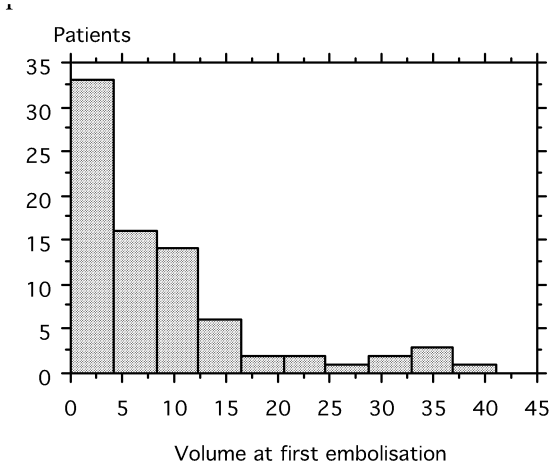

Fig.30. Volume distribution before the first embolisation (cm^3).

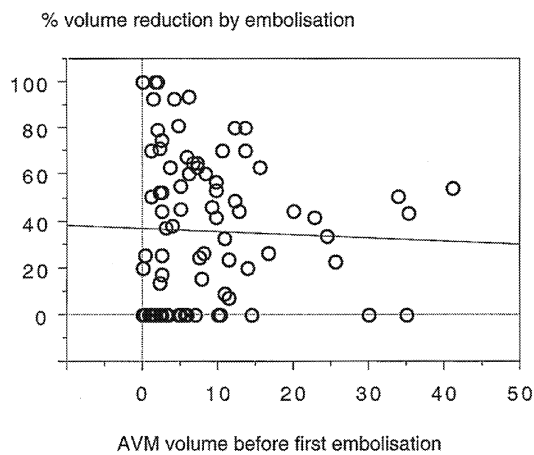

Fig.31. Relative volume reduction as a function of volume at first embolisation (cm^3).

THE OUTCOME COMPARISON

There was no difference between groups A and B significant on the 10% level, neither for the material of 54 patients with AVM ≤10ml, nor for the 26 patients with AVM >10ml. The predicted number of haemorrhages in two-year latency period did not differ between the treatment strategies.

For the total material of 88 patients Karlsson's model (83) predicted between one and two haemorrhages during time at risk. A calculation based on retrospective data from partly the same patient population Meisel's study (129) reached the same number of events. No haemorrhage was recorded during time at risk among our patients.

The risk for complications, regardless of treatment, was significantly larger in the group of patients with AVM >10ml than in those with AVM ≤10ml ($p<0.01$).

DISCUSSION

Haemorrhages, complications and morbidity

The haemorrhagic events during the perioperative 30-day period after embolisation all brought neurological sequelae and were counted as complications. The risk of mortality or permanent morbidity from a haemorrhage (62, 85, 137, 148) or complication is a matter of controversy. Complications from radiosurgery, the vast majority of which appear during the period 6–18 months after the treatment, leave roughly 50% of the patients with a permanent deficit (54).

We have defined the permanency of a complication from embolisation from the residual symptoms at 30-day follow up. This temporal window is narrow, but was chosen because it allowed a 100% follow up rate. The 8 "permanent" complications from embolisation were of such a nature that it is reasonable to expect that 4 of them will resolve in the near future and 4 will remain permanent. Therefore, the complications from radiosurgery and embolisation were considered to bring about the same permanent morbidity, roughly 50%.

Outcome comparison

AVM >10ml are usually not considered for primary radiosurgery, but are most often treated by embolisation or surgery before radiosurgery is considered. In contrast, AVM ≤10ml are often treated primarily with radiosurgery. The material was therefore divided into two groups according to volume.

To allow a comparison of the outcome it is necessary to standardise the treatment strategies with regard to the number of obliterations or complications. Thus to arrive at the same *total* number of obliterations for group A and group B, the minimum dose was reduced from 25 to 22Gy in the dataset B, AVM≤10ml (Table 6). The predicted outcome of radiosurgery of the residuals after embolisation thus became 37 obliterations carrying 3 complications (Table 6). Since embolisation brought about 4 obliterations, the two management strategies both entailed 41 obliterations. Embolisation carried 3 permanent complications, which adds up to a total of 6 complications for group B, to be compared to the 6 complications predicted from radiosurgery alone (group A).

In AVM>10ml, no obliteration was obtained by embolisation whereas 17 obliterations

were predicted from radiosurgery of groups A and B. For group A, 6 complications were predicted. For group B, the corresponding numbers from radiosurgery were four complications. Embolisation brought about no obliterations and five permanent complications. Thus for an equal number of obliterations in groups A and B, AVM>10 ml, the predicted outcome of radiosurgery alone was 6 complications, while the predicted outcome of the combined treatment with embolisation and radiosurgery was 9 complications.

For each of the two management alternatives (groups A and B) two haemorrhages were predicted during the two-year latency period after GKRS (Table 1).

Demographic differences

The outcome models were based on data from roughly 1500 patients treated with GKRS for AVM at a tertiary referral centre (I–III), and therefore there is a patient inclusion bias regarding AVM volume and perhaps otherwise (67). In addition there are no data on genetic or population differences. A study from the AVM centre where the endovascular treatment was performed showed a slightly higher risk of haemorrhage than the one the outcome models is based on, and demonstrated that embolisation reduced the number of haemorrhages during time at risk (129). However, in our study the predicted number of haemorrhages during time at risk was too small to allow statistical analysis.

The aim of the treatment

It may be argued that the immediate outcome with regard to volume is an unsuitable parameter to measure when evaluating the results of endovascular treatment of AVMs, undertaken with the aim to reduce the risk for haemorrhage and relieving neurological symptoms, with volume reduction as a secondary goal. Naturally, an embolisation targeted at a dural supply with the aim to alleviate headache will probably not result in a significant volume reduction. Neither will an emergency embolisation of a ruptured feeder aneurysm. However, only two such cases are included in the series. In most cases volume reduction and obliteration is the ultimate morphological goal, and has the advantages of both being measurable and having predictive value.

The concept of "weak structures" in the nidus as targets for the embolisation is appealing and intranidal aneurysms have been put forward as correlated to presentation with haemorrhage (186). However, the large retrospective study by Mansmann et al (122) demonstrated that several angioarchitectural features are related to the risk of presentation with haemorrhage, but the two most readily identified targets for embolisation, i.e. intranidal aneurysms and fistulae, did not increase the risk of presentation with haemorrhage. On the other hand, in the same material, intranidal aneurysms had a significant correlation to rehaemorrhage before treatment ($p<0{,}002$) (128) and embolisation targeted against those potential rupture sites entailed a significant decrease in the long term risk of haemorrhage (128, 129). However, at the same time a volume and flow reduction was achieved, possibly with changes in haemodynamic stress, factors that may also have impact on the risk of haemorrhage. This aspect was not investigated in the present study, but is obviously important, particularly if it is impossible to obliterate the AVM. A prospective study, using a common "language" for angioarchitectural analysis, has been proposed to provide data for a more thorough analysis of these issues (121, 122, 133).

GENERAL DISCUSSION

The outcome models from GKRS of AVM thus accurately predict the probabilities of obliteration, complication and haemorrhage in the two years latency period after GKRS. The overall aim of this work was to implement the models onto the general management of the same disease, particularly embolisation and combined treatment, i.e. embolisation and GKRS. A study of this kind does not prospectively tell which individual patient should be offered which treatment, but rather if the results, in retrospect, are similar or differ between treatments. In the long perspective this knowledge may change the way patients are managed, particularly in institutions with access to all treatment facilities.

The models and methods created and investigated are for better or worse influenced by the treatment philosophy of radiosurgery. The advantages are that patient, AVM and treatment parameters are easily quantified and that the GKRS results are predictable, within the individual variations in radiation sensitivity. In addition the number of patients treated with GKRS under similar circumstances permits the creation of well-founded models. However, after an embolisation the AVM may undergo progressive volume changes for some time (Fig.26) (60), which has not been accounted for in paper VII. In addition, it is sometimes very difficult to delineate the nidus if acute flow changes are present. The method of evaluating the volume of the lesion on images from the angiography immediately after embolisation may therefore not correctly demonstrate the long-term haemodynamic changes.

At the Karolinska hospital AVM larger than 10ml are rarely treated primarily with the Gamma Knife and thus we lack empirical data to support the models for AVM >10ml. However, data from another centre supports the models for larger volumes albeit that the number of cases is still to few too allow a proper model to be designed (56). Nevertheless, in the clinical situation a patient with an AVM >10ml would not normally have been treated primarily by radiosurgery, and thus the scenario is not very realistic for these patients. Since absolute volume reduction was most prominent in this cohort of patients with large AVM, and the beneficial effects of radiosurgery decrease as volume increases, it seems that in AVM >10 ml primary treatment with embolisation, in most cases followed

by radiosurgery, has comparative advantages. It should be emphasised that the synergistic effect has not been addressed, i.e. embolisation facilitates radiosurgery, but the converse is not true. There are also indications that radiosurgery facilitates surgery (179).

On the other hand, for AVM <10ml, where the outcome models from GKRS are well supported, radiosurgery should be considered as a primary treatment alternative. However, it must be kept in mind that only 75–80% of the patients irradiated with a D_{min} of 25Gy are actually cured by radiosurgery. The remaining 20–25% of the patients are left to experience the natural course of the disease, other treatments or a second irradiation with higher predicted morbidity than the first (80). It should also be noted that primary surgery was a realistic treatment alternative in several of the patients.

Many of the patients in paper VII were not fully treated by the end of the study period and the final outcome for the majority is unknown. It must be borne in mind that this has no impact on the results of the study, since what has been measured is the outcome within a defined time period. A more thorough follow up at a later date is necessary to assess the final outcome and compare it to that predicted by the models.

Finally, the number of parameters poses a conceptual problem for the managing physician who is trying to assess risks and benefits in AVM management. It is virtually impossible to perform these calculations "intuitively", and of course even more difficult if other parameters, such as angioarchitecture and AVM location are added. It is therefore necessary to build models to be able to predict the consequences of our decisions. These models will in the beginning be crude, like this attempt, but will over time, as data are gathered, hopefully become more sophisticated.

CONCLUSIONS

- The probability of obliteration after GKRS depends only on the minimum dose to the periphery of the AVM.
- The probability of complications after GKRS depends on the amount of radiation delivered to a reference volume of 20cm^3, which may be expressed in terms of minimum dose to the periphery of the AVM and AVM volume. It also depends on the location of the AVM, previous haemorrhage and previous irradiation.
- The probability of haemorrhage during the two years latency period after GKRS depends on the minimum dose to the periphery of the AVM, patient age and AVM volume.
- The geometric distortion in DSA has limited impact on volume measurement. It can be corrected for with a calibration-correction scheme.
- The volume of an AVM can be measured in an uncomplicated way from diagnostic angiography. There is a reasonable correlation between volumes measured with the intersecting cone method and treatment volumes from GKRS.
- Volume measurement from angiography and outcome models from Gamma Knife radiosurgery can be used as reference standards in the management of AVM with a nidus volume of 10ml or less.
- Absolute volume reduction from embolisation was most prominent for arteriovenous malformations larger than 10ml and thus facilitated subsequent radiosurgery.
- For AVM smaller or equal to 10ml, primary radiosurgery should be considered as an alternative to primary embolisation, particularly if no significant volume reduction or obviously beneficial effect of targeted embolisation is expected. However, further prospective studies are necessary to identify subgroups amenable to each treatment, and modify the outcome models accordingly.

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