Guido Pecchioli, Lorenzo Bordi
Gamma Knife Unit
Neurochirurgia
AOU CAREGGI
Firenze
Sommario

• Radio-Neurochirurgia
• La Gamma knife
• Le indicazioni: MAV cerebrali
**Radiosurgery**

**Leksell’s Definition**
Leksell’s definition was “... Stereotactic radiosurgery is a technique for the non-invasive destruction of intracranial tissues or lesions that may be inaccessible to or unsuitable for open surgery”

**AANS’s Definition**

(a) “Stereotactic radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head and spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.”

(b) Stereotactic radiosurgery typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.

(c) Technologies that are used to perform stereotactic radiosurgery include linear accelerators, particle beam accelerators, and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.
Lars Leksell 1907-1986
Gamma Knife: concentrazione energia
Definizione Radiochirurgia

Radiochirurgia – Gamma Knife
Gamma Knife: concentrazione energia
Giorno trattamento

1. Montaggio del casco
2. Imaging
3. Treatment planning
4. Treatment
5. Follow-up
Giorno trattamento

(0,0,0)
Giorno trattamento

MONTAGGIO DEL CASCO
Giorno trattamento
Giorno trattamento
Giorno trattamento

Angio

MR

CT

PET
IMAGING e PLANNING

MRI 1.5 T
TC
PET
AGF
Giorno trattamento
La macchina: evoluzione

50 anni uso clinico 1967-2017
“The tools used by the surgeon must be adapted to the task and where the human brain is concerned no tool can be too refined”
L. Leksell
Leksell Gamma Knife®
OVER 1 040 000 PATIENTS TREATED THROUGH 2016, WORLDWIDE
Leksell Gamma Knife®
TREATMENTS BY INDICATION 1968 – 2016, WORLDWIDE

- Malignant Tumors: 44.2%
- Vascular Disorders: 11.3%
- Benign Tumors: 36.8%
- Functional Disorders: 7.1%
- Ocular Disorders: 3.3%

The percentage of centers submitting their numbers each year has varied between 68-100% from 1968 to 2016.
117,000 AVM trattate dal 1968 al 2016

<table>
<thead>
<tr>
<th>Vascular Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Meningioma</td>
</tr>
<tr>
<td>Vestibular Schwannoma</td>
</tr>
<tr>
<td>Pituitary Adenoma</td>
</tr>
<tr>
<td>Meningioma Grade I (typical)</td>
</tr>
<tr>
<td>Other Benign Tumor</td>
</tr>
<tr>
<td>Benign Glioma Tumors (Grade I and II)</td>
</tr>
<tr>
<td>Craniohypophyseal</td>
</tr>
<tr>
<td>Trigeminal Schwannoma</td>
</tr>
<tr>
<td>Pineal Region Tumor</td>
</tr>
<tr>
<td>Other Schwannoma</td>
</tr>
<tr>
<td>Glomus Tumor</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
</tr>
<tr>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td>Meningioma Grade II (atypical)</td>
</tr>
<tr>
<td>Ependymoma</td>
</tr>
<tr>
<td>Jugular Foramen Schwannoma</td>
</tr>
<tr>
<td>Hamangioma</td>
</tr>
<tr>
<td>Neurocytoma</td>
</tr>
<tr>
<td>Meningoepithelioma, Grade II</td>
</tr>
</tbody>
</table>

Courtesy Leksell Gamma Knife Knife Society 2017
Vascular
- AVM
- AVDF

Tumors
- Meningiomas
- Pituitary Adenomas
- Acoustic Schwannomas
- Metastasis
- Gliomas
- Uveal Melanoma

Functional
- Trigeminal Neuralgia

Research areas
- Movement disorders
- Pain
- Cluster headache
- Epilepsy
- Glaucoma
- OCD
- Grosse arterie afferenti
- Grosse vene di drenaggio dilatate
- Presenza di nido vascolare consistente in un groviglio di vasi tortuosi
- Assenza di letto capillare
- Passaggio di sangue arterioso direttamente in quello venoso
- Presenza di tessuto nervoso fra i vasi malformati
MAV CEREBRALI

ROBERT GERONIMO
with THOMAS MAUER

KINGDOM OF BLOOD
MAV cerebrali: 2-4% rate annuale rottura

ESCLUSIONE DAL CIRCOLO
ESCLUSIONE DAL CIRCOLO
Classificazione neuro-istologica (Waltimo 1983)

- MAV compatte senza o con minimo tessuto nervoso normale interposto fra i vasi patologici

- MAV diffuse vasi disseminati in uno o più lobi, intramezzati da tessuto nervoso normale
MAV CEREBRALI: classificazioni

<table>
<thead>
<tr>
<th>Spetzler-Martin Grading</th>
<th>Points</th>
<th>Supplementary Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size, cm</td>
<td></td>
<td>Age, y</td>
</tr>
<tr>
<td>&lt;3</td>
<td>1</td>
<td>&lt;20</td>
</tr>
<tr>
<td>3-6</td>
<td>2</td>
<td>20-40</td>
</tr>
<tr>
<td>&gt;6</td>
<td>3</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Venous drainage</td>
<td></td>
<td>Bleeding</td>
</tr>
<tr>
<td>Superficial</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Deep</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Elocuence</td>
<td></td>
<td>Compactness</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3
Determination of AVM score*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVM volume (cm³)</td>
<td>0.1</td>
</tr>
<tr>
<td>patient age (yrs)</td>
<td>0.02</td>
</tr>
<tr>
<td>AVM location†</td>
<td>0.3</td>
</tr>
<tr>
<td>frontal or temporal = 0</td>
<td></td>
</tr>
<tr>
<td>parietal, occipital, intraventricular, corpus callosum, or cerebellar = 1</td>
<td></td>
</tr>
<tr>
<td>basal ganglia, thalamic, or brainstem = 2</td>
<td></td>
</tr>
</tbody>
</table>

* AVM score = (0.1)(AVM volume) + (0.02)(patient age) + (0.3)(AVM location).
† When an AVM involves multiple sites, fractional values are used according to the number of sites (0.5 for two sites, 0.33 for three sites).

Pollock-Flickinger score
AVM grading for radiosurgery

Classification

<table>
<thead>
<tr>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVM score = 0.1 * volume + 0.02 * age + 0.3 * location</td>
</tr>
</tbody>
</table>

Parameter info
- volume in ml cc
- age in yrs
- location: superficial (hemispheric/corpus callosum/cerebellum) = 0; deep (basal ganglia/thalamic/brainstem) = 1

Interpretation

Chance (in %) of excellent outcome (with 95% CI)
- AVM score ≤ 0.50: 98.7 (98.4-99.0)
- AVM score 0.51 - 1.50: 87.15 (85.96-88.34)
- AVM score 1.51 - 2.00: 64.0 (61.71-66.32)
- AVM score ≥ 2.01: 46.0 (43.26-48.84)

Chance (in %) of modified Rankin Scale decline (with 95% CI)
- AVM score ≤ 0.50: 0.0 (0.0-0.0)
- AVM score 0.51 - 1.50: 12.6 (11.29-13.91)
- AVM score 1.51 - 2.00: 20.1 (18.27-22.03)
- AVM score ≥ 2.01: 36.0 (34.00-38.00)
CONFUSIONE
Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial

J P Mohr*, Michael F Paradis*, Christian Stapf†, Eiken Moquete, Claudia S May, Jessica R Ovseych, Rustam Al-Shal Salam, Eric Vicaux, William L Young†, Emmanuel Houdart, Charlotte Cardonner, Marco A Stefani, Andreas Hartman, Rüdiger von Kummer, Alessandra Bondì, Joachim Berkel, Catharina M Klip, Kirsty Hardiness, Richard Libman, Xavier Rameau, Alan J Moskovitz, for the international ARUBA investigators†

Summary
Background. The clinical benefit of preventive eradication of unruptured brain arteriovenous malformations remains uncertain. A Randomised trial of Unruptured Brain Arteriovenous malformations (ARUBA) aims to compare the risk of death and symptomatic stroke in patients with an unruptured brain arteriovenous malformation who are allocated to either medical management alone or medical management with interventional therapy.

Methods. Adult patients (≥18 years) with an unruptured brain arteriovenous malformation were enrolled into this trial at 39 clinical sites in nine countries. Patients were randomised (by web-based system, in a 1:1 ratio, with random permuted block design [block size 2, 4, or 6]) stratified by clinical site to medical management with interventional therapy (ie, neurosurgery, embolisation, or stereotactic radiotherapy, alone or in combination) or medical management alone (ie, pharmacological therapy for neurological symptoms as needed). Patients, clinicians, and investigators are aware of treatment assignment. The primary outcome is time to the composite endpoint of death or symptomatic stroke; the primary analysis is by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT003389181.

Findings. Randomisation was started on April 4, 2007, and was stopped on April 15, 2013, when a data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health recommended halting randomisation because of superiority of the medical management group (log-rank Z statistic of 4.10, exceeding the prespecified stopping boundary value of 2.87). At this point, outcome data were available for 223 patients (mean follow-up 33.3 months [SD 19.7]), 111 assigned to interventional therapy and 102 to medical management. The primary endpoint had been reached by 11 (10-156) patients in the medical management group compared with 35 (30-79) in the interventional therapy group. The risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group (hazard ratio 0.27, 95% CI 0.14-0.54). No harms were identified, other than a higher number of strokes (45 vs 12, p=0.0001) and neurological deficits unrelated to stroke (14 vs 1, p=0.0008) in patients allocated to interventional therapy compared with medical management.

Interpretation. The ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months. The trial is continuing its observational phase to establish whether the disparities will persist over an additional 5 years of follow-up.
Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre study


Summary
Background The clinical benefit of preventative therapy is uncertain. A randomised trial of unruptured death and symptomatic stroke in patients with arteriovenous malformations (AVMs) is underway. The primary endpoint was the risk of death or symptomatic stroke.

Methods Adult patients (≥18 years) with a trial at 39 clinical sites in nine countries. The study used a permuted block design with block size 2, 4, or 8, and was open to randomisation at any time during the study period. The primary analysis of the results will be performed in accordance with the study protocol.

Findings Randomisation was started on December 1, 2014. The study will be completed on March 31, 2016. The study will be closed to randomisation on May 31, 2016. The study will be continued until all patients have completed the follow-up period.

Conclusion The study is powered to detect a significant difference in the risk of death or symptomatic stroke between the two groups.

Position statement from the Italian Society of Neurosurgery on the ARUBA Study

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Vascular Committee of the Italian Society of Neurosurgery (SINeh – Società Italiana di Neurochirurgia), Rome, Italy

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ABSTRACT

As the conclusions of the ARUBA Study are strongly oriented towards therapeutic abstention, we think it is appropriate to express the concern of the Italian Society of Neurosurgery for the impact that this study might have on the health of patients, if not properly evaluated. The vast majority of patients (76-81%) included in the study was treated with endovascular or radiotherapy treatments, alone or in combination. Only 18 patients (19%) had surgery. It is well known that a partial treatment of arteriovenous malformations (AVMs), as is often the case with endovascular therapy, may increase the risk of bleeding. The primary endpoint (death or symptomatic stroke) in the treated group was reached in 30.7%, i.e. almost one-third of the subjects. This has no comparison in the current surgical literature. Considering permanent and transient neurological deficits along with headaches and seizures all together in the same outcome evaluation parameter may be inappropriate and misleading. The graph with all results from the ARUBA Study, which claims to be the demonstration that natural history is better than treatment, clearly shows that what is assumed to be treated has not actually been treated. In some cases, treatment may result in the disease not cured and patients received a partial — therefore ineffective, if not dangerous — treatment. An effective treatment, as surgery is, must have a flat follow-up curve. The ARUBA Study shows that incomplete treatment leads to negative outcome, confirming that an integrated multidisciplinary strategy has to be plotted out before starting any treatment and that a complete exclusion of the AVM must be achieved.


Key words: Intracranial arteriovenous malformations - Outcome and process assessment - Treatment failure - Randomized clinical trials.
Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentric

Position statement from the Italian Society of Neurosurgery on the ARUBA Study

Marco CENZATO *, Alberto DELITALA, Roberto DELFINI, Alberto PASQUALIN, Giulio MAIRA, Vincenzo ESPOSITO, Francesco TOMASELLO, Edoardo BOCCARDI

Vascular Committee of the Italian Society of Neurosurgery (SINeh – Società Italiana di Neurochirurgia), Rome, Italy

*Corresponding author: Marco Cenzato, Department of Neurosurgery, marco.cenzato@gmail.com

Methods Adult patients (≥18 years) with a trial at 39 clinical sites in nine countries. Permitted block design (block size 2, 4, or therapy [i.e., neurosurgery, embolisation, management alone (i.e., pharmacological investigations are aware of treatment assignment or symptomatic stroke; the primary analysis number NCT00389181).

Findings Randomisation was started on all monitoring board appointed by the National Health recommended halting randomization (log-rank Z statistic of 4.10, including the 1 were available for 223 patients (mean ± standard deviation) was 50. No harms were identified or neurological deficits unrelated to stroke (J). With medical management.

Interpretation The ARUBA trial showed that interventional therapy for the prevention of arterial malformations followed up for 33 months disparities will persist over an additional 5 years.

European consensus conference on unruptured brain AVMs treatment (Supported by EANS, ESMINT, EGKS, and SINCH)

Marco Cenzato 1 *, Edoardo Boccardi 2, Ettore Beghi 3, Peter Vajkoczy 4, Istvan Szikora 5, Enrico Motti 6, Luca Regli 7, Andreas Raabe 8, Shalva Eliava 9, Andreas Gruber 10, Torstein R. Meling 11, Mika Niemela 12, Alberto Pasqualin 13, Andrey Golanyov 14, Bengt Karlsson 15, Rolf Kesternich 16, Roman Lisek 17, Bodo Lippitz 18, Matthias Radatz 19, Alessandro La Camera 20, René Chapot 21, Civan Ilak 22, Laurent Spelle 22, Alberto Debernardi 23, Elio Agostoni 24, Martina Rozay 25, Michael K. Morgan 26

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Microsurgery for ARUBA Trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformation)-Eligible Unruptured Brain Arteriovenous Malformations.

Wong J1, Slomovic A1, Ibrahim Q1, Radovanovic I1, Tymianski M2.

Stereotactic Radiosurgery for ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-Eligible Spetzler-Martin Grade I and II Arteriovenous Malformations: A Multicenter Study.


The benefit of radiosurgery for ARUBA-eligible arteriovenous malformations: a practical analysis over an appropriate follow-up period.

Tonetti DA1, Gross BA1, Atcheson KM1, Jankowitz BT1, Kano H1, Monaco EA 3rd1, Niranjan A1, Flickinger JC2, Lunsford LD1.
European consensus conference on unruptured brain AVMs treatment (Supported by EANS, ESMINT, EGKS, and SINCH)

Marco Cenzato1,2, Eduardo Boccardi1, Ettore Beghi1, Peter Vajkoczy4, Istvan Szikora1, Enrico Motti1, Luca Regli3, Andreas Rasbe3, Shulva Eliava3, Andreas Gruber1, Torstein R. Meling11, Mika Niemela22, Alberto Pasqua1m, Andrey Gohane16, Bengt Karlsson17, Andrus Kennedy20, Roman Liscak21, Rudo Lipsitz18, Matthias Radtke19, Alessandro La Camera19, René Chuper21, Civan Ilič31, Laurent Spekk17, Alberto Debernardi1, Elio Agoston13, Martina Revay1, Michael K. Morgan25

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- Brain arteriovenous malformation (AVM) is a complex disease associated with potentially severe natural history.
- The results of a randomized trial (ARUBA) cannot be applied equally for all unruptured brain arteriovenous malformation (uBAVM) and for all treatment modalities.
- Considering the multiple treatment modalities available, patients with uBAVMs should be evaluated by an interdisciplinary neurovascular team consisting of neurosurgeons, neurointerventionalists, radiologists, and neurologists experienced in the diagnosis and treatment of brain AVM.
- Balancing the risk of hemorrhage and the associated restrictions of everyday activities related to untreated unruptured AVMs against the risk of treatment, there are sufficient indications to treat unruptured AVMs grade 1 and 2 (Spetzler–Martin).
- There may be indications for treating patients with higher grades, based on a case to case consensus decision of the experienced team.
- If treatment is indicated, the primary strategy should be defined by the multidisciplinary team prior to the beginning of the treatment and should aim at complete eradication of the uBAVM.
- The main factors to be taken into account for the management are:
  - Treatment-related severe complication rate of <5% for grade 1 and 2 (Spetzler–Martin) malformations
  - Life expectancy justifying acceptance of the risk associated with the selected treatment modality (Severe treatment-related complications are defined as those resulting in unprecedented permanent disability (mRS 2–6) at 12 months)
- After having considered the pros and cons of a randomized trial vs. a registry, the panel proposed a prospective European Multidisciplinary Registry.
Treatment of Brain AVMs (TOBAS) Study (TOBAS)

This study is currently recruiting participants.

See ▶ Contacts and Locations

Verified November 2015 by Jean Raymond, Centre hospitalier de l'Université de Montréal (CHUM)

Sponsor:
Centre hospitalier de l'Université de Montréal (CHUM)

Objectives

The general objective of the TOBAS trial is to offer a care trial context for the management of patients with brain AVMs (ruptured or unruptured) [41].

The primary objective of the first randomized study is to compare the effect of conservative versus interventional management (i.e. neurosurgery, radiosurgery, embolization, alone or combined) on a composite of disabling stroke or death from any cause at 10 years in patients with unruptured AVMs (patients with ruptured AVMs will be analyzed separately in secondary analyses).

The primary objective of the second randomized study is to compare the effects of embolization prior to neurosurgery or radiotherapy versus neurosurgery or radiotherapy alone, in the management of patients with ruptured or unruptured AVMs, on a composite outcome of complete obliteration of the AVM combined with an independent functional outcome at the end of the management plan.
2-3 years after treatment

Occluded AVM
Pre Gamma Knife Surgery

2 years post Gamma Knife Surgery

Courtesy L. Steiner
Normalizzazione del parenchima
STAGED

Courtesy P. Picozzi
### MAV CEREBRALI e LINAC

#### Table 7.1
Summary of arteriovenous malformation (AVM) obliteration rates after radiosurgery

<table>
<thead>
<tr>
<th>Series (year)</th>
<th>Number of patients</th>
<th>AVM volume, margin dose, delivery system</th>
<th>Obliteration rate</th>
<th>Adverse events</th>
<th>Predictors of obliteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touboul et al. (1998)</td>
<td>100</td>
<td>1.9 cm³, 19 Gy, LINAC</td>
<td>51</td>
<td>Hemorrhage 10%, overall morbidity 8%, permanent ARE 1%, radionecrosis 1%</td>
<td>Margin dose, SM grade</td>
</tr>
<tr>
<td>Chang et al. (2000)</td>
<td>128</td>
<td>12.1 cm³, 16 Gy, GK and LINAC</td>
<td>79</td>
<td>Hemorrhage 7%, radiologic ARE 12%, symptomatic ARE 5%, permanent ARE 0.4%, cyst formation 0.4%</td>
<td>Diameter, single draining vein, compact nidus</td>
</tr>
<tr>
<td>Schlienger et al. (2000)</td>
<td>169</td>
<td>2.5 cm³, 25 Gy, LINAC</td>
<td>64</td>
<td>Hemorrhage 2%, de novo seizures 2%, overall morbidity 2%, permanent morbidity 0.6%, radionecrosis 1%</td>
<td>Lack of prior embolization, mono isocentric irradiation, margin dose (in-field and overall obliteration), male gender (in-field obliteration)</td>
</tr>
<tr>
<td>Flickinger et al. (2002)</td>
<td>351</td>
<td>5.7 cm³, 20 Gy, GK</td>
<td>75</td>
<td>NR</td>
<td>SM grade, margin dose</td>
</tr>
<tr>
<td>Friedman et al. (2003)</td>
<td>269</td>
<td>8.4 cm³, NR, LINAC</td>
<td>53</td>
<td>Hemorrhage 10%, overall morbidity 5%, permanent morbidity 1%</td>
<td></td>
</tr>
<tr>
<td>Bollet et al. (2004)</td>
<td>118</td>
<td>7.4 cm³, 18 Gy, LINAC</td>
<td>56</td>
<td>Annual hemorrhage rate 1.7%, overall morbidity 7%, permanent morbidity 2%</td>
<td>Volume &lt;7 cm³</td>
</tr>
<tr>
<td>Shin et al. (2004)</td>
<td>400</td>
<td>1.9 cm³, 20 Gy, GK</td>
<td>74 at 3 years, 88 at 5 years</td>
<td>Annual hemorrhage rate 1.9%, symptomatic ARE 7%, permanent ARE 2%</td>
<td>Prior AVM hemorrhage, diameter, margin dose</td>
</tr>
<tr>
<td>Liscak et al. (2007)</td>
<td>330</td>
<td>3.9 cm³, 20 Gy, GK</td>
<td>92</td>
<td>Annual hemorrhage rate 2.1%, radiologic ARE 21%, symptomatic ARE 8%, permanent morbidity 3%, mortality 1%</td>
<td>Male gender, prior AVM hemorrhage, volume &lt;10 cm³, SM grade I or II, margin dose &gt;19 Gy, maximum dose &gt;35 Gy</td>
</tr>
<tr>
<td>Colombo et al. (2009)</td>
<td>102</td>
<td>5.2 cm³, 19 Gy, CK</td>
<td>72</td>
<td>Hemorrhage 8%, transient morbidity 1%, mortality 1%</td>
<td>Volume, noneloquent location, low transdural flow, no or mild arterial enlargement, absence of perimalle angiogenesis</td>
</tr>
<tr>
<td>Taishineetnakul et al. (2012)</td>
<td>139</td>
<td>3.8 cm³, 19 Gy, GK and LINAC</td>
<td>66</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fokas et al. (2013)</td>
<td>164</td>
<td>4.0 cm³, 19 Gy, LINAC</td>
<td>61</td>
<td>Annual hemorrhage rate 1.3%, worsened neurologic deficit 3%, worsened seizure status 2%</td>
<td>Volume</td>
</tr>
<tr>
<td>Franzin et al. (2013)</td>
<td>127</td>
<td>2.7 cm³, 22 Gy, GK</td>
<td>69</td>
<td>Annual hemorrhage rate 2.1%, permanent neurologic deficit 7%, radionecrosis 5%, cyst formation 2%, worsened seizure status 7%, mortality 4%</td>
<td></td>
</tr>
<tr>
<td>Starke et al. (2013)</td>
<td>1012</td>
<td>3.5 cm³, 21 Gy, GK</td>
<td>69</td>
<td>Annual hemorrhage rate 1.1%, radiologic ARE 38%, symptomatic ARE 10%, permanent ARE 2%</td>
<td></td>
</tr>
<tr>
<td>Hattingadi-Gluth et al. (2014)</td>
<td>248</td>
<td>3.5 cm³, 15 Gy, PB</td>
<td>65</td>
<td>Hemorrhage 5%, de novo seizures 9%, major neurologic morbidity 1%, mortality 1%</td>
<td></td>
</tr>
<tr>
<td>Missios et al. (2014)</td>
<td>152</td>
<td>6.3 cm³, 18 Gy, GK</td>
<td>46</td>
<td>Hemorrhage 4%, new neurologic symptoms 23%, neurologic worsening 2%, mortality 2%</td>
<td></td>
</tr>
<tr>
<td>Paul et al. (2014)</td>
<td>662</td>
<td>3.6 cm³, 19 Gy, GK</td>
<td>75</td>
<td>Annual hemorrhage rate 1.2%, overall morbidity 4%, mortality 2%</td>
<td></td>
</tr>
<tr>
<td>Wang et al. (2014)</td>
<td>116</td>
<td>4.7 cm³, NR, LINAC</td>
<td>82</td>
<td>Annual hemorrhage rate 1.9%, new neurologic deficit 1%, edema 5% radionecrosis 3%, cyst formation 5%, de novo seizures 6%</td>
<td>Prior AVM resection</td>
</tr>
</tbody>
</table>

46-92% obliterazione, media 80%
Long Term Side Effects of Radiosurgery for Arteriovenous Malformations

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Table 1. Incidences and latency periods of complications after irradiation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Patients with complications</th>
<th>Latency periods months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear accelerator system</td>
<td>Colombo et al. [6]</td>
<td>180</td>
<td>9 (5.0%)</td>
</tr>
<tr>
<td>Friedman et al. [8]</td>
<td>158</td>
<td>5 (3.2%)</td>
<td>11–15</td>
</tr>
<tr>
<td>Gamma Knife</td>
<td>Steiner et al. [17]</td>
<td>1,000</td>
<td>35 (3.5%)</td>
</tr>
<tr>
<td>Lunsford et al. [11]</td>
<td>227</td>
<td>10 (4.4%)</td>
<td>4–18</td>
</tr>
<tr>
<td>Yamamoto et al. [18]</td>
<td>121</td>
<td>6 (5.0%)</td>
<td>less than 601</td>
</tr>
<tr>
<td>Yamamoto et al. [19]</td>
<td>885</td>
<td>24 (2.7%)</td>
<td>4–24 (mean, 12.2)</td>
</tr>
<tr>
<td>Liscak et al. [20]</td>
<td>330</td>
<td>24 (7.3%)</td>
<td>6–57 (median, 13.5)</td>
</tr>
<tr>
<td>Present study</td>
<td>181</td>
<td>15 (13.6%)</td>
<td>9–215 (mean, 105)2</td>
</tr>
</tbody>
</table>

1Although the latency period was not available, the maximum follow-up period in this series was 60 months.

2In 1 patient who experienced radiation-induced injury of the pons 19 months after radiosurgery, a second ictus occurred 81 months after Gamma Knife radiosurgery.

Background and Purpose—We evaluated risk factors associated with the development of adverse radiation effects (ARE) after stereotactic radiosurgery (SRS) for cerebral arteriovenous malformations (AVMs).

Method—We evaluated 755 patients with AVM who underwent a single Gamma Knife SRS procedure with at least a 2-year minimum follow-up. Eighty-seven patients (12%) underwent previous resection and 128 (17%) had previous embolization. The median target volume was 3.6 mL (range, 0.1–26.3 mL). The median margin dose was 20 Gy (range, 13–27 Gy).

Results—Fifty-five patients (7%) developed symptomatic ARE at a median follow-up of 75 months. The cumulative rates of symptomatic ARE were 3.2%, 5.8%, 6.7%, and 7.5% at 1, 2, 3, and 5 years, respectively. Factors associated with a higher rate of developing symptomatic ARE included larger AVM volume, higher margin dose, larger 12-Gy volume, higher Spetzler–Martin grade, and higher radiosurgery-based score. The rates of developing symptomatic ARE were higher in the brain stem (22%) or thalamus (16%), compared with AVMs located in other brain locations (4%–48%). Nineteen patients (5%) sustained irreversible new neurological deficits related to ARE, and 1 patient died. The rates of irreversible symptomatic ARE were 0.8%, 1.9%, 2.1%, and 2.8% at 1, 2, 3, and 5 years, respectively. The 5-year cumulative rates of irreversible symptomatic ARE were 9.1% in thalamus, 12.1% in brain stem, and 1.4% in other locations.

Conclusions—The knowledge of ARE risk rates after AVM radiosurgery can assist informed consent for patients with AVM, their families, and healthcare providers.

Key Words: adverse radiation effects • arteriovenous malformation • complication • Gamma knife • radiation necrosis • stereotactic radiosurgery • T2 changes

ARE 7% f-u media 75 mesi, 755 pz

Long term side effect 2.7-13%
MAV CEREBRALI meccanismo azione GK

DANNO INIZIALE CELL ENDOTELIALI VASI MALFORMATI

PROCESSO RIPARATIVO - CONNETTIVO

MIOFIBROBLASTI
ISTIOCITI
COLLAGENE
FIBRINA

OBLITERAZIONE

PROLIFERAZIONE INTIMA, MIGRAZIONE SM CELL, OCCLUSIONE LUME
Nelle prime fasi spiccata POSITIVITA’ SMA (smooth muscle actin) e COLLAGENE TIPO IV (mb basale). La POSITIVITA’ SMA si perde nelle fasi finali.
3. FASE DEGENERAZIONE/ AUMENTO MATRICE EXTRACELL

Persistenza matrice collagene

Degenerazione (les.cistica)
MAV CEREBRALI meccanismo azione GK

MIOFIBROBLASTI
ISTIOCITI
COLLAGENI
FIBRINA

PROLIFERAZIONE INTIMA, MIGRAZIONE SM CELL, OCCLUSIONE LUME
OBIETTIVI:

• Obliterazione 70 – 80 % (dipende Vol NIDUS e dose al margine)

• ↓ rischio rottura
• ↓ rate crisi comiziali
RISCHI:

- Iperintensità T2 30 - 40 %
- Sintomatica 10 %
- Permanente 2-3 %
- Formazione cisti post-trattamento 2 %
- Crisi comiziali de novo 1-2 %

PERSISTE RISCHIO ROTTURA
Management strategies (after Soderman et al 2003)

- Single, easily catheterised feeder or nidal aneurysms or large fistulae: embolisation
- Cortical, vol nidus <10 ml: surgery ± embolisation
- Central, vol nidus <10 ml: radiosurgery
- Vol nidus >10 ml: targeted partial embolisation + radiosurgery or surgery, depending on the angioarchitecture
- Vol nidus >20 ml: ??

J. Régis. U 751 Functional Neurosurgery – APM - CHU Timone Marseille
Tumefactive Cysts: A Delayed Complication following Radiosurgery for Cerebral Arterial Venous Malformations
Whitney B. Edmister, John I. Lane, Julie R. Gilbertson, Robert D. Brown and Bruce E. Pollock
American Journal of Neuroradiology May 2005, 26 (5) 1152-1157;
Does multimodality therapy of arteriovenous malformations improve patient outcome?

Masaaki Uno, Koichi Satoh, Shunji Matsubara, Junichiro Satomi, Norio Nakajima and Shinji Nagahiro

Department of Neurosurgery, School of Medicine, The University of Tokushima, Tokushima, Japan

The strategy for treating arteriovenous malformations (AVMs) has undergone changes and long-term follow-up results remain unclear. To compare the outcomes of different treatment strategies, we divided 112 patients with 113 AVMs into groups with hemorrhagic (n = 71, 62.8%) and nonhemorrhagic (n = 42, 37.2%) AVMs and subdivided these according to the period in which they were treated (before/after 1990). In the more recent period, treatment more frequently involved the use of the γ-knife and microembolization to the AVM as well as combination therapy. Long-term follow-up showed that the complication rate was lower and the Rankin scale better, in the more recently treated group. Based on our findings we suggest that AVMs should be treated aggressively using a multimodality strategy. [Neuroly 2004; 26: 50–54]

Keywords: Arteriovenous malformation; surgical resection; embolization; gamma-knife; outcome

Stereotactic radiosurgery alone or combined with embolization for brain arteriovenous malformations: a systematic review and meta-analysis.

Russell D1, Peck T1, Ding D2, Chen C2, Taylor DG2, Starkie RM2, Loo CC4, Sheehan JJP2.

Author information

Abstract

OBJECTIVE Embolization of brain arteriovenous malformations (AVMs) prior to stereotactic radiosurgery (SRS) has been reported to negatively affect obliteration rates. The goal of this systematic review and meta-analysis was to compare the outcomes of AVMs treated with embolization plus SRS (E+SRS group) and those of AVMs treated with SRS alone (SRS group). METHODS A literature review was performed using PubMed to identify studies with 10 or more AVM patients and obliteration data for both E+SRS and SRS groups. A meta-analysis was performed to compare obliteration rates between the E+SRS and SRS groups. RESULTS Twelve articles comprising 1716 patients were eligible for analysis. Among the patients with radiological follow-up data, complete obliteration was achieved in 46.4% of patients (330/681) in the E+SRS group compared with 62.7% of patients (613/978) in the SRS group. A meta-analysis of the pooled data revealed that the obliteration rate was significantly lower in the E+SRS group (OR 0.51, 95% CI 0.41–0.64, p < 0.00001). Symptomatic adverse radiation effects were observed in 6.6% (27/412 patients) and 11.1% (48/433 patients) of the E+SRS and SRS groups, respectively. The annual post-SRS hemorrhage rate was 2.0%–6.5% and 0%–2.0% for the E+SRS and SRS groups, respectively. The rates of permanent morbidity were 0%–6.7% and 0%–13.5% for the E+SRS and SRS groups, respectively. CONCLUSIONS Arteriovenous malformation treatment with combined embolization and SRS is associated with lower obliteration rates than those with SRS treatment alone. However, this comparison does not fully account for differences in the initial AVM characteristics in the E+SRS group as compared with those in the SRS group. Further studies are warranted to address these limitations.
37 MAV

6 vergini
31 embolizzazioni parziali

1 caso complicato da emorragia fatale 5 mesi dopo GKRS entro 1 anno da embolizzazione parziale.
• INDICAZIONI:

Multidisciplinare!!!

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