Search strategy:

**Medline**

("cavernoma:" OR "cavernous angioma:" OR "Cavernous haemangioma:" OR "Cavernous haemangioma:" OR "Cavernous malformation:" OR "haemangioma cavernosum:" OR "hemangioma cavernous" OR "cavern hemangioma:" OR "Cavernous, Central Nervous System"[Mesh]) AND ("Central Nervous System"[Mesh] OR "CNS" OR "spinal cord" OR "spin*" OR "medulla*" OR "brainstem" OR "cerebell*" OR "cerebr*" OR "orbit*" OR "tentori*" OR "cranial nerve" OR dura") AND (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word] OR natural history OR epidemiology)

**EMBASE (From Ovid interface)**

((cavernoma: or cavernous angioma: or Cavernous haemangioma: or Cavernous malformation:).mp. or cavernous hemangioma/) and (exp central nervous system/ or CNS.mp.) and (exp disease course/ or risk:.mp. or diagnos:.mp. or follow-up.mp. or ep.fs. or outcome.tw. or natural history.mp.)

**Web of Science**

("cavernoma:" OR "cavernous angioma:" OR "Cavernous haemangioma:" OR "Cavernous haemangioma:" OR "Cavernous malformation:" OR "haemangioma cavernosum:" OR "hemangioma cavernous" OR "cavern hemangioma:" ) AND ("central nervous system" OR "CNS" OR "spinal cord" OR "spin*" OR medulla* OR brainstem OR cerebell* OR cerebr* OR orbit* OR "pontine" OR "tentori*" OR "cranial nerve" OR dura") AND (incidence OR mortality OR Follow-up OR prognos* OR predict* OR course OR "natural history" OR outcome OR epidemiology)

Assessment of publication bias

Publication bias arises when the dissemination of research findings is influenced by the nature and direction of results. Publication bias is mostly an issue in clinical trials assessing the effect of a health care intervention. In studies assessing a natural history of cavernous malformation (CM), the result of the study seems not to influence the reporting of the findings. Therefore, we did not assess publication bias since we believe it is irrelevant.

Measurement of outcomes

**Binary data**

We tried to calculate the incidence rate in PY (person year) or LY (lesion year) and its confidence interval (using poison approximation) if not specifically mentioned in studies. We did not mix incidence rates based on PY or LY unless otherwise specified. We did not extract the outcome measures that did not consider the time of follow up such as odds ratio or relative risk or analysis using chi square method since it introduces bias by ignoring the time of follow up.

**Continuous data**

We extracted or calculated the mean or median (if the data believed to be skewed) and their standard deviations. We assessed skewness based on the method provided in Cochrane handbook.

Assessment of risk of bias

Parameters assessed are as follow: number of assessed individuals, population based or surgical series, type of enrollment (consecutive or non-consecutive), clear definition of inception cohort, quality of censoring (best censoring was defined as either the end of follow up or at the time of treatment), number of patients followed till the end of the study. We also evaluated how the authors were certain about the diagnosis (e.g. definition of CM or hemorrhage). Studies in which uncertainty of diagnosis was believed to be biased were excluded but other studies in which the diagnosis was interpreted as “certain” or “highly
suspicious" were included in the study and sensitivity analysis were applied to assess their effect on the pooled summary statistics.

**Assessment of heterogeneity**

Some predefined reasons for evaluating the heterogeneity were location of the CM (cerebral hemisphere, brain stem, cerebellum, spinal cord, superficial, or deep), type of individuals assessed (Familial or sporadic), multiplicity (multiple or single CM), age of the patients, sex, status of anticoagulation (being on anticoagulant or not), presenting symptom (hemorrhage, seizure or others), associated developmental venous anomaly, method of calculating the incidence, whether the patient excluded or remained in the study after the event, grading of the cavernoma, size of the lesion and time of the study.

**Data synthesis:**

Random effect variance shift model (RVSM) adds an extra-unknown random effect coefficient to a REML model. This allows for additional variance component for the outlying study. An outlier study is defined as an observation (study result) with an inflated random effect variance and was tested using likelihood ratio test statistics. In any analysis, if an outlier study was identified and no explanation could be found for their apparently outlying results, we used RVSM for meta-analysis for down weighting the outlier study while not omitting it completely from the analysis. Provided number of individuals in some analysis is just an approximation of number of individuals since exact number of patients was not extractable with certainty in some studies for some outcomes.

Meta-regression covariates:

We tried to extract the proportion of brainstem cases separately for cases to assess risk of hemorrhage and of rehemorrhage. If it was not possible, the proportion of brainstem cases was estimated using the proportion of brainstem cases in total number of cases in the study.

**Results:**

**Hemorrhage versus re-hemorrhage:**

With calculation of incidence rate ratio we avoided entering one individual in the analysis twice. This also accounts for some possible confounders like the location of cavernomas. The proportion of lesions in different locations is much closer to each other in hemorrhage and re-hemorrhage groups inside each study compared with between studies.

**Re-hemorrhage before and after two years:**

In Hasegawa 2002 and Al-Shahi Salman 2012 studies rates were derived using the figure and the text. In Flemming 2012 study, we calculated the rates based on the tables and the text of the article. In Barker 2001 and Amin-Hanjani 1998 studies, we calculated the rates based on individual patient data. Incidence rate ratio was calculated for each study by dividing before two years incidence of bleeding by after two years (PY). The confidence interval of incidence rate ratio was derived using poison approximation.

With inclusion of 323 patients from 5 studies using REM meta-analysis (Q=15.8 df (4), P=0.003, Between study variance =0.3), the overall incidence rate ratio (re-hemorrhage before versus after two years) was 2.3 (95%CI 1.2-4.3, P=0.013). Since Flemming 2012 study had exaggerated estimate compared with the other studies, we performed sensitivity analysis with omitting this study. The difference remained significant (1.65, 95%CI=1.01-2.70, P=0.043).
Other locations:

Most of the studies mixed the hemorrhage and re-hemorrhage rates in locations other than brainstem (e.g. thalamus, basal ganglia, and spinal cord lesions)\(^1\), \(^6\)-\(^9\), were non-consecutive\(^10\), or investigated less than 20 patients\(^11\)-\(^14\). Due to few studies that pure hemorrhage or re-hemorrhage rate in different locations were extractable from them\(^4\), \(^5\), \(^15\), \(^16\), we decided not to perform meta-analysis.

Median time of re-hemorrhage

One study reported event rate but not hemorrhage rate in brainstem cases\(^17\). Four studies evaluated only brainstem cases\(^17\)-\(^20\). Another study defined hemorrhage as extra-lesional hemorrhage\(^21\). Two other studies reported the mixture of hemorrhage and re-hemorrhage together\(^21\), \(^22\). Moreover, in one study, 46.7th percentile was reported (6 months)\(^19\). In another study 58.6 percentile was reported (6 months)\(^20\). We considered the median 6 months for the sake of the meta-analysis in previous two studies. Omitting all of these studies in a sensitivity analysis increased the PE by 5 months.

Other factors:

We tested the association of different study level data on the risk of re-hemorrhage and hemorrhage using meta-regression analysis. Being a surgical series article appeared to influence the reported incidence rate both for hemorrhage and re-hemorrhage. Among studies that did not limit their cases to just brainstem lesions, we identified moderate correlation between type of the article (surgical or stereotactic series N=3 \(^1\), \(^4\), \(^5\) versus non-surgical series N=6 \(^2\), \(^3\), \(^8\), \(^9\), \(^22\), \(^23\)) and incidence of re-hemorrhage (r\(_{s}=0.45\), P=0.2), however, this correlation did not reach statistical significance probably due to low sample size. Therefore, higher percentage of brainstem lesions might explain the higher incidence of re-hemorrhage in surgical series. For hemorrhage there was only one surgical series\(^19\) and we did not calculate the spearman correlation. Mean time of follow-up as a covariate in the meta-regression did not show any relation with incidence of re-bleeding. However, since we just included the average time of follow-up into the analysis, there is the possibility of “epidemiology fallacy”.

Event rate:

Due to the mixture of patients at the risk of first and recurrent event in included studies\(^2\), \(^22\), \(^23\) and significant heterogeneity among studies, we decided not to carry out meta-analysis.

Predictors of subsequent bleeding

Gender and risk of bleeding

We did not perform meta-analysis to evaluate the effect of gender on bleeding. After excluding papers that mixed hemorrhage and re-hemorrhage only 4 papers remained for analysis (two reported HR and two IR).

Age and risk of hemorrhage
After excluding studies that reported the mixture of hemorrhage and re-hemorrhage, two studied remained for analysis. We decided not to combine them.

Size and hemorrhage

Because of the following reasons, we decided not to carry out meta-analysis. Firstly, the definition of hemorrhage was different among included studies\textsuperscript{21, 23-25}. Secondly, only one study\textsuperscript{25} reported the difference between mean size of lesions in patients at risk of first bleeding. In other studies\textsuperscript{21, 23, 24}, mixture of bleeding and re-bleeding was reported. Thirdly, only one study\textsuperscript{24} reported mean difference in different lesion types. Our calculated overall mean size difference between hemorrhagic and non-hemorrhagic group was so exaggerated compared with the difference in each lesion type separately. Therefore, this finding may indicate that conclusions based on overall mean size might be biased. Fourthly, since the PY of follow-up was not incorporated in the comparisons between hemorrhagic and non-hemorrhagic groups, we could not ascertain the same follow-up for hemorrhagic and non-hemorrhagic groups.

Type of lesions:

We extracted incidence of hemorrhage based on the type of the lesions in two studies\textsuperscript{3, 26}. We decided not to combine them without controlling for timing of recurrent hemorrhage and location of the lesions.

Developmental venous anomaly:

In studies that reported the association of DVA and subsequent bleeding\textsuperscript{2, 3, 20, 25, 27}, only one study\textsuperscript{3} incorporated the follow up period in its calculations. Therefore, we decided not to combine the data.

Multiple versus single:

Some studies compared the risk of hemorrhage between multiple or single lesions\textsuperscript{2, 3, 7, 9, 15}. However, important confounders were not controlled in these studies (hemorrhage or re-hemorrhage, location, timing of re-hemorrhage). Therefore, we decided not to combine the results.

Case fatality rate:

For calculating the case fatality rate, we just included subsequent hemorrhages in the meta-analysis. This was done to avoid underestimation of fatality rate due to prevalent case bias. In three studies no death occurred as a result of subsequent hemorrhage\textsuperscript{9, 22, 26}. Because of the low sample size of these studies, adding “one” to each of these studies would result in exaggerated case fatality rate. Therefore, to enter these studies into meta-analysis, we combined the number of events in these 3 studies to use it as a denominator of combined case fatality rate and added one to the nominator of the formula for deriving combined case fatality rate.

Hemorrhage in brainstem location can theoretically have a higher chance of mortality. However, this was not addressed in the studies so far. Among the studies that we included, only one\textsuperscript{28} was restricted to brainstem cases. We did not find this article as an outlier (using likelihood ratio test) and decided to keep it in the general analysis.
Table e-1. Characteristics of included studies (part 1)

<table>
<thead>
<tr>
<th>Study year [ref]</th>
<th>Follow-up period mean (range)</th>
<th>Complete follow-up</th>
<th>No. of Centers or type of inclusion</th>
<th>Diagnosis method</th>
<th>Definition of hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiba et al. 1995</td>
<td>4.25y in hem, 7.98y in seizure, 2.39y in incident (Longest 15 y)</td>
<td>93%</td>
<td>1</td>
<td>MRI or histology</td>
<td>Acute or subacute onset of FND or raised ICP + a fresh clot outside the CM at surgery or intra or peri-lesional clot density in CT scan that decrease in size and density in F/U</td>
</tr>
<tr>
<td>Al-holou et al. 2012</td>
<td>Mean: 3.5+/−3.2y</td>
<td>-</td>
<td>1</td>
<td>MRI (1.5-3tesla)+GE</td>
<td>Both new-onset clinical symptoms and imaging evidence</td>
</tr>
<tr>
<td>Al-shahi salman et al. 2012</td>
<td>Median: 5 y</td>
<td>97%</td>
<td>Population based</td>
<td>MRI</td>
<td>Hemorrhage+ symptom</td>
</tr>
<tr>
<td>Amin-hanjani et al. 1998</td>
<td>4.7 y Median: 2.45</td>
<td>-</td>
<td>1</td>
<td>MRI or CT (angiography in some patients)</td>
<td>Hemorrhage + symptom</td>
</tr>
<tr>
<td>Barker et al.2001</td>
<td>Median: 5y, range: 1-18</td>
<td>74% confirmed with CT or MRI 26% suspected with clinical criteria</td>
<td>Population based MRI</td>
<td>Acute onset or exacerbation of new neurological symptoms appropriate for the location of CM,</td>
<td></td>
</tr>
<tr>
<td>Canto et al. 2005</td>
<td>Prospective: ~5y, retrospective: P(Y.birth):4561</td>
<td>92%</td>
<td>Population based MRI (0.5 tesla), Some had CT/angiography and pathologic specimen</td>
<td>Neurologic symptoms compatible with acute hemorrhage attributable to CCA that were documented with an MRI</td>
<td></td>
</tr>
<tr>
<td>Curling et al. 1991</td>
<td>Retrospect study</td>
<td>-</td>
<td>1</td>
<td>MRI (some firstly diagnosed with CT, angiography EEG prior to the advent of MRI) others 1.5 tesla</td>
<td>Clinically significant radiologically identified hemorrhage</td>
</tr>
<tr>
<td>Ferroli et al. 2005</td>
<td>Pre-op F/U:about 5 years</td>
<td>92%</td>
<td>Population based MRI</td>
<td>Neurological event (focal deficit,seizure or headache) = radiology or autopsy</td>
<td></td>
</tr>
<tr>
<td>Flemming et al. 2012</td>
<td>Median: 7.3y (0-25 y) Median symptoms: 5.7y</td>
<td>-</td>
<td>1</td>
<td>CT and MRI</td>
<td>Sudden onset or an aggravation of clinical symptoms in conjunction with the presence of radiological signs of recent bleeding.</td>
</tr>
<tr>
<td>Fritschi et al. 1994</td>
<td>30.3 m retrospective</td>
<td>-</td>
<td>2+ literature cases MRI</td>
<td>A new clinical event (focal deficit,seizure or headache) = radiology or autopsy</td>
<td></td>
</tr>
<tr>
<td>Hasegawa et al. 2002</td>
<td>4.33 (0.17-18) (bleed to radiosurgery)</td>
<td>-</td>
<td>1</td>
<td>MRI</td>
<td>a symptomatic, ictal event that consisted of new neurological symptoms with a neurological deficit and imaging confirmation of new bleeding on MRI/CT</td>
</tr>
<tr>
<td>Hauk et al. 2009</td>
<td>Pre-op F/U median:8 wks (26h,4ys)</td>
<td>98%</td>
<td>1</td>
<td>MRI</td>
<td>Neurological event</td>
</tr>
<tr>
<td>Kim et al. 1997</td>
<td>22.4m (12-24)</td>
<td>-</td>
<td>1</td>
<td>MRI</td>
<td>Neurologic symptoms + imaging (Not exactly mentioned)</td>
</tr>
<tr>
<td>Kondziolka et al. 1995</td>
<td>34month (1 to 82m)</td>
<td>74%</td>
<td>1</td>
<td>MRI +/- CT scan</td>
<td>Symptomatic hemorrhage</td>
</tr>
<tr>
<td>Kupersmith et al. 2001</td>
<td>Prospective: 4.9y (SD:5.4y),</td>
<td>-</td>
<td>2</td>
<td>All confirmed with MRI (some diagnosed with CT)</td>
<td>A bleeding event (initial or subsequent) was diagnosed if acute thrombus or blood was observed in the lesion on MRI scans and the patient exhibited new or worsened symptoms.</td>
</tr>
<tr>
<td>Labauge et al. 2001</td>
<td>2.1y median: 2 y (0.5-4.5)</td>
<td>45%</td>
<td>National survey MRI (1 or 1.5 tesla)</td>
<td>GRE Re-exam and MRI in 2nd year</td>
<td>Just based on MRI</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Follow-up</td>
<td>MRI Details</td>
<td>Hemorrhage Definition</td>
<td>Other Details</td>
</tr>
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<td>---------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Li et al. 2013</td>
<td>2013</td>
<td>Pre-op: about 1 year (244.8 PY/242)</td>
<td>1 MRI</td>
<td>MRI an intra- or extra-lesional hemorrhage as determined by MRI and an acute, new-onset, or worsening focal neurological deficit corresponding to the location of the hemorrhage.</td>
<td></td>
</tr>
<tr>
<td>Mathesen et al. 2003</td>
<td>-</td>
<td>-</td>
<td>1 MRI</td>
<td>Retrospective for hemorrhage rate (from birth)</td>
<td></td>
</tr>
<tr>
<td>Menon et al. 2011</td>
<td>2011</td>
<td>48 months</td>
<td>96.2%</td>
<td>Not mentioned</td>
<td></td>
</tr>
<tr>
<td>Mortainy et al. 1999</td>
<td>1999</td>
<td>Mean: 5.2 y</td>
<td>-</td>
<td>Not mentioned</td>
<td></td>
</tr>
<tr>
<td>Pandey et al. 2013</td>
<td>2013</td>
<td>571.5 person year</td>
<td>Almost all</td>
<td>MRI (angiography in a subset of patients to rule out AVM)</td>
<td></td>
</tr>
<tr>
<td>Porter et al. 1997</td>
<td>1997</td>
<td>Mean: 46 m Median41 m</td>
<td>95%</td>
<td>MRI+GE Acute or subacute blood outside the hemosiderin ring (on imaging) or an increase in lesion size by 20% or more in diameter on serial imaging with associated mass effect and/or edema / All encountered hemorrhages were symptomatic</td>
<td></td>
</tr>
<tr>
<td>Porter et al. 1999</td>
<td>1999</td>
<td>Mean: 33/median9.5/mode 2 m range (3-21m)</td>
<td>-</td>
<td>MRI 1) Lesion hemorrhage Inside/outside the hemosiderin ring 2) large sinusoids filled with blood + acute onset of FND; and/or 3) clinical history of apoplectic hemorrhage (last one was the most important factor used to define hemorrhage)</td>
<td></td>
</tr>
<tr>
<td>Robinson et al. 1991</td>
<td>1991</td>
<td>Retrospective Prospective follow up: 26 months</td>
<td>86%</td>
<td>MRI MRI signal of acute/subacute blood outside the &quot;hemosiderin ring&quot; of the lesion. Evidence of previous hemorrhage on lumbar puncture 3. Evidence of fresh clot outside the confines of the lesion at the time of surgery Even though not mentioned exactly it seems that all hemorrhages were clinically symptomatic</td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2003</td>
<td>2003</td>
<td>Pre-op F/U 21.8m (0.03-288m) retrospective</td>
<td>-</td>
<td>MRI Acute/ subacute blood either out/inside the cavernoma + sudden onset or aggravation of clinical symptoms.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MRI: Magnetic Resonance Imaging, CT: computed tomography, GE: Gradient Echo, Pre-op: Pre-operation, FND: Focal Neurologic Deficit, EEG: Electroencephalogram, ICP: intra-cranial pressure CCA: Cerebral cavernous angioma, p: patient, F/U: follow up
<table>
<thead>
<tr>
<th>Study year [ref]</th>
<th>Age (year)1</th>
<th>Sex (male)</th>
<th>Multiplicity (percent of multiple lesions)</th>
<th>Location</th>
<th>Baseline symptoms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiba et al. 19957</td>
<td>Age &lt; 60</td>
<td>55%</td>
<td>Not reported</td>
<td>Coexisting lesions excluded: Hemorrhage 48% supra 52% infra 48%</td>
<td>56.3% hem 22.7% seizure 21% asympt</td>
<td>41/62 hemorrhagic patient underwent surgery in the follow up 2/62 patient presented incidentally or with seizure underwent surgery in the follow up</td>
</tr>
<tr>
<td>Al-holou et al. 201220</td>
<td>Children</td>
<td>51%</td>
<td></td>
<td>Hemispheric 77% Cerebellum 9% BG/thalamus 5% Brainstem 9% (large amount of supratentorial lesions were excluded)</td>
<td>30% acute symptoms 9% chronic symptoms 61% incidental</td>
<td>Person year of follow up does not match with provided incidence rate</td>
</tr>
<tr>
<td>Al-shahi salman et al. 20122</td>
<td>Incidental:4 5 seizure:34 IC III or FND: 38</td>
<td>42%</td>
<td>17.2%</td>
<td>Deep: thalamus BG Lobar: 90 (67.2%) Deep: 9 (6.7%) Cerebellar: 18 (13.4%) Brainstem 17 (12.7%)</td>
<td>Asymp 45.5% seizure: 26% ICH or FND: 28.5%</td>
<td>For hemorrhage rate all asymptomatic patients and those with symptoms not attributable to CM (e.g. headache) were included</td>
</tr>
<tr>
<td>Amin-hanjaniet al. 19988</td>
<td>30.8 ± at D/FU</td>
<td></td>
<td></td>
<td>Hemispheric: 22% Thalamus: 9.5 Brainstem: 61.5% BG: 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barker et al. 20014</td>
<td></td>
<td></td>
<td></td>
<td>Spinal cord: 7.5% Cerebellum: 10.5% Brainstem: 20% hemispheric: 62%</td>
<td>Overt hemorrhage</td>
<td>Pre-intervention follow up Teritary center</td>
</tr>
<tr>
<td>Cantu et al. 20055,20</td>
<td>34.3±14.6</td>
<td>50.4%</td>
<td>13%</td>
<td>Lobar 58.4% Deep hemispheric: 10.4% Brainstem: 20% Cerebellum: 6.4% Spinal cord: 4% Supra/infratentorial: 7.2%</td>
<td>ICH 58.65% Others 41.65% retrospective</td>
<td></td>
</tr>
<tr>
<td>Curling et al. 199110</td>
<td>Age at last F/U: 37.6 (16-72)</td>
<td>53%</td>
<td>19%</td>
<td>80% supratentorial</td>
<td>19% asymptomatic</td>
<td>7/32 patients underwent surgery (no effect on retrospective hemorrhage rate)</td>
</tr>
<tr>
<td>Ferroli et al. 2005</td>
<td></td>
<td></td>
<td></td>
<td>Brainstem 100%</td>
<td>50/52 (96%) symptomatic</td>
<td>In re-hemorrhage calculation even though it seems that only 18 patients remained in the analysis, because of long term follow up we decided to enter the data in the analysis. For retrospective hemorrhage data on 52 patients were analyzed.</td>
</tr>
<tr>
<td>Flemming et al. 20122</td>
<td>45.8 (3.5-88.9)</td>
<td>47.3%</td>
<td>18%</td>
<td>Cortical 51.9% Supratentorial subcortical 13.7% Infratentorial 28.4%</td>
<td>32.5% incidental 5.2% unrelated symptoms 62.3% symptom related: hem 25.3% seizure 26% obj ND6.5% subj ND 4.45%</td>
<td>Prospective hem were calculated based on definitive and probable hemorrhage 78/292 underwent intervention sometime during the follow up period</td>
</tr>
<tr>
<td>Fritschi et al. 199420</td>
<td>31.8±11.8</td>
<td>49%</td>
<td>4.5%</td>
<td>Brainstem 100%</td>
<td>All symptomatic 12% gradual 88% acute event</td>
<td>In 93/139 patients CM was removed surgically some point in follow up (no effect on retrospective hemorrhage) Not consecutive (gathered some of the cases from the literature)</td>
</tr>
<tr>
<td>Hasegawa et al. 20021</td>
<td>Mean age at DxFU: 37.7 (4-81)</td>
<td>56%</td>
<td></td>
<td>Brainstem: 63.4% thalamus 11% BG 4.9% cerebellum: 1.2% hemisphere 19.5%</td>
<td>100% hemorrhage high risk patients</td>
<td>All patients were high risk Pre-intervention follow up Teritary center</td>
</tr>
<tr>
<td>Hauk et al. 200927</td>
<td>Median 37.5 (10-77)</td>
<td>32%</td>
<td>14%</td>
<td>Brainstem 100%</td>
<td>All symptomatic</td>
<td>Short term follow up, no proper definition of event Pre-intervention follow up</td>
</tr>
</tbody>
</table>
Kondziolka et al. 199515
37.3(4-82) 49% 20%
Brainstem:35% BG or thalamus 17% Cerebral or cerebellar:48%
50% no hem 50% hem 23% seizure 15% headache
Tertiary care center
Multiple hemorrhage were not censored, PY of rehem was not calculated exactly after hemorrhage
14/122 underwent surgery in follow up

Kupersmith et al. 200112
37.5
SD:19.2
(6-73)
40%
- 100% brainstem
5% asympt 73% hem

Labauge et al. 200125
40.8 (13-65)
82.4%
85% 7.1/p Median:3
20(80% supra 33(14%) infra
Asympt 100%
Mean follow up was calculated based on the PY of follow up and number of patients
Pre-up follow up, Tertiary center

Li et al. 2013
31.6±12.7 (at orsaet)
57%
11.6%
Brainstem 100%
All symptomatic

Mathiesen et al. 200310
- 53%
20%
BG:26.3% Thalamus 26.3% Mesencephalon 15.8% Pons 15.5%
Cerebellar peduncle 21%
32.3% asymptomatic

Menon et al. 201116
25.4 56%
15%
Brainstem 100%
76.9% hem 17.4%
FND 5.7% incidental
Very poor reporting of outcomes considerable surgical withdrawal
Only measures about fatality rate and functional status of patients were extractable

Mortaroy et al. 199911, 35
Mean 34.6
(range 7.8-78.5)
35%
33% 1.4/p (1 excluded) In familial: 85% multiple in non-familial 25% multiple
Frontal 25% temporal 26% parietal 9%
occipital 9% insula 4% deep supratentorial 4% other supratentorial 3% cerebellar hemisphere 5% brainstem 14%
extralensial hem 13% asympt.
1.5% headache 65% seizure 49%
FND 46% (symptoms have overlap)
Definition of hemorrhage was restricted (extra-lesional hemorrhage was only considered as hemorrhage)

Pandey et al. 20137
Mean:39.2(r
ange:3m-72Y)
46.2%
17%
BG:14.8%
Thalamus: 9.1%
Brainstem:76.1%
98% hemorrhage
This is was done on the patients who referred for surgical intervention to the tertiary center.

Porter et al. 199722
Age DX: 37.5 (median 34.5)
51%
17.5% In multi: Median:4 mean 10.6 Range 2-73
Supra-tentorial 64.2%
Infra-tentorial 35.8% Superficial 63% deep 37%
therm cerebellar nuclei 30%
Cerebellar hemisphere 15.8%
BG/thalamus 6.9% corpus callosum 0.6% frontal 27.7%
Temporal 17.3% Insular 1.2% parietal 6.9%
occipital 3.5%
Sympt 87.9%
Seizure 35.8%
Hem 25.4%
FND w/o hem 20.2%
Headache 6.4%
Incidental 2.1%
Hemorrhage strictly defined
Low exclusion due to surgery some point during follow up (7/110)

Porter et al. 199920
37(3-64)
38%
24%
Brainstem 100%
97% bleeding 3% incidental
86/100 patients underwent surgery somewhere in follow up (no effect on retrospective hemorrhage rate)
tertiary center

Robinson et al. 199130
34.6 (4 m to 84y)
54%
10%
Infratentorial 25.7%
Deep (diencephalon,septal) 6%
Hemispheric 83.3% (it is related to 66 patients not 57 that analyzed at last)
All 57 patients in the study were symptomatic
9 asymptomatic patients were excluded

Wang et al. 200339
33.5 (3.5-70)
58%
-  
Brainstem 100%
Nearly all symptomatic
Retrospective hemorrhage rate
Pro-intervention follow-up (re-hemorrhage rate)

1) Range was presented in parenthesis, SD was presented after mean:
mean+/- SD
Figure e-1. Flowchart of the study

**Database search**
ISI Web of Science (1976-May 2015), \( n=880 \)
Medline (1950-May 2015), \( n=562 \)
EMBASE (1980-May 2015), \( n=1553 \)

Duplicates omitted

2750 records screened

2620 records excluded by title and abstract

130 papers and abstracts assessed for eligibility

82 records excluded
39 review articles
11 less than 20 patients
32 other aspects of CM (non natural history)

48 potentially eligible studies

23 records excluded
16 poor reporting or different definition of hemorrhage
5 duplicate record (1 conference abstract)
2 abstracts (full article not found)

Data from 25 studies analyzed
Figure e-2. Re-hemorrhage within two years of first hemorrhage versus after that

Solid vertical line represents the null hypothesis value. Dashed vertical line represents pooled value. Analysis has been done on logarithmic scale and the x-axis is shown with transformation to normal scale.
References