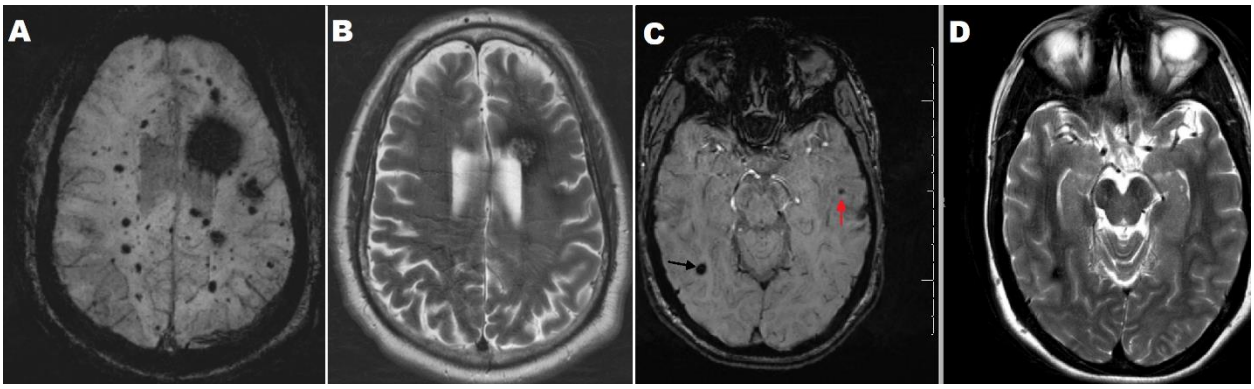
# SUPPLEMENTMENTAL MATERIAL

## Debate on surgery versus conservative management

Due to the very low risk of seizure in incidental CCM cases and the potential risks associated with surgical interventional the conservative approach versus surgical management has always been a debate.[1-3] Surgical resection might be considered for easily reachable asymptomatic lesions in non-eloquent area, in order to avoid any future bleeding, psychological burden, expensive and time-consuming follow-ups, in patients who might require anticoagulation therapy, or to accommodate lifestyle or career decisions.[8] Numerous studies have investigated the effectiveness of conservatives approach for management of CCMs and reported mixed outcomes.[4-6] Fernandez et al. did not find any significant difference between the two approaches while Porter et al. found worse long-term outcomes in conservatively managed patients (42% poorer outcome) versus the patients who had surgical intervention (9%). [4, 5] In studies on patients who were managed and followed conservatively Garrett and Spetzler reported that 50% of the 14 patients improved or remained at their baseline, while Bozinov et al. reported that none of their 50 patients ever suffered a life-threatening bleed. [6, 7] However, these and many other similar studies dealing with this issue previously had small cohorts, were not randomized clinical trials (RCT) and many other biases from patient selection to long term follow-up. Therefore, an RCT evaluating conservative management versus early surgery is highly warranted.

With improving technology, microsurgical resection of CCMs has gained recognition in the early 21$^{st}$ century. Other less invasive methods like radiosurgery have not gained momentum in CCM management due to associated complications.[8] However, various groups have reported benefit with stereotactic radiosurgery in selective cases including deeper cavernomas.[9, 10] Gamma Knife radiosurgery is still being utilized in patients with CCM who are high risk for resection.[11, 12] Various studies have advocated for brain stem cavernoma resection after ICH. Dukatz et al reported good outcomes in 71 patients after microsurgical resection of brainstem cavernomas.[13] However, a population-based Scottish study comparing surgical excision to conservative approach has raised question regarding the surgical option.[14] In this nonrandomized prospective study, Moultrie et al have reported poorer 5 years outcome with higher risk of symptomatic ICH and new onset FND in CCM patients undergoing surgery.[14] Hence, after decades of neurosurgical practice and extensive research relating to CCM, evidence supporting surgical resection of CCM remains conflicting. Thus, an RCT evaluating conservative management versus early surgery is highly warranted.

**Supplemental figure I:** MRI of FCCM patient with SWI (A) demonstrates multifocal cavernomas in bilateral cerebral hemispheres while the same slice location on conventional T2 (B) shows the single periventricular classic "popcorn" lesion correlating with the large left frontal lobe cavernoma on SWI but does not clearly show the smaller lesions. Similarly, in another FCCM patient SWI (C) demonstrates right posterior temporal cavernoma (black arrow) and another much smaller lesion in the mid-temporal region (red arrow) while the conventional T2 sequence does not show the smaller lesion.




**Supplemental table I:** Type of molecular genetic testing and proportion of pathogenic variants detected in FCCM.

| Gene | Proportion of FCCM Attributed to Pathogenic Variants in this Gene | Proportion of Pathogenic Variants Detected by Test Method | |
|---|---|---|---|
| | | Sequence Analysis | Gene-targeted deletion/duplication analysis |
| KRIT1 | 53%-65% | 85%-95% | 5%-15% |
| CCM2 | 20% | 40%-70% | 30%-60% |
| PDCD10 | 10%-16% | 80%-90% | 0%-10% |

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