From Eye to Insight

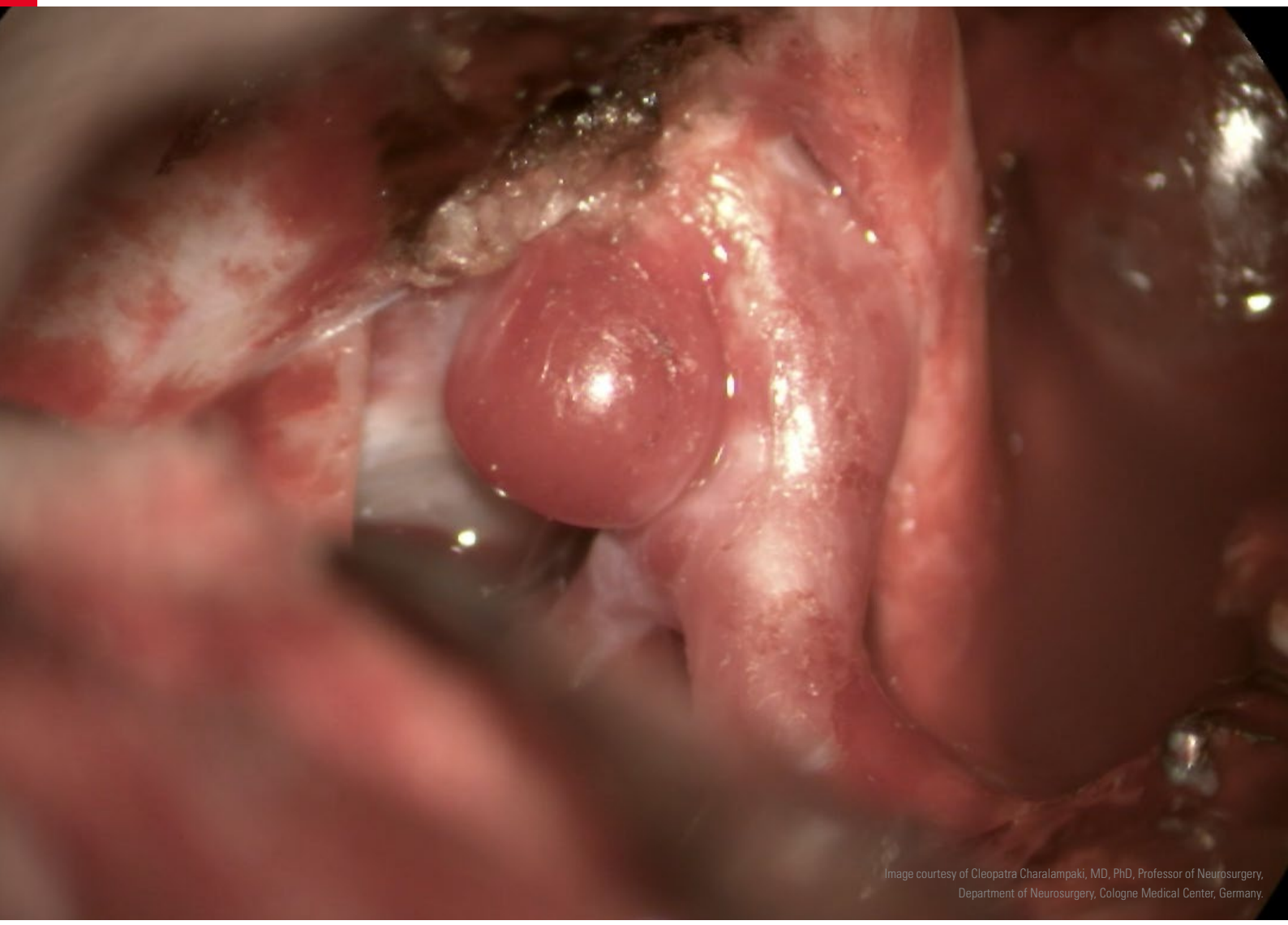

Image courtesy of Cleopatra Charalampaki, MD, PhD, Professor of Neurosurgery, Department of Neurosurgery, Cologne Medical Center, Germany.

REVIEW PAPER

UNRUPTURED INTRACRANIAL ANEURYSMS

Overview, treatment and intra-operative imaging techniques

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1. Abstract

Unruptured intracranial aneurysms (UIAs) are localized dilations of the cerebral artery walls which are prone to rupture and bleeding. Although UIAs are considered to have a relatively low annual risk of rupture, when rupture does occur it can lead to significant morbidity and mortality. Approximately 33% of UIA ruptures result in fatality and about 17% in severe disability (Steiner et al., 2013). From 1973 to 2002 the fatality rate decreased by 17% and patient recovery and regaining of independent state increased by 1.5% per year (Steiner et al., 2013).

Managing UIAs is complex and usually involves one or a combination of three options – conservative, endovascular, or surgical treatment. During surgical treatment the ability to simultaneously visualize and assess the anatomical structures and blood flow is one of the biggest challenges of neurovascular surgery. It is even more challenging to view this in real time. Aneurysms, like all other vascular malformations, are delicate structures with the potential to rapidly deteriorate. Having imaging techniques that provide adequate visualization and assessment of both blood flow and the related anatomical structures enhances decision making.

Nickele et al. (2018) reported that surgeons are looking for faster, more accurate, and more reliable methods to gain information about flow through the cerebral vasculature in the OR. The preferred method would not require interruption of the surgical procedure. The ideal tool in intraoperative vascular neurosurgery is an efficient imaging modality that gives accurate information, is safe, and does not delay the surgical task at hand (Nickele et al. 2018).

2. Intracranial Aneurysms: Introduction

The prevalence of UIAs in the general population is between 2% and 3.2%, with a male to female ratio of 1:2 (Vlak et al., 2011, Toth et al., 2018, Thompson et al., 2015). Bleeding from these aneurysms are the leading cause of hemorrhagic stroke, accounting for 85% of subarachnoid hemorrhages (SAH) (van Gijn et al., 2007). With increasing use of high-resolution imaging of brain, UIAs are more frequently detected, particularly after hemorrhage from another aneurysm, or incidentally during examination of neurological symptoms of an unrelated condition, or a sudden and severe headache (Thompson et al., 2015).

Aneurysms typically develop near a bifurcation point due to an underlying structural abnormality. They often involve a thin or absent tunica media, as well as fragmented or absent internal elastic lamina in the vessel wall (Toth et al., 2018). Approximately 85% of all aneurysms are located in the anterior circulation of the circle of Willis (Schievink, 1997). In most aneurysms, the tunica adventitia is present, sometimes with associated fibrinous material.

The biggest identified modifiable risk factors for aneurysms are smoking and hypertension.

Table 1 shows the risk factors and corresponding odds ratios (Toth et al., 2018, Vlak et al., 2013).

Risk Factors for UIA	Odds Ratio
Excessive Alcohol Consumption	1.1
Smoking	2.8
Sex (Female/Male Ratio)	1.5
Genetic Factors	-
Older Age	-
Overweight (Body Mass Index > 30)	1.3
Regular Exercise	0.6
Family History	
Stroke	1.6
Myocardial Infarction	1.7
Medical history	
Hypertension	2.6
Hypercholesterolemia	1
Diabetes Mellitus	0.9
Atrial Fibrillation	1.4
Heart Disease	0.9
Migraine	0.6
Smoking + Hypertension Combined	8.3

Table 1: Risks factors for UIA and corresponding odds ratio (Toth et al., 2018, Vlak et al., 2013).

Saccular aneurysms are by far the most common, about 90% (Keedy, 2006). Other types include microaneurysms (smaller than 2 mm in diameter and usually observed on small perforator vessels due to chronic hypertension), fusiform (involving a longer segment of the vessel), traumatic, dissecting (resulting from a minor tear on the inner wall) and giant aneurysms (diameters over 25 mm).

The risk of rupture is considered to be higher for specific aneurysm types, particularly aneurysms of larger diameter (> 7 mm), multilobed aneurysm, and aneurysms with selected morphological characteristics such as size relative to the parent artery and irregular aneurysm dome (Thompson et al., 2015).

Other potential risk factors for aneurysm rupture include younger age, smoking, hypertension, family history of SAH, female sex, and aneurysmal growth (Korja et al., 2014; Chien et al., 2013). These factors are summarized in table 2 below.

Risk Factors Associated with Aneurysm Rupture	
Aneurysm Characteristics	Diameter > 7 mm Multilobed Irregular Dome High Growth Rate (> 4 mm/year)
Aneurysm Cerebral Location	Posterior Circulation
Patient Characteristics	Younger Age Smoking Hypertension Family history of SAH Female sex

Table 2: Risks factors for aneurysm rupture (Mehan et al., 2014, Thompson et al., 2015, Korja et al., 2014, Chien et al., 2013).

The overall annual rupture rate of UIAs is estimated at 0.49–1.8% (Clarke et al., 2005). Approximately half of the patients die within the first month of aneurysm rupture, and among the patients who survive more than one month 40% remain dependent for the rest of their lives (Hop et al., 1997). Despite considerable improvements in the management of SAH, overall fatality remains high, reaching 40% of all cases (Nieuwkamp et al., 2009; Steiner et al., 2013). This significant sequelae, associated morbidity and costs often compels intervention into UIAs to reduce the risks of rupture (Juvela et al., 2013).

3. Treatment Strategies for Unruptured Intracranial Aneurysms

The treatment to be used is based on both clinical and anatomical factors, including the patient's age, family history of IA, associated conditions (including autosomal dominant polycystic kidney disease), symptomatic aneurysms, aneurysm size, and location (Pierot & Wakhloo, 2013). Indications for treatment of UIAs continue to evolve, as there are currently multiple existing guidelines.

Generally, three management options are available once an aneurysm is discovered: conservative, endovascular, or surgical treatment.

Conservative Treatment

This close watch-and-wait approach involves regular scans and reviews. Medications may also be given to manage any underlying diseases and mitigate risk factors. To optimize patient outcomes, aneurysmal rupture risk associated with observation must be weighed against the risks associated with intervention. The risks and benefits of treatment and conservative management need to be assessed on an individual basis due to variations in both patient-specific and aneurysm-specific factors.

Endovascular Treatment

Endovascular management of UIAs emerged as a treatment modality in the 1990s and mostly involves the introduction of platinum coils into the aneurysm, resulting in local thrombosis and isolation of the aneurysm from the parent artery (Williams & Brown, 2013). In addition, techniques such as balloon inflation or stent placement at the aneurysm neck can be used in more difficult cases (Naggara et al., 2012). Other endovascular treatments of IAs include flow diversion, flow disruption and embolization using liquid embolic agents (Pierot & Wakhloo, 2013).

Endovascular treatments have a successful occlusion rate of 86.1%, with recurrence in 24.4% of cases, and need for retreatment in 9.1% of cases (Naggara et al., 2010). Small neck aneurysms appear to be the most ideal for endovascular treatment with standard coiling or balloon- or stent-assisted coiling (Pierot & Wakhloo, 2013).

Endovascular treatment is not often recommended for treatment of certain types of UIAs, including large aneurysms, aneurysms with a wide neck, high dome-to-neck ratio, or those with difficult intravascular approaches (Dovey et al., 2001).

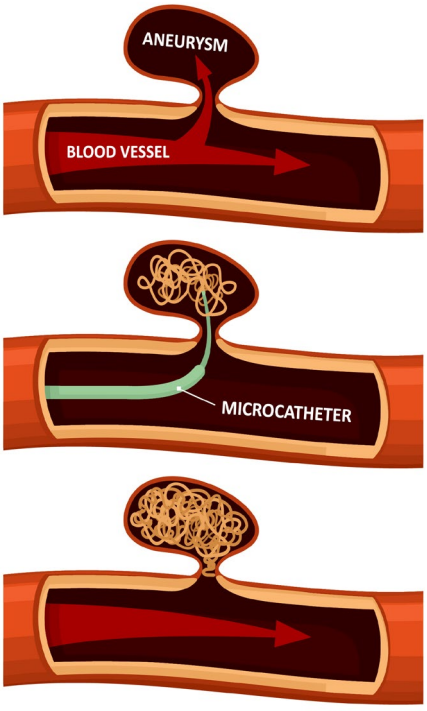

Fig. 1: Endovascular treatment of cerebral aneurysms

Risks Associated with Endovascular Treatment

According to existing reviews and meta-analyses, the risk of unfavorable outcomes following endovascular coiling of UIAs is approximately 4%–5%, including a risk of mortality of 1%–2% (Naggara et al. 2010). In a prospective randomized trial, the International Subarachnoid Aneurysm Trial (ISAT) directly compared surgical clipping to endovascular coiling for ruptured IAs. The results of the study demonstrated a lower risk of death or dependency in the endovascular treatment group (23.5%) compared to the neurosurgical group (30.9%), with a statistically significant risk reduction of 7.4% (Molyneux et al., 2005).

However, other studies have demonstrated similar risk ratios of death, bleeding, cerebral ischemia, occlusion of aneurysm, and independence in daily activities following coiling and surgical clipping of UIAs (Ruan et al., 2015).

Bohnstedt et al. (2017) showed postoperative complications of cranial nerve deficits and hemiparesis were more common in patients treated microsurgically than endovascularly (Bohnstedt et al., 2017). However, the same study also found that aneurysm remnants and need for retreatment occurred at a higher frequency in the endovascular patient group compared to the microsurgical group (Bohnstedt et al., 2017).

Surgical Treatment

Surgical treatment for UIAs is mostly surgical clipping, although other treatment options, such as bypass and wrapping can be used in treatment of more complex situations. Surgical clipping typically involves accessing the aneurysm through an open craniotomy and placing a small metallic clip at the neck of the aneurysm to isolate it from the circulation (Williams & Brown, 2013).

Surgical clipping is considered as an effective strategy, with complete occlusion achieved in over than 90% of cases (David et al., 1999), and low associated morbidity and mortality. While the results vary, surgical clippings tend to show better outcomes than non-intervention for selected patients, and better outcomes than for rupture of the aneurysms.

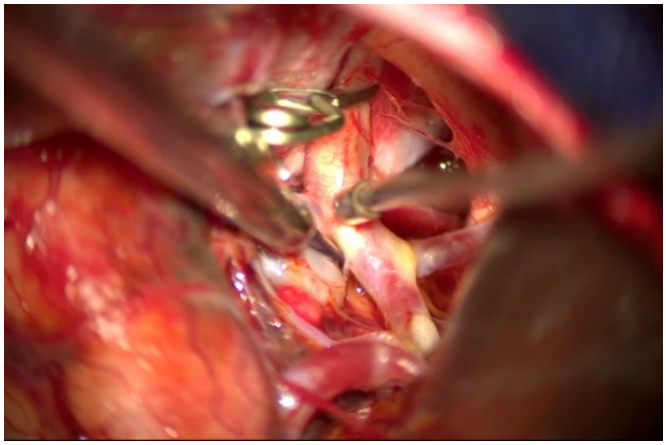

Fig. 2: Microsurgical Clipping a cerebral aneurysm. Image courtesy of Prof. Dr. Feres Chaddad, Head of Vascular Neurosurgery at the Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

Multiple meta-analyses and large studies have demonstrated these:

Title	Study Type	Characteristics	Mortality (%)	Morbidity (%)
King et al. 1994	Meta-Analysis	High percentage of smaller and anterior aneurysms	1	1.4
Raaymakers et al. 1998	Meta-Analysis	Posterior circulating & Giant aneurysms	2.6	10
Kotowski et al. 2013	Large Study	Multiple	1.7	5

Microsurgical Treatment of Aneurysms

Advances in microsurgery techniques have allowed the use of minimally invasive approaches and customization of the surgical exposure to each patient's unique anatomy while still providing adequate exposure. Numerous studies have demonstrated that surgical clipping of aneurysms has excellent durability and effective application in most types of aneurysms, demonstrating its relevance and efficacy (CARAT Investigators, 2006).

Studies have demonstrated the potential benefits of early microsurgical intervention for UIAs. Early microsurgical neck clipping can significantly decrease the incidence of rupture and of postoperative cerebral vasospasm (Grasso & Perra, 2015), and has demonstrated a positive effect in cases of high-risk aneurysm rupture (Kim et al., 2014).

Risks Associated with Surgical Clipping

The size and location of UIAs have been most consistently associated with surgical risk. Aneurysm size of >12 mm has been demonstrated to be a significant predictor of poor outcome (Wiebers et al., 2003). According to one study, non-giant (<25 mm) anterior circulation aneurysms were associated with the lowest mortality estimate of 0.8% (1.9% morbidity) when compared to non-giant posterior circulation aneurysms at 3%

(12.9% morbidity), giant anterior circulation aneurysms at 7.4% (26.9% morbidity), and giant posterior circulation aneurysms at 9.6% (37.9% morbidity) (Kotowski et al., 2013).
Other aneurysm features that adversely affect surgical outcome include age ≥ 50 years (Wiebers et al., 2003), non-saccular morphology, presence of a thrombus, and calcification (Thompson et al., 2015).

4. Intraoperative Angiography

Intraoperative angiography (IOA), often referred to as Digital Subtraction Angiography (DSA), is frequently used as an assessment adjunct to surgical repair of cerebral aneurysms and has shown an accuracy rate of 95% in detecting abnormalities (Tang et al., 2002). Since up to 5-7.3% of surgically treated aneurysms can be unexpectedly incompletely occluded, resulting in need for additional treatment or to increased risk of rupture, IOA used during aneurysm repair is considered to be a safe and effective tool that facilitates confirming complete occlusion of the aneurysm and visualizing the patency of surrounding vasculature during aneurysm repair (Friedman & Kumar, 2009, Kivisaari et al., 2004).

Parent vessel occlusion occurs in approximately 3 – 9% of cases during surgical clipping, and can lead to permanent neurological deficit or death (Kivisaari et al., 2004; Tang et al., 2002). Because parent vessel occlusion and blood flow restoration must be carried out quickly to prevent irreversible ischemia of brain parenchyma, postoperative examination is typically insufficient for a successful intervention (Friedman & Kumar, 2009). IOA can demonstrate both incomplete aneurysm occlusion and parent vessel occlusion easily and quickly in order to determine the need for corrective intervention during the initial craniotomy.

However, IOA comes with its own set of risks and significant limitations that include high costs, impact on workflow, and potential complications, such as stroke, emboli, dissection and hematoma, with previous studies having reported complication rates of IOA in the range of 0.4% to 2.6% (Hauck et al., 2008; Alikhani et al., 2007). IOA struggles with to demonstrate occlusion of small perforating arteries, which can occur unnoticeably during aneurysm clipping in most common locations (Martin et al., 1990).

The impact on the operative workflow starts with significant added time to the surgery, often an extra 30 – 60 mins to setup, acquire, process and review the images. There is also extra expertise needed, in the form of a radiographer. All this comes with added financial costs. The impact on time and workflow is not to be underestimated. Intracranial vascular operations are delicate procedures with potential for rapid deterioration especially from significant bleeding. Doing IOA requires the surgical team to step away from the operating table while the radiographer carries out the DSA, which leaves the patient even more vulnerable than they already were. If the patient is already unstable, the freedom to do a needed angiography is much reduced.

In spite of the challenges, IOA remains the gold standard for assessing occlusion and patency.

5. The Use of ICG-VA in Neurovascular Surgery

The main objective of aneurysm surgery is to completely exclude the aneurysm sac from the circulation while conserving the patency of parent, branching and perforating arteries. Consequently, incomplete clipping increases the potential risk of aneurysm rebleeding and increases the risk of stroke due to iatrogenic vessel compromise (Lin et al., 1989; Friedman et al., 2001). The prevalence of aneurysm remnants after surgical intervention has been reported in 4% to 8% of patients (Sindou et al., 1998; David et al., 1999).

Indocyanine green (ICG) is a near-infrared fluorescent compound originally used in the diagnosis of retinal and liver pathologies. The dye is

administered intravenously, and is subsequently bound by plasma proteins, remaining intravascular and allowing for visualization of blood vessels when the tissue is illuminated and observed at wavelengths of 805 and 835 nm, respectively. In the recent decades, technological improvements have allowed the integration of the illumination system into operative microscope, making indocyanine green video angiography (ICG-VA) an attractive technique in neurosurgery.

The use of ICG-VA in intracranial aneurysm surgery, well described by Raab et al. (2003), has several important advantages, including the relatively low cost of the procedure, ease of use, high resolution, and quick image acquisition. But, perhaps the most important advantage is the integration into the surgical operating microscope. This allows the surgical team to control acquisition of the images and directly view the images on the microscope, all with much reduced impact on workflow.

Using ICG-VA, parent vessel stenosis, as well as occlusions of small perforating arteries, can be detected and resolved during surgery, with reduced impact on workflow, thereby potentially reducing postoperative ischemic deficits (Jing et al., 2010).

A large cohort study demonstrated ICG-VA to be an effective intraoperative tool, leading to a significant intraoperative clip modification rate of 15% (Roessler et al., 2014). The study concluded that ICG-VA is a safe and easy-to-perform intraoperative method for evaluation of compromised intravascular circulation within both small and large parent and branching vessels, as well as the occluded dome or neck of a cerebral aneurysm during surgery. Moreover, the study determined a low complication rate (0.0019% risk of severe adverse events). A number of other studies have suggested that ICG–VA can reduce the morbidity and complications associated with aneurysm clipping and improve patient outcomes when combined with the intensity diagram (Oda et al., 2011; Nishiyama et al; 2012).

6. Limitations of ICG-VA in Neurovascular Surgery

Despite the undoubted usefulness of ICG-VA in cerebrovascular surgery, it has several important limitations. Although the technique provides visualization of vessels, other structures, including occluded vessels, clips and occluded vessels cannot be observed during ICG-VA (Sato et al., 2018). The large cohort study by Roessler et al. (2014) has also shown that intraoperative ICG-VA had missed small, < 2-mm-wide neck remnants and a 6 mm residual aneurysm in up to 10% of the patients. In some cases, the residual may give rise to recurrent aneurysms in the long-term, making it necessary to utilize post-operative DSA in order to look for potential errors in aneurysm clipping. The authors of the study had determined that ICG-VA seems reliable only when the complete vascular anatomy is properly dissected and the clipped aneurysm can be visualized completely. Moreover, ICG-VA is not a reliable technique to visualize hidden parts of the parent, branching, and perforator vessels, in addition to undissected parts of the aneurysm dome, especially in cases where the ability to manipulate is limited by the applied aneurysm clips (Roessler et al., 2014).

One of the most important limitations of these techniques is the inability to simultaneously visualize flow and anatomical detail, and the acquisition of only black and white images.

Fig. 3: Aneurysm viewed with ICG and NIR fluorescence. Image courtesy of Cleopatra Charalampaki, MD, PhD, Professor of Neurosurgery, Department of Neurosurgery, Cologne Medical Center, Germany.

The use of NIR fluorescence in conjunction with ICG is highly effective in neurovascular surgery, but requires the use of different optical filters for illumination and imaging for each mode. Since the selection of each imaging mode activates an automatic exchange to the appropriate filters in the microscope, the different imaging modes can only be accessed in a sequential manner.

Consequently, the surgeon needs to separately choose and view each imaging mode in order to carry out detailed assessment of the tissue and blood flow prior to carrying out the treatment, such as clipping an aneurysm. Since the surgeon is required to mentally merge all the information observed using each filter, this activity demands considerable time and effort, while also increasing the risk of overlooking important details before or after the intervention.

Another important limitation of NIR fluorescence is the weak signal of fluorescence only, which is significantly affected by the magnification levels used, as well as by the microscope's working distance. Therefore, it is only possible to compare fluorescence intensity within an image, and not between different positions or surgeries.

In summary, the drawbacks of ICG-VA are:

1. The videos and images are in black white with loss of the anatomical background.
2. The images viewed are not in real time, which limits the surgeons ability to work live on the diagnostic information-filled images.
3. The surgeon has to spend considerable time and effort mentally reconciling two separate images – the black and white fluorescence and the white light anatomical – in order to make a decision and an intervention.
4. Limited visualization and identification of structures or objects that are not blood flow.
5. The absence of 360-degree view and unreliability when visualizing hidden parts of the parent, branching, and perforator vessels, in addition to undissected parts of the aneurysm dome, especially in cases where the ability to manipulate is limited by the applied aneurysm clips.

7. GLOW800 in Neurovascular Surgery

GLOW800 augmented reality (AR) fluorescence from Leica Microsystems represents the latest advances in visualization of vascular blood flow, and is designed to be used with Leica's advanced surgical operating microscopes during vascular neurosurgery. GLOW800 is an innovative Augmented Reality module designed to overcome many of the limitations of NIR fluorescence used in conjunction with ICG.

This novel technology combines the NIR fluorescence signal of ICG with traditional white light illumination into a single view, permitting the surgeon to visualize the information of both ICG fluorescence and white light in a single image and at the same time, in real time. GLOW800 makes it possible to evaluate blood flow and anatomical detail in full multispectral color. When activating the GLOW800 mode, the white light illumination of the Leica microscope is extended to near infrared to excite the fluorophore (ICG). The filtered NIR fluorescence signal of the fluorophore (ICG) is acquired by a highly sensitive NIR camera and processed in the GLOW800 video processing unit (VPU).

GLOW800 provides two observation modes: the white light object view with the embedded fluorescence signal in pseudo color and the black and white NIR fluorescence view. In both views, the fluorescence video signal can be observed on a video monitor or through the microscope oculars using the CaptiView image injection from Leica Microsystems.

GLOW800 employs augmented reality fluorescence algorithms to obtain a high degree of synchronization of the white light and fluorescence, which provides the natural appearance of color which is fully integrated into the image regardless of the viewing platform (video monitor or microscope oculars). These algorithms are designed to limit asynchronous movements or delays.

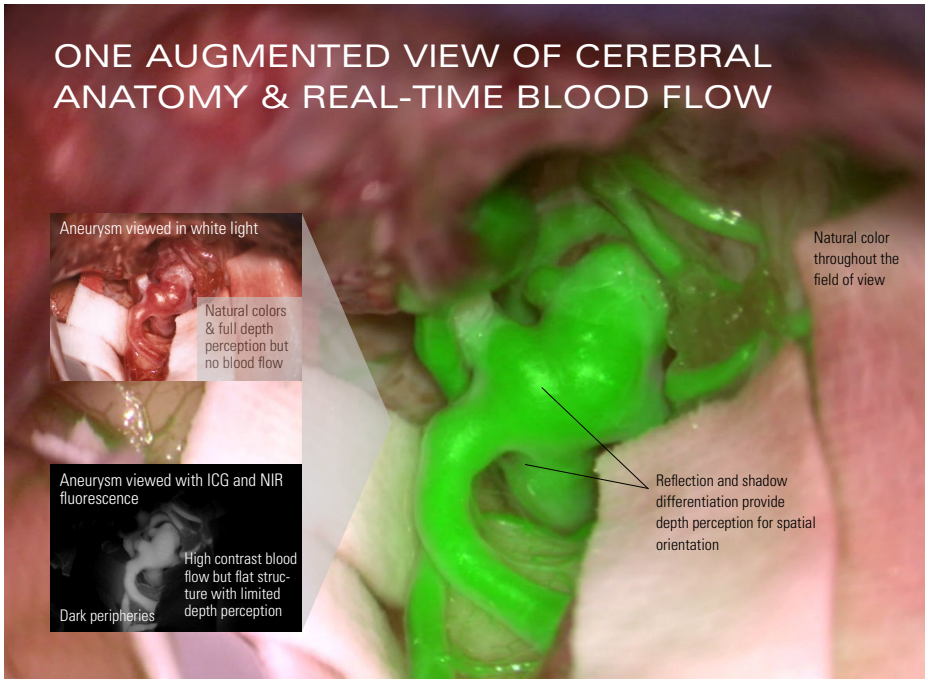

Fig. 4: Aneurysm viewed with ICG and GLOW800 AR Fluorescence. Image courtesy of Cleopatra Charalampaki, MD, PhD, Professor of Neurosurgery, Department of Neurosurgery, Cologne Medical Center, Germany.

The GLOW AR platform allows accurate visualization of fluorescence intensity independent of magnification, working distance, and inhomogeneities in the illumination. This accuracy allows surgeons to evaluate and compare fluorescence intensities between different imaging positions, operations and even patients.

Nickele et al., (2018) compared Leica's GLOW800 with 3 other intraoperative visualization modalities that are widely used – ICG-VA, DSA, and Micro-Doppler Ultrasound (MDUS).

Four major parameters were assessed:
1. Patency – of bypass or of parent vessels
2. Occlusion – leakage from bypass, or obliteration of aneurysm
3. Efficiency – time taken to perform that modality (how long did it take to obtain the images and assess them
4. Ergonomics – physical convenience of the modality (how easy and convenient is it to see what you are doing or what you have done)

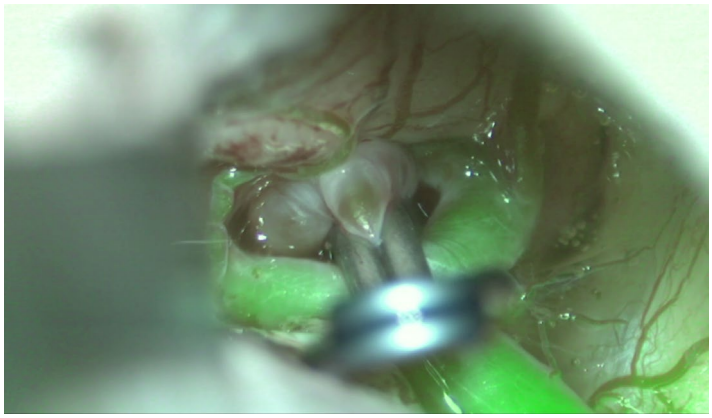

Fig. 5: Clipped Aneurysm viewed with ICG and GLOW800 AR Fluorescence. Image courtesy of Prof. Dr. med. Nils Ole Schmidt, Neurosurgeon, University Hospital Hamburg Eppendorf

Nickel et al. concluded that while DSA remains the gold standard for assessing blood flow, with GLOW the surgeon can continue to work as the display reveals the fluorescence within the vasculature. GLOW can be viewed through the ocular pieces of the microscope. This viewing method allows the surgeon to see the fluorescent signal laid over the surgical anatomy and the fluorescence while he or she is manipulating the tissue in the field (Nickele et al., 2018).

The table below summarizes the major other conclusions of the paper

Ability to continue working while the images is being acquired and displayed, interruption of the surgical workflow and need for re-orientation of the surgeon	With GLOW800 the surgeon does not need to interruption his/her workflow in order to acquire and view the blood flow fluorescence. All the other modalities require interruption of surgery and re-orientation which is time-consuming and can impact confidence. Only GLOW800 allows the surgeon to keep working on the operative field while imaging.
Real Time Information	Only GLOW80 provides the fluorescence in real-time and in full multispectral color.
Full Integration into the accustomed working space	GLOW800 offers the best integration because it if fully integrated into the surgical operating microscope, the images are generated and displayed in real time, can be injected into the eyepieces, and does not require the surgeon interrupt his/her workflow.
Full integration into the accustomed surgical microscope	GLOW800 offers the best integration. ICG-VA also provides integration into the into surgical microscope, but with GLOW800 the images are generated and displayed in real time, can be injected into the eyepieces, and does not require the surgeon interrupt his/her workflow.
Images that can be accessed and reviewed over again	GLOW800, ICG-VA and DSA all provide the ability to review the acquired images over again.
Need for extra equipment besides the microscope to view the image	All four imaging solutions require special equipment, but only GLOW and ICG-VA are physically integrated into the microscope and fully controllable by the operating surgeon.
Need for extra personnel besides the surgical operating team to setup and acquire the images	All except DSA can be fully operated by the surgical operating team.
Need for Image Processing	GLOW800, ICG-VA and DSA all require some level of image acquisition and processing. However, only GLOW800 provides a real time image, and in multispectral color. MDUS gives no image.

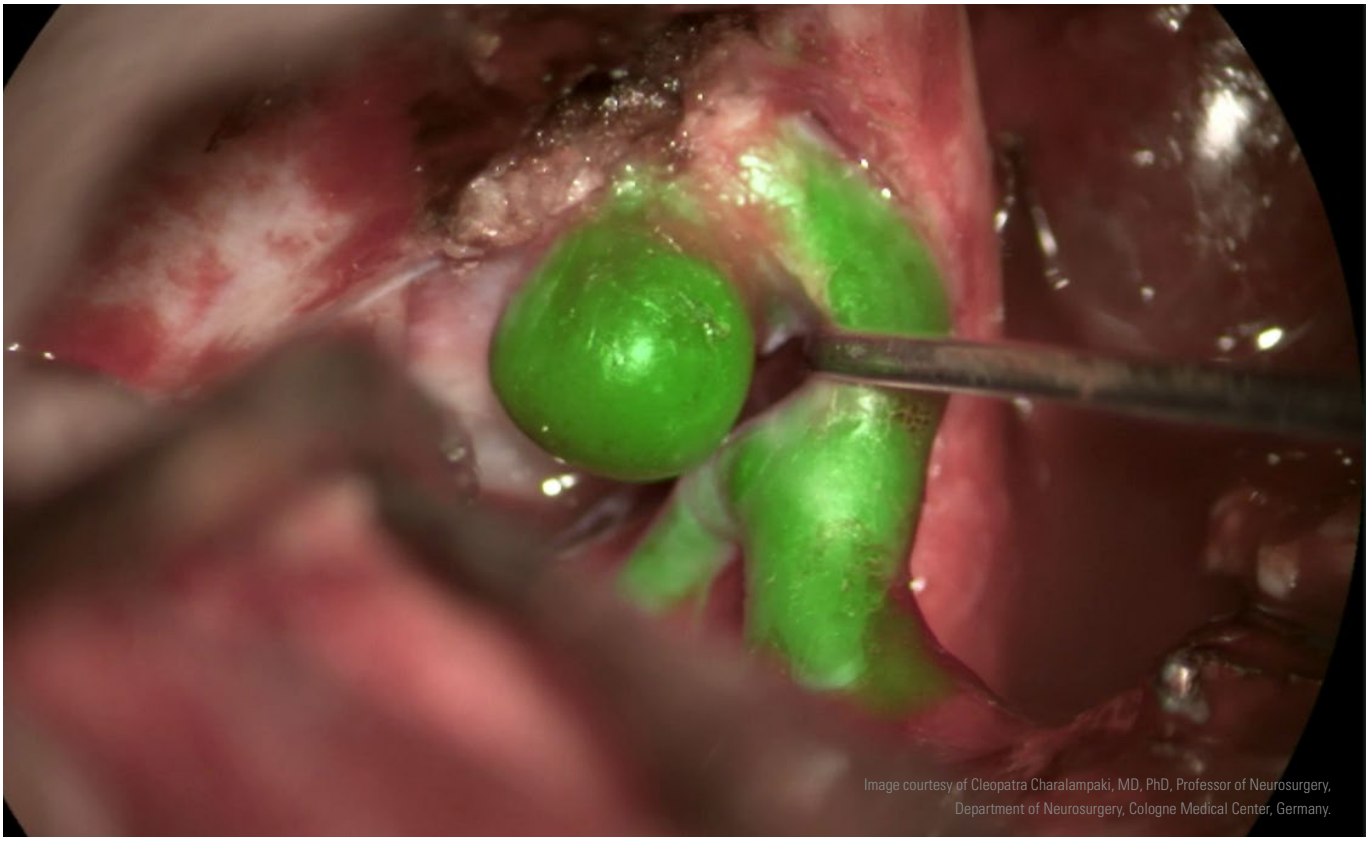

Image courtesy of Cleopatra Charalampaki, MD, PhD, Professor of Neurosurgery, Department of Neurosurgery, Cologne Medical Center, Germany.

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