Application of Intraoperative Indocyanine Green Angiography for CNS Tumors: Results on the First 100 Cases

P. Ferroli, F. Acerbi, E. Albanese, G. Tringali, M. Broggi, A. Franzini, and G. Broggi

Abstract *Purpose*: To investigate the application of indocyanine green (ICG) videoangiography during microsurgery for central nervous system (CNS) tumors.

Methods: One hundred patients with CNS tumors who underwent microsurgical resection from December 2006 to December 2008 were retrospectively analyzed. The diagnosis was high grade glioma in 54 cases, low grade in 17 cases, meningioma in 14 cases, metastasis in 12 cases and hemangioblastoma in 3 cases. Overall, ICG was injected intraoperatively 194 times. The standard dose of 25 mg of dye was injected intravenously and intravascular fluorescence from within the blood vessels was imaged through an ad hoc microscope with dedicated software (Pentero, Carl Zeiss Co., Oberkochen, Germany). Pre-resection and post-resection arterial, capillary and venous ICG videoangiographic phases were intraoperatively observed and recorded.

Results: ICG videangiography allowed for a good evaluation of blood flow in the tumoral and peritumoral exposed vessels in all cases. No side effects due to ICG were observed.

Conclusions: ICG video-angiography is a significant method for monitoring blood flow in the exposed vessels during microsurgical removal of CNS tumors. Pre-resection videoangiography provides useful information on the tumoral circulation and the pathology-induced alteration in surrounding brain circulation. Post-resection examination allows for an immediate check of patency of those vessels that are closely related to the tumor mass and that the surgeon does not want to damage.

Keywords Indocyanine green (ICG) videoangiography · Intracranial tumors · Surgical resection · Venous drainage

Introduction

Angiography with ICG has been first developed in the seventies in Ophthalmology to evaluate choroidal microcirculation [1–6]. Recently, microscope-integrated near-infrared ICG videoangiography has been introduced in Neurosurgery in order to visualize cerebral vessels in case of aneurysm clipping, bypasses and vascular malformations. It has been proven that intraoperative videoangiography with ICG may help to evaluate cerebral vessels that are visible in the surgical field in order to get a real time diagnose of the degree of aneurysm occlusion, vessel patency including the perforating arteries and, in vascular malformations, to distinguish pathologic vessels from normal vessels and arteries from veins based on the timing of fluorescence with the dye [7–20].

To our knowledge, there are no studies in the literature evaluating the potential role of ICG videoangiography during resection of CNS tumors. Therefore, our investigation focused on whether this technique could be used as an intraoperative diagnostic tool to study vascular physiopathology in CNS tumors and whether the information retrieved could be integrated in the decision making-process during surgical removal.

Patients and Methods

In the period between December 2006 and December 2008, almost 1,200 patients affected by CNS tumors were admitted at the III Neurosurgical Unit of the Department of Neurosurgery at the Fondazione IRCCS Istituto Neurologico Carlo Besta in Milan. One hundred of these patients, 67males and 33 females (mean age of 56 years), underwent intraoperative ICG videoangiography and were retrospectively reviewed (Table 1). All patients gave their written informed consent.

Ferroli, Acerbi and Albanese equally contributed to the paper.

P. Ferroli (✉), F. Acerbi, E. Albanese, G. Tringali, M. Broggi, A. Franzini, and G. Broggi
Department of Neurosurgery, Fondazione Istituto Neurologico Carlo Besta, Via Celoria 11, 20133 Milano, Italy
e-mail: ferrolipaolo@hotmail.com

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Table 1 Types of tumors evaluated by Intraoperative ICG video-angiography in our series

Tumor	# Cases
Meningioma	14
Low-grade glioma	17
High-grade glioma	54
Metastasis	12
Hemangioblastoma	3

Surgery was performed using a near-infrared videointegrated microscope (Pentero, Carl Zeiss Co., Oberkochen, Germany). The video records images from the operating microscope, illuminated with a light source including the ICG excitation wavelength, through an optical filter that allows only fluorescence in the ICG emission wavelength. Only vessels directly visible in the surgical field can be visualized. The ICG video angiography was performed before and after tumor removal, following the standard protocol described elsewhere [14–17, 21–29]. Briefly, ICG was administered intravenously by the anesthesiologist (25 mg in 5 ml of saline). Vessel fluorescence appeared after a few seconds and was cleared within 10 min, allowing for additional injections. The resultant video was shown on the microscope screen in the operative room during surgery and recorded for further visualizations.

Histological diagnoses were obtained in all cases and were analyzed together with the intraoperative findings in order to investigate the tumor-related videangiographic features.

Results

ICG Videoangiography was performed before tumor removal in all cases. In 6 cases the operating surgeon avoided to repeat post-resection ICG injection because it was considered useless. No adverse reaction was observed.

ICG videoangiography allowed intra-operative real-time assessment of the exposed vessel with excellent image quality and resolution. Arterial, capillary, and venous phase could be always recognized.

The post-resection arterial phase was able to show, as already demonstrated for vascular cases [7, 8, 12, 14–17, 19, 20], patency of big cerebral arteries that underwent manipulation for the removal of tumors in contact with or fully encasing them (1 planum sphenoidalis meningioma, 2 lesser wing meningiomas, and 2 sylvian metastases). In addition, the arterial phase was considered particularly useful to confirm patency of small arteries dissected free and preserved during tumor removal because they were traversing the surgical field and nourishing at least in part the normal brain parenchyma (Fig. 1). This occurred in 3 out of 54 cases of high grade gliomas and in 4 out of 17 cases of low-grade gliomas. Furthermore, both arterial and capillary phases were useful to diagnose fronto-temporal ischemia after removal of a huge right frontal high grade glioma encasing the middle cerebral artery, due to its intra-operative thrombosis (Fig. 2).

The ICG videoangiographic pre-operative late arterial-capillary phase provided good quality images and videos of the vascular pattern of the CNS area exposed by surgery, well depicting both specific tumor-related alterations and aspecific mass-effect changes. In particular, when the tumor abutted the CNS surface, ICG videoangiography evidenced the pathologic characteristic of the tumor vasculature, both in cases of neo-angiogenic vascular pattern and in cases in which the tumor showed hypoperfused or avascular areas such as in cystic or necrotic masses. In addition, in this context, it was possible to identify artero-venous fistulas, which were common in high grade gliomas, and were identified in 45 out of 54 cases (Fig. 3), typical of hemangioblastomas (3 out of 3 cases) and sometimes observed in metastases (2 out of 12 cases) and rarely in meningiomas (1 out of 14 cases). Aspecific mass-effect changes i.e. brain gyri compressed by the tumor and edema, and congested, were evident in a greater number of cases (all the 71 cases of low and high grade tumors and 5 out of 12 cases of metastases, 5 out of 14 cases of meningiomas).

Regarding the venous phase of ICG videoangiography, this was found useful to identify impaired venous outflow and consequent congestion. This was evident in case of arterovenous fistulae, as detailed above, and in case of direct venous compression by the tumor itself (5 out of 54 cases of high-grade gliomas, 1 out of 12 cases of metastases, 3 out of 14 cases of meningiomas). In addition, ICG videoangiography allowed to identity, when present, the retrograde outflow trough anastomotic veins. These data were useful to decide whether or not to cut a draining vein in order to provide a wider and safer surgical corridor to the tumor itself (10 cases) or to obtain a radical tumor resection (8 cases). Specifically, in case of arterovenous fistulae, when normal veins afferent to the arterialized vein did not show a retrograde flow, these veins were considered the only outflow for the peri-tumoral CNS area. Therefore they were preserved in all cases in order to re-establish a physiologic pre-tumoral condition. On the contrary, when a collateral flow through an anastomotic circle was evident, the arterialized vein was considered un-needed and therefore was cut, without any related post-operative complication. The same considerations were made in cases of a direct venous compression by the tumor.

ICG videoangiography was also used to perform occlusion test with temporary clipping of veins that showed an

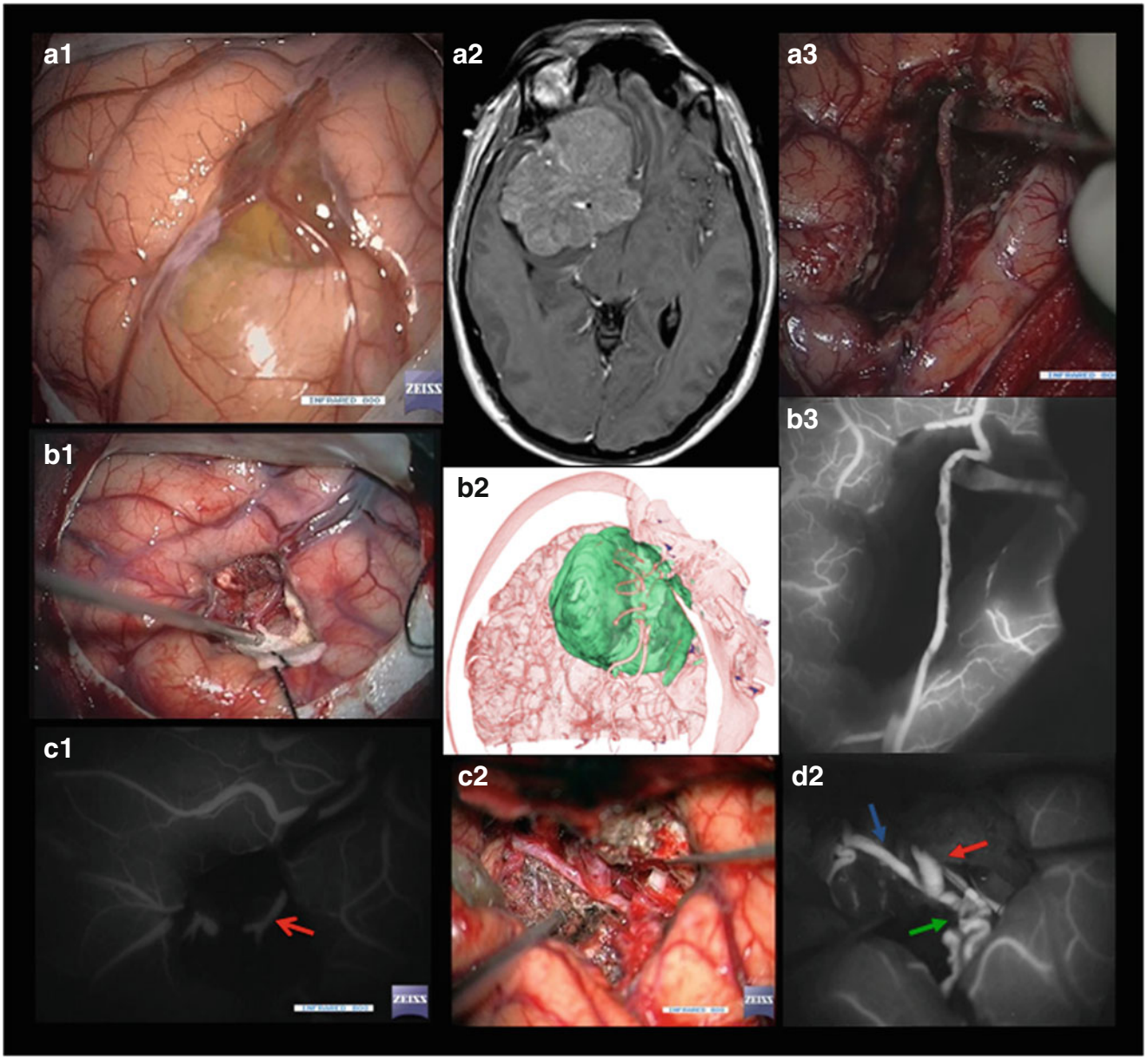

Fig. 1 **a1.** Cystic metastasis: intraoperative view. **b1.** *Post resection view*: the middle cerebral artery and its branches (*arrow*) are visible under the microscope. **c1.** Post-resection ICG videoangiography, arterial phase: the middle cerebral artery (MCA) is well injected (*arrow*). **a2.** Pre-operative MRI (cT1): right etmoido-sphenoidal meningioma with MCA encasement. **b2.** Dextroscope 3D reconstruction to emphasize the encasement of the MCA. **c2.** *Intraoperative view*: post-resection image showing the right internal carotid artery, the anterior and middle cerebral arteries. **d2.** ICG videoangiography, arterial phase: the right internal cerebral artery (*red arrow*), the anterior (*blue arrow*) and middle (*green arrow*) cerebral arteries are patent. **a3.** Post-resection microscopic view in a case of righ rolandic high-grade glioma: the artery over the resected tumor is picked up. **b3.** Post-resection ICG videoangiography: the artery is well injected and patent

intimate relationships with the tumors. This test was used to evaluate the presence of anastomotic circle allowing for venous sacrifice in order to increase the degree of tumor resection.

A summary of videoangiographic results in different tumors is shown in Table 2.

Discussion

The intraoperative ICG videoangiography is a relatively new technique of intraoperative investigation that has been recently applied in the field of Vascular Neurosurgery. Routine or selective use of this technique during surgery of

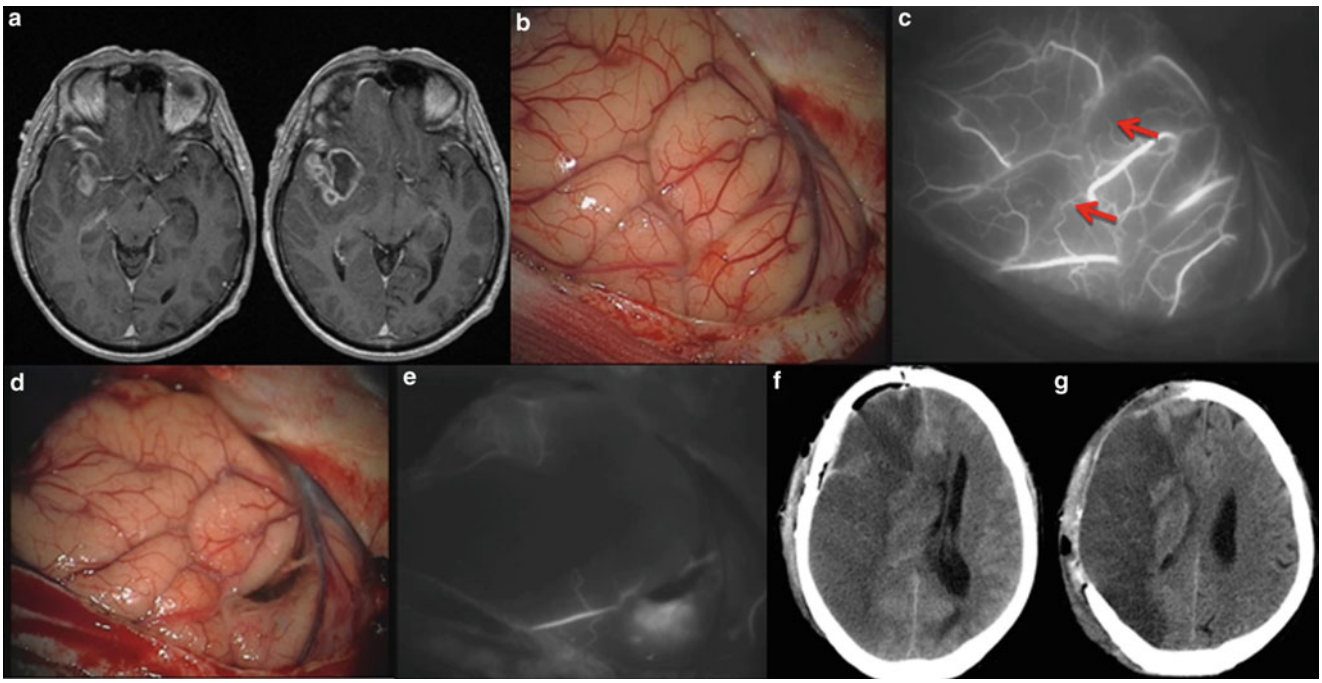

Fig. 2 (**a**) Pre-operative MRI (cT1) showing a fronto-temporal GBM on the right side in close relation with the homolateral middle cerebral artery (MCA). (**b**) Intraoperative view after right fronto-temporal approach and dural opening. Although mannitol was given to the patient, under the microscope the exposed cortex appears congested due to the edema. (**c**) Pre-resection ICG videoangiography: a stagnant flow within the cortical vessels is detected (*arrows*). (**d**) Post-resection view. After tumor removal the surrounding brain appears decompressed. (**e**) Post-resection ICG videoangiography showing no injection of the exposed area of the frontal lobe. An ICP monitoring was therefore positioned (**f**) Due to the increasing of the ICP the patient underwent an early post-operative CT scan. A huge ipodensity of the right hemisphere associated with shift of the structure of the midline was detected. An hemicraniectomy was therefore performed. (**g**) Post-operative CT after decompressive craniectomy

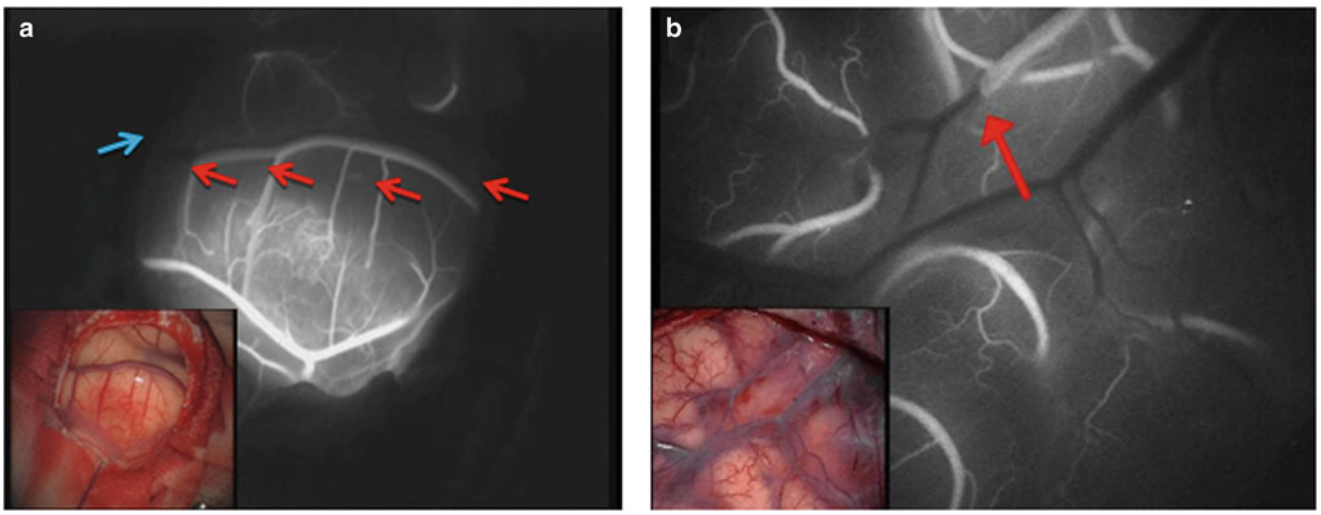

Fig. 3 (**a**) Pre-resection ICG videoangiography in one case of right frontal metastasis (intraoperative microscopic picture in the left corner): in late arterial/capillary phase early injection of arterialized venous vessels (*red arrows*), artero-venous (A-V) fistula, together with physiologic injection of the capillars are visible. The dye is not yet filling the non-arterialized vein (*blue arrow*). (**b**) Pre-resection ICG videoangiography in one case of left frontal high-grade glioma (intraoperative microscopic picture in the left corner): in late arterial/capillary phase an A-V fistula is present (*red arrow*)

vascular malformations and revascularization procedures has been suggested by many authors. It has been proven that intraoperative videoangiography with ICG may help to evaluate cerebral vessels that are visible in the surgical field in order to get a real time diagnose of the degree of aneurysm occlusion and vessel patency including the perforating arteries. In cases of vascular malformations, it can be used to distinguish pathologic vessels from normal vessels and

Table 2 ICG videoangiographic characteristics identified in the three phases, specified for each tumor

Tumor	Arterial phase	Capillary phase	Venous phase
Meningioma	Post-resection vessel patency (3/14)	Pre-resection A-V shunt (1/14)	Pre-resection A-V shunt (1/14)
Low-grade glioma	Post-resection vessel patency (4/17)		
High-grade glioma	Post-resection vessel patency (3/54)	Pre-resection A-V shunt (45/54)	Pre-resection A-V shunt (45/54)
	Post-resection ischemia (1/54)		
Metastasis	Post-resection vessel patency (2/12)	Pre-resection A-V shunt (2/12)	Pre-resection A-V shunt (2/12)
Hemangioblastoma		Pre-resection A-V shunt (3/3)	Pre-resection A-V shunt (3/3)

arteries from veins based on the timing of fluorescence with the dye [7–20].

To our knowledge, there are no studies in the literature investigating the potential role of ICG videoangiography during resection of CNS tumors. The angiographic evaluation of CNS tumor vasculature before surgical removal was the only pre-operative radiological information before the advent of Computerized Tomography and, more recently, Magnetic Resonance. In the early 1920s, Egas Moniz introduced and developed the idea of utilizing X-rays as a method of making visible the blood vessels of the brain and to locate brain tumors. After mapping the normal distribution of the intracranial blood vessels, he clinically used his method in 1927, outlining with X rays the location and size of a patient's brain tumor by the tumor's displacement of injected arteries[25–27]. At that time he defined the angiographic phases that are still used today: arterial, capillary, early and late venous phase. Direct and indirect signs were used to diagnose a brain tumor. The direct signs, i.e. morphological features of the pathological vessels, were utilized to define the nature of the lesion and the indirect signs, i.e. the displacement of the cerebral arteries due to the lesion, were used to locate the tumor [22, 28–31]. Nowadays, the diagnosis of CNS tumors is based mainly on computed tomography and magnetic resonance imaging, however, selective cerebral angiography is still utilized when the neurosurgeon is considering a combined endovascular-surgicalstrategy of treatment in selected cases and it's still the gold standard to evaluate the patency of the dural sinus in oncological cases [32–36].

In this study we had the opportunity to evaluate whether ICG videoangiography could provide some information regarding vascular physiopathology of CNS tumors. We studied a heterogeneous population consisting mainly on high grade gliomas, but including also low grade gliomas, meningiomas, metastases and hemangioblastomas. As already known from previous studies on vascular cases, ICG videoangiography allowed intra-operative real time assessment of the exposed vessel with excellent image quality and resolution. Therefore, we could evaluate only the area exposed by the craniotomy, which, especially for minimally invasive approaches that we routinely use for most of our cases, not always represented the entire area with direct and indirect signs of the tumor's presence. However, arterial, capillary, and venous phase could be recognized in all cases. Therefore, the neovascular architecture, alteration of the calibre, morphology and course of vessels, and the haemodynamic patterns could be studied. The ICG transit time in tumoral vessels was found to be normal or shortened such as in case of malignant tumor (i.e. high grade gliomas and metastases). A short flow-time, due to pathological low-resistance vessels that results in arteriovenous shunting, was found to be common in high grade gliomas, as is the presence of neovascular architecture, dysplastic vessels and thrombosed veins, as previously demonstrated with traditional cerebral angiography [21, 37, 38]. Although the arteriovenous shunts were not always found (45 out of 54 high grade gliomas), an early visualization of the venous compartment was always present. Because arteriovenous shunting causes an arterial steal that leads to hypoperfusion of the surrounding parenchyma, it has been speculated that this mechanism could contribute to local ischemia, eventually causing tissue necrosis. The presence of multiple areas of necrosis suggests that the neovasculature fails to supply the rapidly growing tumor tissue [24]. Sometimes, superficial avascular areas in case of high grade glioma and metastasis, have been seen during pre-resection ICG videoangiography. Although the presence of these vascular characteristics of GBMs have been known for decades, in the last WHO classification there are still controversies on arteriovenous shunts and particularly on the presence/absence of necrosis in GBMs [23, 39]. Although the number of cases studied is low, all the hemangioblastomas, which are peculiar types of tumor, showed the presence of superficial pathologic vessel architecture, with arterovenous fistulae, and arterialized and dilated vein draining the tumor nodule.

Despite the permeability of the blood–brain barrier, the dye does not penetrate the membrane and we were unable to define the margins of the tumor in gliomas and metastases.

Another opportunity offered by this study was to investigate whether the information retrieved by the use of intraoperative ICG videoangiography could be integrated in the decision making process during surgical removal.

First of all, apart from direct visual observation and microvascular Doppler, intraoperative ICG videoangiography was found to be a useful tool for intraoperative assessment of post-resection vessel patency. Microscope-integrated near-infrared ICG videoangiography can confirm

the presence of good flow through the arteries that have been exposed during tumor resection. In addition, in the case of intra-operative diagnosis of stroke, as happened for one of the patient in this series (Fig. 2), the early evidence of this complication leaded to ICU admission with ICP monitoring that allowed for further diagnosis and immediate decompressive craniectomy to reduce intracranial hypertension.

Particularly interesting were the pieces of information provided by ICG videoangiography during the venous phase. The possibility of post-operative complications in case of venous sacrifice during neurosurgical procedures has always been debated [40, 41]. However, there are not definite data on post-operative complications rate, related to the sacrifice of single veins in every patient. Although this risk can be related to the variability of individual pattern of venous drainage, which could be evaluated by pre-operative angiography, it is not possible to investigate the real entity of anastomotic circles because an occlusive test on single veins can not be performed. Our data on ICG videoangiography provide some insights into this discussion. In fact, we could evaluate the pattern of venous drainage of the tumor and the surrounding brain parenchyma in every patient. When vein outflow was impaired, as in case of arterovenous fistulae or direct vein compression by the tumor, ICG videoangiography could offer a unique possibility to intraoperatively evaluate the presence of anastomotic circulation. This result could be achieved through a temporary clipping test of veins closely related to the tumor that evaluated the ICG clearance time of the tested vein. We used this information to evaluate whether vein sacrifice could safely be performed. Interestingly, even if these data have been retrieved on few patients, the favourable outcome in these cases is encouraging and the ICG videoangiography seems to add useful information regarding individual venous variability.

Conflict of interest statement We declare that we have no conflict of interest.

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