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# Confocal Neurolasermicroscopy - Modern Perspectives for Glioma Resection on a Cellular Level

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## 1. Introduction

Confocal neurolasermicroscopy (NLM)(Schlosser et al., 2009 (Epub)) is the current front end of the innovative process in neurosurgery for optimizing the operative results. Hence NLM is the continuance of a protracted development. Microscopic imaging technologies in neurosurgery invented 50 years ago revealed new strategies and possibilities for surgeons. These techniques were first used with magnifying lenses in research for introducing blood into the subarachnoid space in the region of circle of Willis in dog (Lougheed and Tom, 1961). It was further used in cerebrovascular diseases (Jacobson et al., 1962) (Chou, 1963), graft interposition (Woringer and Kunlin, 1963) (Lougheed et al., 1971) and aneurysm surgery (Pool and Colton, 1966) (Rand and Jannetta, 1967). From studies assessing radical surgery in the excision of fluorescence labelled tumours (Stummer et al., 2006) (Stummer et al., 1998) the necessity for a high-resolution imaging technique was clearly evident. Intravital fluorescence microscopy was used in animal studies to investigate tumorangiogenesis and microcirculation (Read et al., 2001) (Vajkoczy et al., 2000).

In the following section our pilot study using NLM in the neurosurgical operating condition is introduced (Schlosser et al., 2009 (Epub)). We aimed to demonstrate a technique with the potential to be adapted intraoperatively to define cellular and subcellular structures during ongoing neurosurgery. Here we show our results of miniaturized confocal lasermicroscopy in normal brain and brain tumor tissue which we termed NLM. Our pilot study was initiated to test the feasibility of this new technique and to open the door for high resolution imaging during ongoing neurosurgery.

## 2. Technical background

We used a miniaturized confocal laser microscope (Optiscan, Australia, Fig. 1) for tissue examination as described earlier (Schlosser et al., 2009 (Epub)). This technique was first described as confocal laser endoscopy in gastrointestinal endoscopy and was used for high-resolution in-vivo imaging while endoscopy of the upper or lower gastrointestinal tract was performed (Kiesslich et al., 2004). The ability to detect or exclude premalignant conditions

and/or other pathologies which were normally not visible created a complete new field of gastrointestinal diagnosis followed by specific treatment before classical histology was accessible (Bojarski et al., 2009). For the use in humans intravenous applied fluorescein sodium distributes throughout the mucosa, however, most of the serum albumin bound fraction of fluorescein highlights the blood vessels and the capillaries.

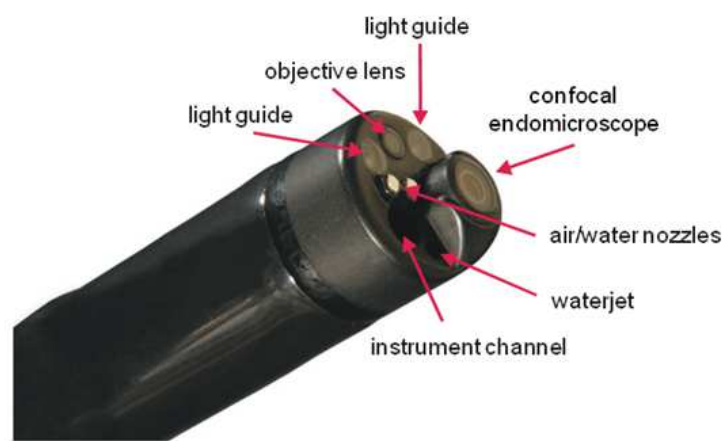


Fig. 1. Distal tip of the confocal endomicroscope EC-3870CIFK (Pentax, Europe) used in gastrointestinal endoscopy. As a protrusion on the end of a conventional endoscope a microscopic lens is mounted (diameter of the lens is 5 mm). All other features of the distal tip are standard in routine endoscopy.

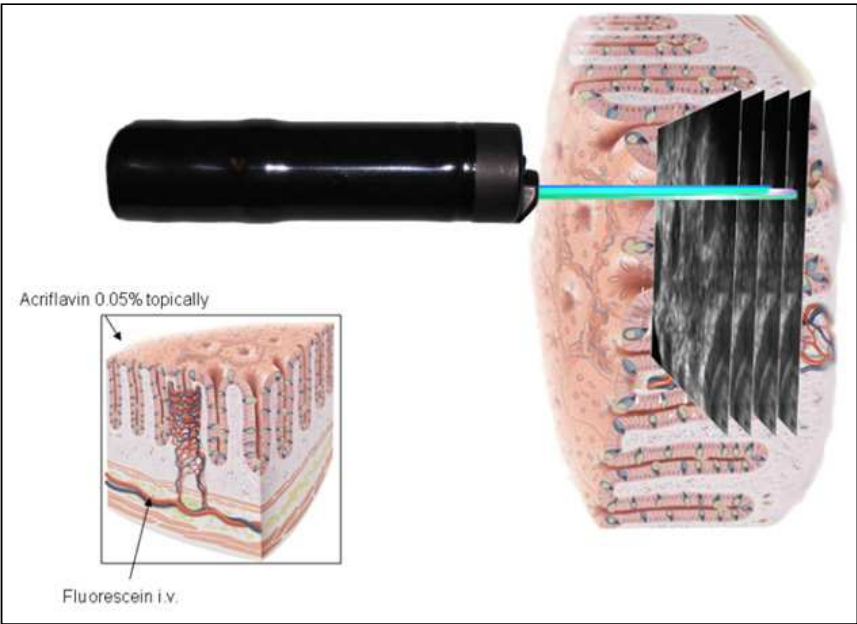


Fig. 2. (With kind permission of Peter Delaney, Optiscan, Australia and Ralf Kiesslich, University Medicine Mainz, Germany). The use of confocal endomicroscopy in human gastrointestinal tract. When the confocal lens was hold in gentle contact with the gastrointestinal mucosa, blue laser light generated a series of images every 7µm up to an imaging depth of 250µm. Typical contrast dyes were fluorescein and acriflavine as indicated.

Topically applied acriflavine hydrochloride (0.05% in saline, Sigma Aldrich, Germany) accentuates the superficial cell borders and their nuclei (Hoffman et al., 2006). Acriflavine is not approved for the use in humans due to a low but theoretical risk of inducing mutagenesis as described in cell culture systems (Ferenc et al., 1999). However, in special clinical indications there are several studies in which this substance was used safely (Leong et al., 2008) (Günther et al., 2010).

### 3. Pilot study

In our pilot study NLM was performed in an ex vivo approach on small tissue samples of patients suspicious to suffer from GBM (WHO IV, n=9) or meningioma (grade I n=2, grade II n=1) after diagnostic radiology. Open tumor resection was performed in the neurosurgical OR in all patients. No prior histological diagnosis was available before neurosurgery. One sample of tumor tissue was used for direct comparison of NLM and histopathology of the same area. After the examination with NLM the specimen was transferred to neuropathology for conventional tissue examination. Additional fragments of the tumor center and border were analysed by NLM. Different additional fragments were sent for conventional pathological diagnosis. These were not marked as study material and therefore assessment and diagnosis was blinded.

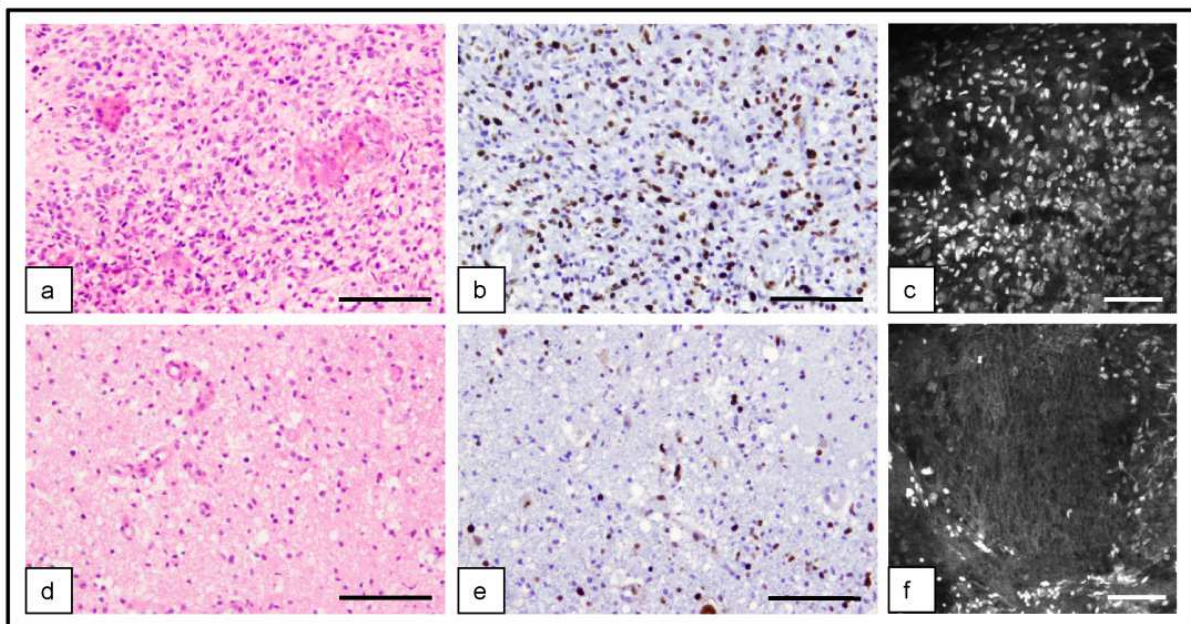


Fig. 3. (Removed with approval Schlosser, *Cen Eur Neurosurg*, 2010, 71(1):13-9)  
Histopathology and Neurolasermicroscopy (NLM) of a GBM (a-f same patient, a-c center; d-f infiltration zone, bar = 100  $\mu$ m). a, d: H&E staining of tumor border (a) and infiltration zone (d). H&E staining of tumor center shows a high density of tumor cells; b, e: immunohistochemical staining with MIB-1 antibody to assess proliferation in tumor center (b) and infiltration zone (e). c, f: NLM of tumor center (c) and infiltration zone (f) with detection of a high density of tumor cells in the center and markedly reduced cell density in the infiltration zone. The margin of the tumor appears similar to a parabolic curve.



Frozen sections were done in 4 out of the 9 patients with GBM and all patients with meningioma (n=3). It was beyond the scope of the present study to directly compare the diagnostic outcome of frozen sections, conventional histology and NLM even because all patients had a final histological confirmation of glioblastoma or meningioma. However, we see some future indications for NLM to contribute to a rapid diagnosis intraoperatively and to reduce the proportion of frozen sections reasonably.

After the tissue sample was coated with acriflavine 0.05% the NLM device was hold in gentle contact with the surface of the tumor and confocal scanning process was initiated. Histological processing included staining with hematoxylin and eosin (HE), periodic acidic Schiff (PAS), silver-impregnation for reticulin or immunohistochemical staining.

Histopathology was performed according to the criteria for GBM of the recent WHO classification respecting the exceptions and subtypes (Louis et al., 2007). In nine patients with histologically proven GBM, in which no case of “small cell glioblastoma” or glioblastoma with oligodendroglial component” occurred, the presence of the following WHO criteria for GBM were analysed in the NLM obtained images: a) cell number and density, b) cell pleomorphism, c) mitotic figures and rate of mitosis (high, moderate, low), d) microvascular proliferation and e) pseudopalisading necrosis. Diagnosis and specific findings of NLM images and conventional histopathology were compared when all data were available. In three patients with histologically proven meningioma typical features were visible with NLM including pleomorphism, onion-skin shaped appearance of tumor cells and single apoptotic cells.

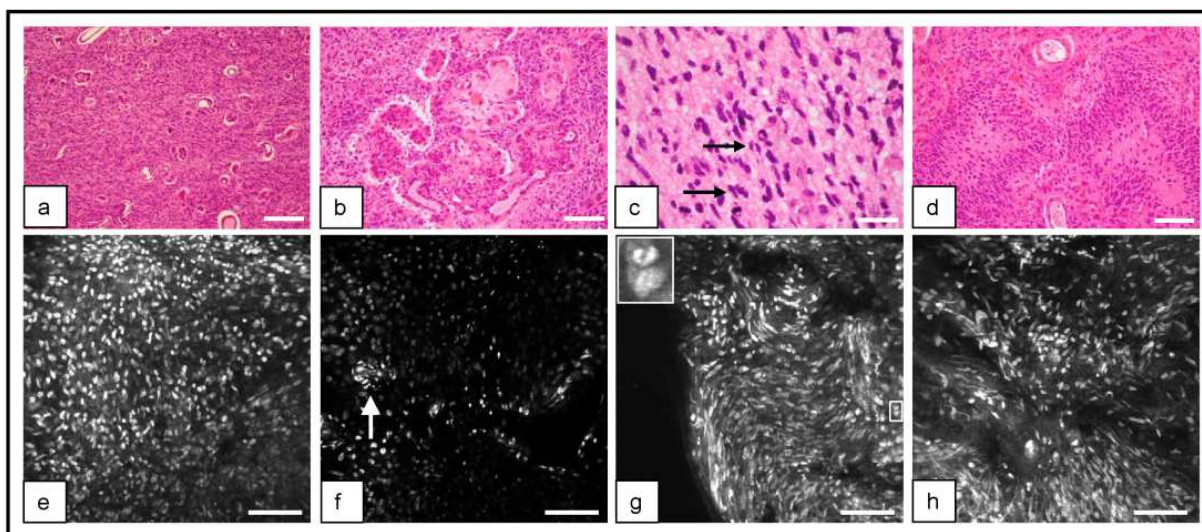


Fig. 4. (Removed with approval Schlosser, *Cen Eur Neurosurg*, 2010, 71(1):13-9) Histology (H&E; a-d, bar = 100  $\mu$ m; c, bar = 50  $\mu$ m) and NLM (e-h, bar = 100  $\mu$ m) of WHO criteria for the diagnosis of GBM. a, e: tumor center with a high density of pleomorphic tumor cells. b, f: microvascular proliferation within the tumor formation (arrow). c, g: mitotic figures (arrows in c, square in g), higher magnification in g shows the mitosis within the nucleus (inset). d, h: pseudopalisading necrosis.

NLM was an easy to handle tool and revealed in all nine patients with GBM and three patients with meningioma typical characteristics of tumor architecture. This unique technique provided evaluable scans for all patients with GBM from the center and from the

border depicting the differences of both areas. The overall image quality was good. In one patient with GBM the scanning images directly correspond to conventional histopathology in all five diagnostic aspects. The WHO criteria for the diagnosis of GBM - cell density, cell pleomorphism, mitoses, microvascular proliferation and pseudopalisading or ischemic necrosis - were all detectable by NLM.

Identification of the infiltration zone or the center of the tumor was possible in any patient by determination of the cell density comparing center and border resection bloc (Fig 3). Further WHO criteria for tumor classification to identify GBM were compared to histology in the same resection bloc and were identified in some but not all patients (Fig. 4).

The NLM images of nine patients with histologically proven GBM were analysed for the presence of WHO criteria of GBM. In all 9 patients cell density and cell pleomorphism were clearly visible with NLM. In 44% of the patients (4/9) microvascular proliferation was visible and in 22% of the patients (2/9) mitosis and stroke like necrosis was identified.

Additional aspects, e.g. apoptotic figures in perinecrotic palisading tumor cells, and important histological structures such as giant cells, fibrillary tumor matrix and blood vessels were also visible with NLM (Fig. 5). Typical features of NLM in patients with histologically proven meningioma are shown in Fig. 6.

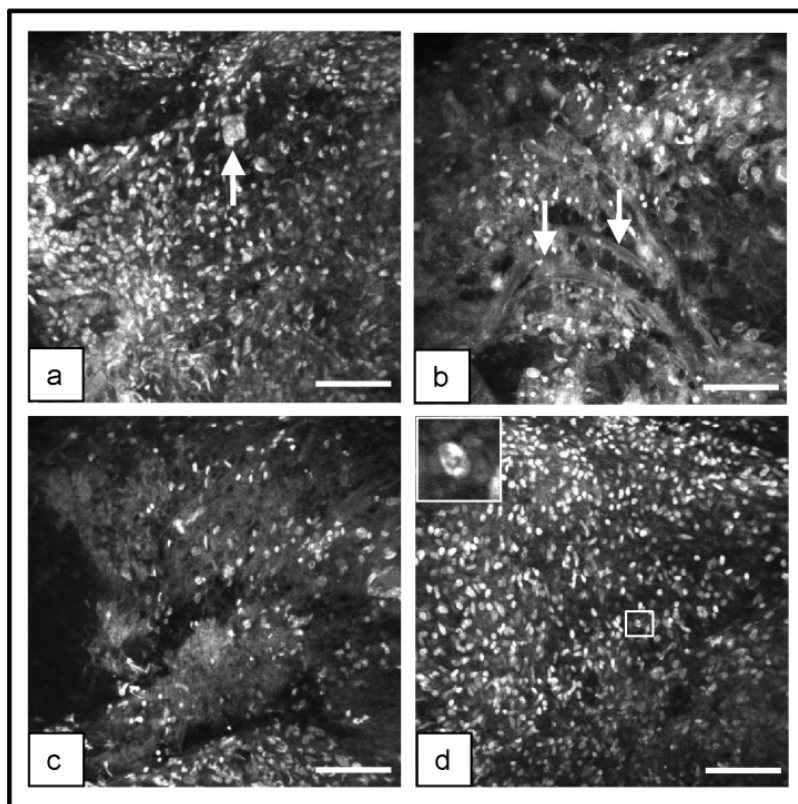


Fig. 5. (Removed with approval Schlosser, *Cen Eur Neurosurg*, 2010, 71(1):13-9) Additional findings of GBM with NLM (bar = 100  $\mu$ m). a: giant cell within the tumor formation. b: pathological blood vessel, the thickened wall of the vessel is clearly visible (arrows). c: necrosis formation in the near of tumor cells. d: apoptotic figure within the tumor center (square), magnification shows characteristic chromatin fragments at the inner side of the nuclear membrane (inset).

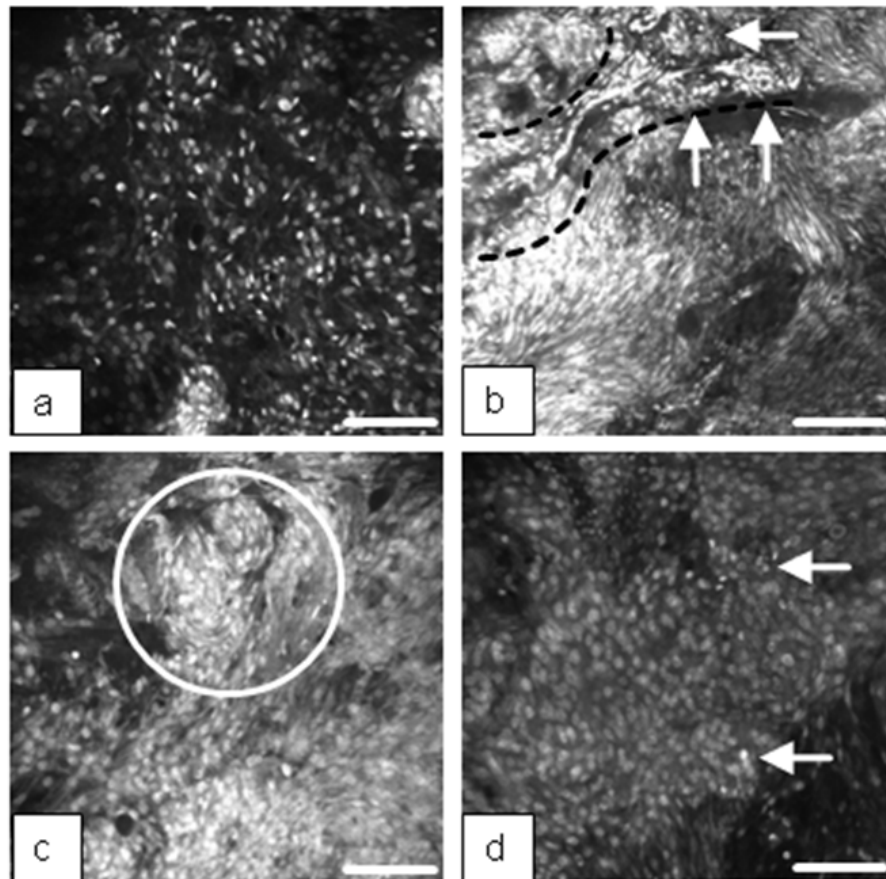


Fig. 6. Representative NLM images from patients with histologically proven meningeoma ( $n=3$ , bar = 100  $\mu\text{m}$ ). a: tumor center with a high density of pleomorphic tumor cells in grade II meningeoma, b: undirected tumor cells with a pathological blood vessel (in between the spotted line) and neoangiogenesis (arrows) in the same patient; c: typical onion-shaped tumor cell configuration in grade I meningeoma (circle), d: single apoptotic cells (arrows) in the tumor border in the same patient.

#### 4. Discussion

Neurolasermicroscopy (NLM) was shown to recognize malignant brain tumor characteristics in patients with histologically proven GBM in our pilot feasibility study (Schlosser et al., 2009 (Epub)). There was a good accordance of the NLM images compared to the histopathological findings with respect to the WHO classification (Louis et al., 2007). The differentiation of more specific tumor entities by NLM should be performed after this promising technique is transferred into the intraoperative situation. Our ex vivo approach opened the door for a neurosurgical in vivo diagnosis on a cellular and subcellular level. Moreover, the combination of confocal laser microscopy and flexible video systems may promote a variety of potential developments eligible for neurosurgical procedures. This ranges from process optimization in the operating room (OR) to new ways to corroborate regenerative therapy (Wessels et al., 2007). Current research data showed the same technique we use in our pilot study to be useful in patients during neurosurgery (Sanai et al., 2011 (Epub), Schlosser, H.G., Bojarski, C. (2011 (Epub)). Confocal Neurolasermicroscopy (NLM). Neurosurgery, Epub.).



## 5. Definition of histological borders

Realizing *in vivo* histology during neurosurgery would contribute to a better definition of the histological borders of the tumor. This would improve the definition of the resection margins significantly. However, due to the infiltrative growth of many primary brain tumours it is not possible to clearly define the exact margins of a tumor mass in all cases, neither by conventional histology nor by NLM. The *in vivo* look on these areas from tumor to intact brain tissue (probably by using a histopathological NLM classification) could provide new insights towards a standardized diagnosis during neurosurgery.

On a cellular basis the excision could be performed as much as necessary but as little as possible which could be beneficial for patients suffering from a brain tumor (Lacroix et al., 2001) (Ammirati et al., 1987). The amount of residual tumor mass after surgery is one of the most important prognostic factors (Burger and Green, 1987) (Wood et al., 1988). NLM scans on a cellular and subcellular level could be more accurate than performing the whole investment of brain navigation even with shift correction (Asthagiri et al., 2007).

Regarding those aspects one has to focus on the appearance of the NLM scans depicting tumor pathologies. Cell types, cell division, neovascularisation and boarder zones have to become acquainted to the observer as well as th possibility for dynamic investigation. This histology is different from the appearance in classical histopathology. So neurosurgeon and pathologist have to share their insight and practically an atlas for defining all pathologies seen in NLM with regard for the process in the theatre has to be developed in the near future.

## 6. Targeted biopsies

Compared to conventional “random” brain tissue biopsies with the possibility of sampling errors NLM allowed “targeted” biopsies which could increase the reliability of the diagnosis when multiple cell types contribute to a tumor.

## 7. Potential indications

By using NLM the process of frozen sections could be influenced considerably. On the one hand thee cellular findings could be discussed between surgeon and pathologist demonstrating different areas and shifting the focus depending on the microscopic results which can affect the further direction of the procedure, on the other hand the NLM scans could be transferred directly to the pathologist via a network with marked reduction of the processing time for serial-cuts. This would also eliminate transfer time of the tissue bloc from the OR to the laboratory.

## 8. Molecular imaging

The presented scans show also vascular and important subcellular aspects contributing to the final diagnosis by predicting typical disease features. The options for biochemical or immunologic *in vivo* imaging by using antibodies or cell surface markers can be evaluated in the future after establishing NLM as an *in vivo* tool for neurosurgery providing a cellular and subcellular view. This subcellular view already enabled physiologic investigations in skin (Lademann et al., 2007) (Suihko et al., 2005).



## 9. Further developments

The next step in evaluating NLM for a diagnostic approach in humans during ongoing neurosurgery would be to utilize an adapted miniaturized confocal instrument specially designed for neurosurgery applications. The technical settings for the laser system can be directly transferred from the system used in this study. However, one important problem should be addressed concerning the reprocessing of the microscopic device. The way of reprocessing will be an essential step to use the microscope in a sterile condition within routine neurosurgical procedures. The first data in humans during ongoing neurosurgery are meanwhile available (Sanai et al., 2011 (Epub), Schlosser, H.G., Bojarski, C. (2011 (Epub)). Neurosurgery, however the problem of reprocessing is not completely fixed. The confocal laser technique for the reusable equipment has been licensed by Zeiss, Germany, for neurosurgery from its initial developer in Australia. Here the integration of NLM into a conventional microscope system is advanced including the option of navigation and matching image-guidance data. A hand-held device has been designed and used in animal research (Sankar et al., 2010) and in humans (Schlosser, H.G., Bojarski, C. 2011 (Epub)). For the reusable system used in endoscopy in the last years a sterilizability has not been achieved. So the application in routine neurosurgical procedures is severely limited. One has to think to introduce a disposable system which is already in clinical use for different applications. An adaptation of a reusable system could be the step to provide a confocal neurolasermicroscope for routine clinical use in neurosurgery.

Furthermore, the use of contrast agents has to be adapted to the in vivo situation. We would prefer using intravenously injected fluorescein (Makale, 2007) instead of topically applied acriflavine. Fluorescein is used for decades in ophthalmology and is permitted as a medical investigational drug with a very low rate of side effects (Lipson and Yannuzzi, 1989). Moreover, fluorescein is an established contrast agent in confocal endomicroscopy in gastroenterology where it distributes the entire gastrointestinal tissue up to 250  $\mu\text{m}$  in depth (Hoffman et al., 2006). When fluorescein is applied in neurosurgery one has to consider the effect of passing the blood brain barrier (BBB), presumably only a small amount of serum albumin unbound fraction of fluorescein will pass BBB and the dye mainly stay intravascular. The amount of cellular staining has to be explored in further studies. In the neoplastic tissue the vessels probably will show a different pattern compared to healthy brain. We would expect abnormal branching and looping of the vasculature as well as abrupt changes in diameter contributing to stricture-like structures. The extravascular distribution of fluorescein, however, in a disturbed BBB as in neoplastic conditions may show the pathologic vascularisation in combination with a cellular staining.

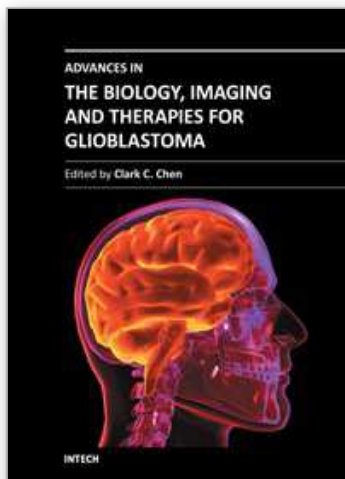
The next step after defining the pathologies in an NLM atlas and after ascertain the affiliated operative proceeding clinical studies have to proof the benefit for the patients depending on the disease.

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This book is intended for physicians and scientists with interest in glioblastoma biology, imaging and therapy. Select topics in DNA repair are presented here to demonstrate novel paradigms as they relate to therapeutic strategies. The book should serve as a supplementary text in courses and seminars as well as a general reference.

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