Clinical Publication Updates Confocal laser endomicroscopy (CLE)

Target group: Sales & HCP
Aim: To provide an overview about recent clinical publications regarding CLE

Author
Medical Affairs MCS

06 February 2026

Neuro indications

Author and Title

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01	Sistiaga IL et al. 2025. Incorporation of intraoperative confocal laser endomicroscopy into the routine workflow of brain surgery
02	Xu Y et al. 2025. A single-institution experience with intraoperative in vivo confocal laser endomicroscopy for brain tumors in 50 patients
03	Muscas G et al. 2025. Operative Microscope In-Field Visualization of Confocal Laser Endomicroscopy Interface (Zeiss CONVIVO®)
04	Carbone F et al. 2025. Confocal Laser Endomicroscopy: Enhancing Intraoperative Decision Making in Neurosurgery
05	Proescholdt MA et al. 2025. MetInfilt: A prospective trial highlighting the importance of the histological growth pattern in brain metastases
06	Restelli F et al. 2025. Confocal endomicroscopy accuracy in identifying central nervous system tumors tissue at the infiltration margins: results from a prospective clinical trial
07	Abramov I et al. 2024. Intraoperative confocal laser endomicroscopy during 5-aminolevulinic acid–guided glioma surgery: significant considerations for resection at the tumor margin
08	Wagner A et al. 2024. Fluorescein-stained confocal laser endomicroscopy versus conventional frozen section for intraoperative histopathological assessment of intracranial tumors

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09	Xu Y et al. 2024. Intraoperative in vivo confocal endomicroscopy of the glioma margin: performance assessment of image interpretation by neurosurgeon users
10	Abramov I et al. 2022. Real-time intraoperative surgical telepathology using confocal laser endomicroscopy
11	Abramov I et al. 2022. Intraoperative confocal laser endomicroscopy: prospective in vivo feasibility study of a clinical-grade system for brain tumors

01 Sistiaga IL et al. 2025

Incorporation of intraoperative confocal laser endomicroscopy into the routine workflow of brain surgery

J Clin Neurosci. 143:111748. Abstract (no open access)

Study design:

- Purpose:
  To evaluate the feasibility of incorporating CLE into the routine workflow of brain tumor surgeries.
- Prospective, single-center
- Patients:
  n=7
- Methods:
  In all cases, the CLE probe was introduced into the surgical field to acquire images at various stages of resection. This was followed by a real-time neuro-pathology assessment of tissue characteristics using a telepathology software platform (TSP). CLE/TSP was employed in conjunction with the planned surgical technique and tools.

Key results:

- **No modifications were required to the planned surgical workflow in any of the cases, and integration of CLE technology alongside standard operating procedures and tools was seamless.**
- The CLE system was used as a co-diagnostic tool in seven consecutive cases. Two cases were performed using minimally invasive approaches. Intraoperative ultrasound was employed in all transcranial cases.
- The surgical microscope was used in four procedures, the exoscope in two, and 5-ALA fluorescence-guided resection was combined with CLE in two cases.

Conclusion:

- **CLE can be successfully integrated into the standard neurosurgical workflow for patients with brain tumors without the need for major procedural modifications, including in microscopic, endoscopic, and minimally invasive tubular approaches.**
- With its seamless integration, CLE holds potential to improve surgical precision, enhance intraoperative decision-making, and contribute to better surgical outcomes.

02 Xu Y et al. 2025

A single-institution experience with intraoperative in vivo confocal laser endomicroscopy for brain tumors in 50 patients

Front Oncol.15:1565935.

ZEISS

Study design:

- Purpose:
  To evaluate the feasibility and diagnostic capability of the first clinically approved CLE system for intraoperative *in vivo* imaging of brain tumors
- Prospective, single-center
- Patients:
  n= 50
  - n=30 were previously analyzed (Abramov et al. 2022)
- Methods:
  CLE images were inter-preted by one CLE-experienced neuro-pathologist as lesional, non-lesional, or non-interpretable and compared to tissue histology

Key results:

- **Overall sensitivity of CLE imaging:** 93%
- **Overall specificity of CLE imaging:** 81%
- **Subgroup analysis:** The specificity differed significantly between core and margin regions of interest (ROIs) in glioma cases (93% vs. 50%, Table 2). Diagnostic performance was not statistically different between new and recurrent glioma cases or between glioma and other tumor types. Subgroup analysis showed consistently high sensitivity (>85%) and PPV (>80%) across all subgroups (Table 2).
- **The diagnostic accuracy rates of CLE imaging and frozen section biopsy results did not statistically differ across all specimens and glioma specimens:** Diagnostic accuracy for all specimens was 89% with CLE and 90% with frozen section. Diagnostic accuracy for Glioma was 87% with CLE and 91% with frozen section.
- **Intraoperative CLE imaging:** The first informative images were acquired within 10.5 s after the initiation of CLE imaging for each ROI. Mean CLE imaging time per case was 8.6 min. Using telepathology consultation extended CLE imaging per case time by 3.8 min.
- **Efficiency of intraoperative CLE imaging:** Telepathology software platform (TSP) consultation enhanced real-time communication between the neurosurgeon and neuropathologist.
- **Cost-effectiveness of CLE imaging:** The cost of CLE imaging is comparable to that of frozen-section biopsies (Table 4).

TABLE 2 Grouped analysis of intraoperative confocal laser endomicroscopy imaging diagnostic accuracy compared with tissue stained with hematoxylin and eosin as the gold standard.

Parameter	Glioma	Glioma core	Glioma margin	Recurrent glioma	New glioma	Non-glioma
Sensitivity	91 (83–98)	94 (81–99)	85 (64–95)	89 (67–98)	92 (78–97)	95 (75–100)
Specificity	77 (60–95)	93 (69–100)	50 (22–78)	78 (55–91)	75 (30–99)	100 (44–100)
PPV	91 (83–98)	97 (85–100)	81 (60–92)	80 (58–92)	97 (85–100)	100 (82–100)
NPV	77 (60–95)	87 (62–98)	57 (25–84)	88 (64–98)	50 (19–81)	75 (30–99)
Diagnostic accuracy (%)	87	94	75	83	90	95

Data are presented as percentage (95% CI), unless otherwise noted.
PPV, positive predictive value; NPV, negative predictive value.

TABLE 4 Cost estimate (US dollars) of three intraoperative diagnostic methods.

Item	Gross cost	Cost per case
Intraoperative CLE imaging*		1,276
CLE system purchase	290,000	223
TSP consultation platform monthly subscription	940 per month	43
Sterile probe sheath	185	185
FNa injection (500-mg vial)	75	75
OR time	5,000 per hour	750
Frozen section biopsy†		1,050
Tissue processing per specimen	200	600
Neuropathologist time per specimen	150	450
Wide-field fluorescence imaging with 5-ALA (1,500-mg vial)	3,350	3,350

*The cost of intraoperative CLE imaging is calculated on a 5-year, five-cases-per-week basis.
†The cost of three specimens per case is shown for frozen section biopsy.
5-ALA, 5-aminolevulinic acid; CLE, confocal laser endomicroscopy; FNa, fluorescein sodium; OR, operating room; TSP, telepathology software platform.

Conclusion:

- The clinically approved CLE system allows intraoperative *in vivo* visualization of tissue histoarchitecture and identification of lesional tissue in real time, without the need for tissue biopsy and processing.
- CLE is efficient and cost-effective, with high diagnostic accuracy at the glioma core. However, CLE imaging at the tumor margin remains challenging.

03 Muscas G et al. 2025

Operative Microscope In-Field Visualization of Confocal Laser Endomicroscopy Interface (Zeiss CONVIVO®)

Oper Neurosurg (Hagerstown). doi: 10.1227/ons.0000000000001560. – Abstract (no open access)

Study design:

- Purpose:
  To explore the impact of an intraoperative integration of the CONVIVO® interface inside the optical field of the operating microscope to allow the neurosurgeon to control both the surgical field and the image quality simultaneously

- Patients:
  n=22
  - n=12 without heads-up integration
  - n=10 with heads-up integration

- Methods:
  The confocal microscopy interface was integrated into the surgical view through the operative microscope (Heads-up display). Patients were randomly allocated to be operated with the heads-up display integration or without it

Key results:

- **Mean CLE usage time:** The mean usage time of the CONVIVO® was 137 seconds, 61.1 seconds for the heads-up display group, and 201.6 seconds for the non–heads-up display group.
- **Usable and nonusable images:** The heads-up display group showed a nonsignificantly higher proportion of usable images (11 vs 50, 21.7%) than the non–heads-up display group (30 vs 163, 18.4%). A significant influence of the intraoperative visualization on overall employment of CLE and a reduced number of images collected (611 vs 2139).

Conclusion:

- By allowing the operator to check the quality of the images directly while still looking inside the operating field, **better-quality images** and a **reduced number of unemployable captures** are obtained, resulting in **more efficient and less time-consuming use of intraoperative confocal microscopy**, ultimately leading to reduced operative length.

Confocal Laser Endomicroscopy: Enhancing Intraoperative Decision Making in Neurosurgery

Diagnostics (Basel).15(4):499. **REVIEW**

Key results:

- **Current fields of application of CLE**: The review gives an overview on current fields of application of CLE in neuro-oncological surgery (Table 2).
- **CLE for the Identification of Glioma Margins:** Recent advancements have demonstrated the value of CLE in intraoperative glioma management. Studies highlight CLE's capacity to delineate infiltrative glioma margins with a diagnostic accuracy that approaches that of conventional histology.
- **Integration of CLE with Deep Learning**: Deep learning techniques, particularly deep convolutional neural networks (DCNNs), are crucial for maximizing the potential of CLE imaging. By automating the analysis of extensive datasets, DCNNs enhance the speed and accuracy of intraoperative diagnoses, addressing critical challenges such as non-diagnostic images, tumor classification, and feature localization.
- **Real-Time Telepathology as an Adjunct in the Surgical Theater:** Telepathology represents a significant development in neurosurgery, improving intraoperative communication and decision making while addressing limitations of traditional diagnostic methods, such as discrepancies caused by imprecise or inadequate tissue sampling, artifacts generated during frozen section preparation, and errors arising from tumor heterogeneity across regions.
- The review provides an overview of direct and indirect visualization tools (Table 1, not shown) and includes a summary of the main outcomes of the *in vivo* experiences of CLE (Table 3, not shown).

Table 2. Current fields of application of CLE in neuro-oncological surgery.

Field of Application	Roles
Tumor Margin Identification	Distinguishes between tumor and healthy brain tissue during surgery, aiding maximal resection while preserving critical structures [46].
Intraoperative Histological Analysis	Provides real-time optical biopsies, enabling rapid pathological assessment without traditional histology [46].
Glioma Surgery	Enhances precision in glioma resection by identifying infiltrative tumor margins, especially in eloquent areas [47].
Brain Metastases	Differentiates metastases from surrounding edema or reactive changes [48].
Guidance for Minimally Invasive Surgery	Integrated into endoscopic procedures for real-time tissue characterization during minimally invasive surgeries [49].
Surgical Training and Research	Provides a platform for neurosurgical education and exploring tissue pathology, advancing research on tumor biology [50].

Conclusion:

- **CLE enhances intraoperative visualization** by distinguishing malignant from healthy tissue in real time. Integrated **fluorescence contrast agents enhance surgical precision** during resection and tissue sampling.
- **Deep learning reduces interpretive challenges**, filtering non-diagnostic images and highlighting critical pathologies.
- **Telepathology platforms further augment CLE's impact by enabling remote, real-time neurosurgeon–pathologist collaborations**, thus expediting decisions.
- **CLE complements established techniques like frozen sections, accelerating workflows and improving diagnostic accuracy.**

05 Proescholdt MA et al. 2025

MetInfilt: A prospective trial highlighting the importance of the histological growth pattern in brain metastases

Transl Oncol. 60:102480.

Study design:

- Purpose:
  To standardize the collection and analysis of the histological growth pattern (HGP) at the macro-metastasis / brain parenchyma interface (MMPIbrain)
- Prospective
- Patients:
  n=50
  n=44 included in analysis
- Methods:
  1. Preoperative: Definition of target area in MRI
  2. Intraoperative: Transference into neuro-navigation, Intravital confocal microscopy & Fluorescein sodium-assisted sample acquisition
  3. Postoperative: Assessment of HGP with immuno-histochemistry (IHC)

Key results:

- **Successful tissue acquisition from the MMPIbrain:** From the 44 patients that were included in the analysis, the MMPIbrain was successfully acquired in 93.2% of the cases (41/44). In 3/41 patients (7.3%), the HGP could not be reliably assessed due to the limited brain tissue. The HGP of the remaining 38 patients (92.7%) in which the HGP could be undoubtedly evaluated was categorized into three groups: noninfiltrative, epithelial infiltrative, and diffuse infiltrative.
- **CONVIVO accurately visualized the MMPIbrain intraoperatively:** In the metastases where a non-infiltrative HGP was determined histologically, the CONVIVO images revealed a clearly demarcated interface (Fig. 3A), whereas in metastases with epithelial and diffuse infiltrative HGPs, infiltrative metastatic cells could be detected in the gliosis already intraoperatively (Fig. 3B-C). Remarkably, in the CONVIVO images of diffuse infiltrative HGPs, the transition area between the metastatic cells and the brain was almost not distinguishable (Fig. 3C).
- **CONVIVO pictures consistently reflected the HGPs confirmed postoperatively by IHC**. Importantly, in most cases in which the MMPI could not be reliably assessed by postoperative histology, either because of the absence of metastatic tissue (radionecrosis) or the limited brain tissue, the CONVIVO endomicroscopy findings were classified as inconclusive.
- **Preoperative MRI patterns strongly correlated with infiltrative HGPs:** MRI findings showed a specificity of 100% and a sensitivity of 79.3% for predicting infiltrative HGPs at the MMPIbrain.
- Exploratory analyses suggest that infiltrative HGPs might negatively impact patient prognosis and represent a potential risk of meningeal metastasis. There was no statistically significant association between primary tumor and HGP.

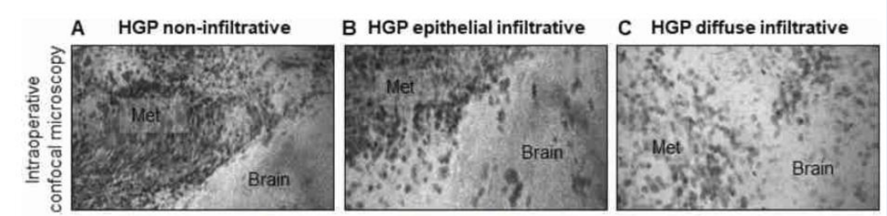

Fig. 3. Evaluation of the HGP at the MMPIbrain. Representative pictures of (A) non-infiltrative, (B) epithelial infiltrative, and (C) diffuse infiltrative HGPs visualized by intraoperative confocal microscopy.

Conclusion:

- This neurosurgical protocol allows the successful and precise acquisition of tissue from the MMPIbrain through presurgical imaging, intraoperative microscopy, and fluorescence-assisted sampling.
- These results demonstrate the adecuacy of intravital CONVIVO microscopy in visualizing the MMPIbrain intraoperatively and point to MRI as a feasible non-invasive method to detect infiltrative HGPs at the MMPIbrain.

06 Restelli F et al. 2025

Confocal endomicroscopy accuracy in identifying central nervous system tumors tissue at the infiltration margins: results from a prospective clinical trial

J Neurosurg Sci. doi: 10.23736/S0390-5616.24.06302-1.

Study design:

- Purpose:
  To assess the intraoperative usefulness of confocal laser endomicroscopy (CLE) in an *in-vivo* setting, focusing on its capability to explore the presence of residual tumor at the resection margins of Central Nervous System (CNS) tumors
- Prospective
- Patients:
  n=75
- Methods:
  1. CLE images from virtual biopsies at the central tumor core and at its margin of resection
  2. Interpretation of permanent or frozen sections (pathologist was totally blinded to histological results)

Key results:

- **Accuracy of CLE in the identification of tumor tissue at the margins:** Considering only GBM and Grade 4 IDH-mutated Astrocytoma an accuracy in identifying tumor tissue at the margins of resection of 82.2% was found (sensitivity 86.5%, specificity 72.7%, PPV 87.7% and NPV 70.6%, see Table 2).

  Considering all tumors together, the accuracy of CLE in identifying tumor tissue at its margins was 85.8% (SN 89.6%, SP 79.4%, PPV 88.0% and NPV 82.0%, see Table 2).
- **Concordance of diagnosis between CLE images and histological analysis at the central core:** At the tumor center, a correct intraoperative diagnosis was obtained in 67.6% of all the cases, and in 80.9% of the GBM/Grade 4 IDH-mutated astrocytoma subgroup (see Table 2).
- **Diagnostic accuracy between frozen and histological sections:** Concordance of 88.9% for the entire group of tumors and 87.8% for GBM/ Grade 4 IDH-mutated astrocytoma.
- **No patient experienced adverse events from FNa administration or intraoperative CLE use.**

TABLE II.—*Analytical results of the study. Results subdivided according to primary/secondary endpoints and tumor margins/tumor center.*

Endpoints	Results	Morphological and cellularity patterns
Primary endpoints		
Tumor margins: tumor identification at the margin of resection in aggressive gliomas ° (CONVIVO® *vs.* HISTOLOGY*)	Accuracy: 82.2% [95% CI 75.0-89.5%] Sensitivity: 86.5% [95% CI 76.5-93.3%] Specificity: 72.7% [95% CI 54.5-86.7%] Positive predictive value: 87.7% [95% CI 77.9-94.2%] Negative predictive value: 70.6% [95% CI 52.5-84.9%]	Complete/partial concordance for morphological discrimination: 80.4% Complete/partial concordance for cellularity discrimination: 96.1%
Tumor center: diagnosis at the tumor center in all tumor subtypes (CONVIVO® *vs.* HISTOLOGY*)	Concordance: 67.6% [95% CI 56.9-78.2] (80.9% [95% CI 69.1-92.8] for aggressive gliomas° only)	Complete/partial concordance for morphological discrimination: 87.8% (100.0% for aggressive gliomas° only) Complete/partial concordance for cellularity discrimination: 91.4% (92.5% for aggressive gliomas° only)
Secondary endpoints		
Tumor margins: tumor identification at the margin of resection in all tumor subtypes (CONVIVO® *vs.* HISTOLOGY*)	Accuracy: 85.8% [95% CI 80.5-91.1] Sensitivity: 89.6% [95% CI 82.2-94.7] Specificity: 79.4% [95% CI 67.3-88.5] Positive predictive value: 88.0% [80.3-93.4] Negative Predictive Value: 82.0% [70.0-90.6]	Complete/partial concordance for morphological discrimination: 83.4% Complete/partial concordance for cellularity discrimination: 97.5%
Tumor center: diagnosis at the tumor center in all tumor subtypes (CONVIVO® *vs.* FROZEN)	Concordance: 61.1% (73.2% for aggressive gliomas° only)	Complete/partial concordance for morphological discrimination: 84.7% (95.1% for aggressive gliomas° only) Complete/partial concordance for cellularity discrimination: 86.8% (89.7% for aggressive gliomas° only)
Diagnosis at the tumor center in all tumor subtypes (FROZEN *vs.* HISTOLOGY*)	Concordance: 88.9% (87.8% for aggressive gliomas° only)	

° GBM and Grade IV IDH-mutated astrocytoma; *for each biopsy and for each comparison histological analysis was always used as the reference exam.

- **Efficient workflow:** The workflow assured by using CLE can be much more efficient, compared to the use of frozen section, with a reduction of workload for the neuropathologist (<4 minutes in average for CLE images interpretation) and a significant shorter timing for the whole process to be completed.

Conclusion:

- CLE images were evaluated intraoperatively by a pathologist who was blinded to the intraoperative tissue fluorescence and to the corresponding histological image. Such aspect strengthens the reliability of CLE as an effective intra-operative tool to correctly guide surgical strategy regarding resection.
- The in vivo application of a newly available CLE system allows for an accurate assessment of the margin of resection during removal of different types of CNS tumors, raising the possibility of exploring CLE meaning in increasing extent of resection (EOR) in CNS tumors.

07 Abramov I et al. 2024

Intraoperative confocal laser endomicroscopy during 5-aminolevulinic acid–guided glioma surgery: significant considerations for resection at the tumor margin

J Neurosurg. p.1-14.

Study design:

- Purpose:
  To analyze the simultaneous use of intraoperative fluorescein sodium (FNa) confocal laser endomicroscopy (CLE) and operating microscope 5-aminolevulinic acid (5-ALA) fluorescence imaging for glioma resection to improve CLE use for better margin discrimination
- Patients:
  n=33 with glioma
- Methods:
  1. CLE imaging of tumor margins
  2. 5-ALA wide-field imaging
  3. Tissue biopsies to compare CLE imaging and 5-ALA imaging to permanent histological sections

Key results:

- **Concordance with permanent histological sections:** Permanent histological sections from the corresponding regions were concordant with the interpretation of FNa CLE images in 57 of 88 (65%) regions of interest (ROIs) and with the interpretation of 5-ALA imaging in 43 of 88 (49%) ROIs.
- **Diagnostic performance for the interpretation of tumor margins:**
  - **Sensitivity of FNa CLE:** 73%
  - **Specificity of FNa CLE:** 41%
  - **Positive predictive value (PPV) for CLE:** 79%
  - **Negative predictive value (NPV) for CLE:** 33%

  Sensitivity of 5-ALA: 38%

  Specificity of 5-ALA: 82%

  Positive predictive value (PPV) for 5-ALA: 86%

  Negative predictive value (NPV) for 5-ALA: 31%
- **Most of tumor-margin ROIs that were correctly discerned by CLE as tumoral lacked 5-ALA–induced fluorescence.**

Conclusion:

- Conventional intraoperative evaluation of tumor margins, based on MRI and wide-field fluorescence imaging, can underestimate the invasiveness of gliomas.
- **Due to FNa CLE accuracy in detecting regions with infiltrating tumors it can be considered as a supplement to 5-ALA in guiding glioma resection at tumor margins.**

08 Wagner A et al. 2024

Fluorescein-stained confocal laser endomicroscopy versus conventional frozen section for intraoperative histopathological assessment of intracranial tumors

Neuro Oncol. 26(5):922-932.

Study design:

- Purpose:
  To evaluate fluorescein-stained intraoperative confocal laser endomicroscopy (CLE) of intracranial lesions in comparison to routine intraoperative frozen section (FS) assessment
- Phase II noninferiority, prospective trial
- Multicenter (3 centers in Germany: Munich, Regensburg, Mannheim)
- Patients:
  n=210

Key results:

Table 3. Accuracies of the CLE and FS Methods Referenced With the Final Histopathological Diagnosis

		Final Histopathology									
		Metastasis	LGG	HGG	Meningioma	Schwannoma	Ependymoma	Reactive	Inflammation	Other	Sum
CLE	Metastasis	42	0	2	0	0	0	2	0	3	49
	LGG	0	5	1	0	0	0	0	0	3	9
	HGG	6	3	73	1	0	0	0	0	1	84
	Meningioma	0	0	1	44	1	0	0	0	0	46
	Schwannoma	0	0	0	1	3	0	0	0	0	4
	Ependymoma	0	0	0	0	0	2	0	0	0	2
	Reactive	0	0	0	0	0	0	1	0	0	1
	Inflammation	0	0	0	0	0	0	0	1	0	1
	Other	1	1	0	0	0	0	0	0	5	7
	Sum	49	9	77	46	4	2	3	1	12	203
FS	Metastasis	41	0	1	1	0	0	0	0	0	43
	LGG	0	7	0	0	0	0	0	1	0	8
	HGG	0	0	72	0	0	0	0	0	0	72
	Meningioma	0	0	0	45	0	1	0	0	0	46
	Schwannoma	0	0	0	0	4	0	0	0	0	4
	Ependymoma	0	0	0	0	0	1	0	0	0	1
	Reactive	0	1	2	0	0	0	2	0	0	5
	Inflammation	0	0	0	0	0	0	0	0	0	0
	Other	8	1	2	0	0	0	1	0	12	24
	Sum	49	9	77	46	4	2	3	1	12	203

Abbreviations: CLE, confocal laser endomicroscopy; FS, frozen section; HGG, high-grade glioma; LGG, low-grade glioma. Orange hue denotes "correct" diagnosis of respective method in concordance with final histopathology; blue hue denotes "incorrect" diagnosis.

- **Diagnostic accuracy compared to final histopathological assessment:**
  CLE was 87% (across all intracranial entities) – [non-inferiority not met]
  FS was 91% (across all intracranial entities)
  Subgroup comparisons should be avoided due to unselected patient population.
- **Concordance between CLE and FS diagnoses** was 76%
- **Median time until intraoperative diagnosis**:
  CLE was 3 min (range 1 – 15 min, whereby only 1 CLE procedure took >10 min)
  FS was 27 min (range 10 – 110 min)
  Mean difference: 27.5 min
- **Adverse events:**
  None of the adverse events graded 3–5 and none of the serious adverse events were rated as related to either the CLE or fluorescein.
- **Reasons why non-inferiority was not met:**
  Unselected patient population with a range of brain tumor entities
  Applying CLE is governed by a learning curve
  Accuracy achieved with FS was relatively high (usually ranges between 85-90%).

Conclusion:

- CLE allowed for a **safe and time-effective** intraoperative histological diagnosis with a **diagnostic accuracy of 87%** across all intracranial entities included.
- The technique achieved **histological assessments in real time with a 10-fold reduction of processing time compared to FS**, which may invariably impact surgical strategy on the fly.

09 Xu Y et al. 2024

Intraoperative in vivo confocal endomicroscopy of the glioma margin: performance assessment of image interpretation by neurosurgeon users

Front Oncol.14:1389608.

Study design:

- Purpose:
  To assess the neurosurgeons' ability to interpret confocal laser endomicroscopy (CLE) images from glioma margins and compare their assessments to those of neuropathologists
- Retrospective, Multicenter
- Assessment by four CLE-experienced neurosurgeons
- n=4275 images from 56 glioma margin regions
- Methods:
  - Numerical scoring system classified in 6 categories based on the FNa signal, cellularity, cytological atypia, and histo-architectural distortion
  - Dichotomous scoring system based on pathological features

Key results:

- **Inter-rater agreement for neurosurgeons:** 61% with the numerical scoring system and 83% with the dichotomous scoring system. The concordance between the numerical and dichotomous scoring systems was 93%.
- **Overall sensitivity:** Overall sensitivity in neurosurgeon group was 78% using the numerical scoring system and 80% using the dichotomous scoring system (Table 4).
- **Overall specificity:** Overall specificity in neurosurgeon group was 32% using the numerical scoring system and 27% using the dichotomous scoring system (Table 4)
- **Positive predictive value (PPV):** PPV in neurosurgeon group was 62% using the numerical scoring system and 61% using the dichotomous scoring system (Table 4).
- **Negative predictive value (NPV):** NPV in neurosurgeon group was 50% using the numerical scoring system and 48% using the dichotomous scoring system (Table 4).
- **No statistically significant differences in diagnostic performance were found between the neurosurgeons and neuropathologists.**

Table 4

Diagnostic performance of confocal laser endomicroscopy imaging at glioma margins*.

Group	Sensitivity	Specificity	PPV	NPV
Neurosurgeons				
Dichotomous scoring system				
Newly diagnosed glioma	79 (68-90)	27 (13-41)	61 (49-72)	48 (26-69)
Recurrent glioma	81 (71-89)	27 (15-40)	62 (52-72)	48 (29-67)
All	80 (73-87)	27 (18-37)	61 (54-69)	48 (34-62)
Numerical scoring system				
Newly diagnosed glioma	78 (67-89)	30 (16-44)	60 (49-71)	50 (30-70)
Recurrent glioma	77 (68-87)	33 (20-47)	63 (53-73)	50 (33-67)
All	78 (70-85)	32 (22-42)	62 (54-69)	50 (37-63)
Neuropathologists				
Numerical scoring system				
Newly diagnosed glioma	76 (65-88)	48 (32-63)	65 (53-77)	61 (44-78)
Recurrent glioma	80 (71-90)	28 (16-40)	61 (51-71)	50 (31-69)
All	79 (71-86)	37 (27-47)	63 (55-70)	56 (43-69)

NPV, negative predictive value; PPV, positive predictive value.

*Values are presented as % (95% confidence interval).

Conclusion:

- Neurosurgeons' performance in CLE image interpretation of glioma margins was comparable to that of neuropathologists.
- **CLE might be used as an intraoperative guidance tool with neurosurgeons interpreting the CLE images** with or without assistance from neuro-pathologists. Nonetheless, this does not obviate the need for neuropathologists' expertise, especially, for example, where imaging shows unusual histoarchitectural features, in rare tumors, or near or in eloquent cortical regions.

10 Abramov I et al. 2022

Real-time intraoperative surgical telepathology using confocal laser endomicroscopy

Neurosurg Focus. 52(6):E9.

Study design:

- Purpose:
  To evaluate the feasibility of using an innovative surgical telepathology software platform (TSP) to establish real-time, on-the-fly remote communication between the neurosurgeon using confocal laser endomicroscopy (CLE) and the pathologist
- Prospective, single-center
- Patients:
  n=11
  - n=6 Glioma
  - n=3 Other primary tumor
  - n=1 Metastasis
  - n=1 Reactive brain tissue

Key results:

- **Durations of acquisition of the optical biopsy:** Mean duration of CLE system use was 1 ± 0.3 minutes/case and 0.25 ± 0.23 seconds/optical biopsy (Fig. 2). Frozen sections were processed within 23 ± 2.8 minutes, which was significantly longer than CLE usage ($p < 0.001$).
- **Duration for first image with identifiable histopathological features:** 6 ± 0.1 seconds
- **Diagnostic accuracy:** Video-flow CLE was used to correctly interpret tissue histoarchitecture in 96% of optical biopsies, which was substantially higher than the accuracy of using still CLE images (63%, Fig. 4) ($p = 0.005$).
- **Complications**: No patient experienced any complications associated with CLE usage or fluorescein sodium (FNa) related adverse effects.

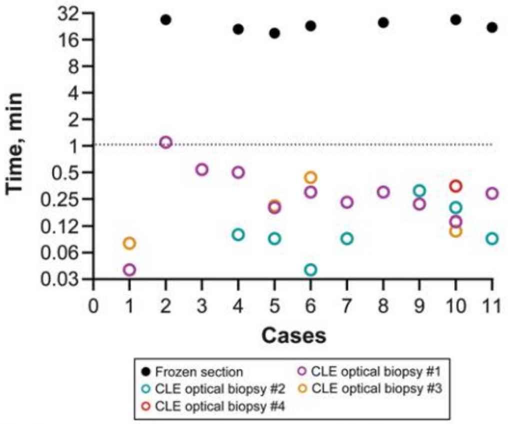

FIG. 2. Scatterplot showing durations of acquisition of the optical biopsy with CLE and frozen section processing per case. On average, acquisition of the optical biopsy with CLE did not exceed 1 minute/case. The *dashed line* represents the 1-minute cutoff.

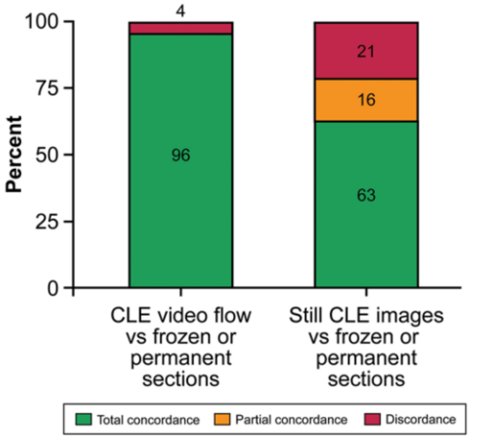

FIG. 4. Diagnostic concordance between video-flow CLE imaging and still CLE image interpretation and frozen or permanent histological analysis.

Conclusion:

- When CLE is employed in tandem with a TSP, neurosurgeons and pathologists can **view and interpret CLE images remotely and in real time** without the need to biopsy tissue.
- The TSP allows neurosurgeons to receive real-time feedback on the optically interrogated tissue microstructure, thereby **improving cross-functional communication and intraoperative decision-making and resulting in significant workflow advantages over the use of frozen section analysis.**

11 Abramov I et al. 2022

Intraoperative confocal laser endomicroscopy: prospective in vivo feasibility study of a clinical-grade system for brain tumors

J Neurosurg. 138(3):587-597.

Study design:

- Purpose:
  To evaluate the feasibility of confocal laser endomicroscopy (CLE) system using fluorescein sodium for intraoperative in vivo imaging of brain tumors
- Prospective, single-center
- Patients:
  n=30 with 31 brain tumors
  - n=13 Glioma
  - n=5 Meningioma
  - n=6 Other primary tumor
  - n=3 Metastasis
  - n=4 Reactive brain tissue

Key results:

- **CLE image acquisition:** Overall, 10,713 CLE images from 335 regions of interest were acquired. The first interpretable image was acquired within a mean of 6 (SD 10) images and within the first 5 (SD 13) seconds of imaging.
- **Interpretable image acquisition**: 4,896 images (46%) were interpretable. Interpretable image acquisition was positively correlated with study progression, number of cases per surgeon, cumulative length of CLE time, and CLE time per case ($p \leq 0.01$).
- **Duration of use of CLE system:** The mean duration of the use of the CLE system was 7 minutes (range 3-18 minutes).
- **Diagnostic accuracy:** The diagnostic accuracy of CLE compared with frozen sections was 94% and compared with permanent histological sections 92% (Table 2).
- **Sensitivity**: The sensitivity of CLE compared with frozen sections was 94% and compared with permanent histological sections 90% (Table 2).
- **Specificity**: The specificity of CLE compared with frozen section was 100% and compare with permanent histological sections 94% (Table 2).

TABLE 2. Predictive attributes of CLE compared with frozen sections and conventional histology sections in samples from 30 patients treated for brain tumors

Value	CLE vs Frozen Sections, All Samples	CLE vs Permanent Histology Sections		
		All Samples	Glioma	Reactive Brain Tissue
Diagnostic accuracy, %	94	92	93	82
Sensitivity, %	94 (72–100)	90 (78–96)	91 (72–98)	0 (0–95)
Specificity, %	100 (18–100)	94 (74–100)	100 (65–100)	90 (60–100)
PPV, %	100 (80–100)	97 (87–100)	100 (84–100)	0 (0–95)
NPV, %	67 (12–98)	81 (60–92)	78 (45–96)	90 (60–100)

Values in parentheses are 95% CIs. Conventional histology sections were stained with H&E.

Conclusion:

- The clinical-grade CLE system allows **in vivo, intraoperative, high-resolution cellular visualization** of tissue microstructure and **identification of lesional tissue patterns in real time**, without the need for tissue preparation.

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