National Board of Examinations - Journal of Medical Sciences
Volume 3, Issue 6, Pages 631–640, June 2025
DOI 10.61770/NBEJMS.2025.v03.i06.002

ORIGINAL ARTICLE

Intraoperative ICG Dye Monitoring for Identification of Pituitary Adenoma in Endoscopic Transsphenoidal Surgery: A Prospective Observational Study

S. Balaji [1,*]
[1]*Department of Neurosurgery, St John's Medical College and Hospital, Bangalore, Karnataka 560034*

Accepted: 17-April-2025 / Published Online: 9-June-2025

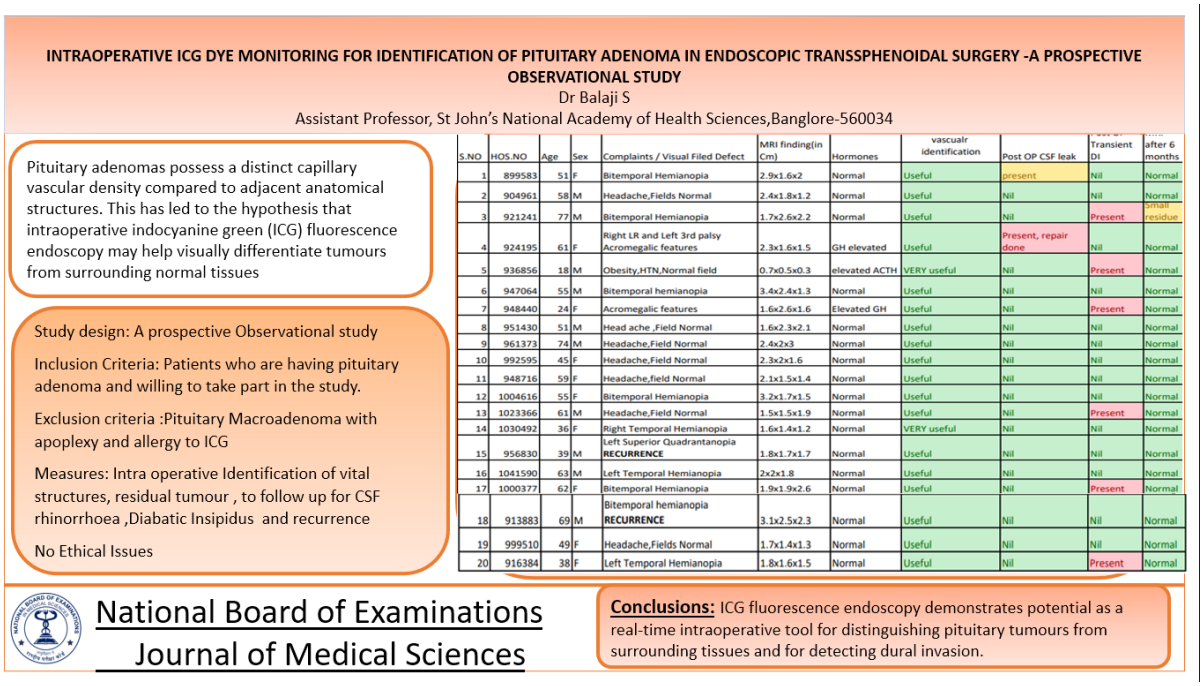
Abstract

Introduction: Histological and imaging studies have shown that pituitary adenomas possess a distinct capillary vascular density compared to adjacent anatomical structures. This has led to the hypothesis that intraoperative indocyanine green (ICG) fluorescence endoscopy may help visually differentiate tumors from surrounding normal tissues such as the pituitary gland and dura. Achieving accurate and complete tumor resection while preserving surrounding structures requires real-time intraoperative information on tumor location and margins. **Aim of the Study:** This study aimed to assess the utility of a novel intraoperative imaging technique—ICG fluorescence endoscopy—during transsphenoidal surgery (TSS) for pituitary tumors, with a focus on real-time visualization and differentiation of tumor tissue. **Methodology:** A conventional endoscopic endonasal approach was employed to access the sellar region. Following exposure of the sellar dura and tumor, a bolus of ICG (12.5–25 mg) was administered intravenously. Under near-infrared light, differences in fluorescence intensity between tumor tissue and adjacent normal structures were observed. These variations in intensity, temporal changes in fluorescence, and tissue-specific patterns allowed differentiation of tumor margins and identification of surrounding structures. Areas of dural invasion by tumor exhibited enhanced fluorescence compared to native dura. The fluorescence examination added approximately 15–20 minutes to the overall operative time under general anesthesia. No complications were noted due to ICG or the fluorescence imaging process. Patients were monitored postoperatively for up to three months, including follow-up MRI to assess for residual tumor or recurrence. **Results:** The use of ICG fluorescence provided valuable assistance in identifying tumor tissue, particularly in cases involving microadenomas. Among currently available fluorophores, ICG appears to be the most effective based on existing literature. However, the technique has certain limitations, such as blood pooling in the operative field and challenges in clearly distinguishing tumor from normal pituitary tissue. Further investigation is needed to better understand the fluorescence characteristics of various adenoma types and to refine the technique. **Conclusion:** ICG fluorescence endoscopy demonstrates potential as a real-time intraoperative tool for distinguishing pituitary tumors from surrounding tissues and for detecting dural invasion. This method may contribute to more complete tumor resections while reducing the risk of damage to adjacent normal structures.

Keywords: Pituitary adenoma, Endoscopic surgery, ICG endoscopy, Real time monitoring, Intra op ICG

*Corresponding Author: S Balaji
Email: narayanasmrithi@gmail.com

Graphical Abstract



Abbreviations

ICG: Indocyanin green
5-ALA: 5-Alpha leuvinic Acid
OLT 4: Folate receptor Agonist
PA: Pituitary Adenoma
DI: Diabetes Insipidus
MRI: Magnetic resonance Imaging
CT: Computer Tomography
Nm: Nano meter
ETSS: Endoscopic Trans Sphenoidal Surgery
ICA: internal Carotid Artery
CS: Cavernous Sinus
ICS: Inter Cavernous Sinus
iMRI: intra operative Magnetic Resonance Imaging
FDA: Food & Drug Administration
SWIG: Second Window Indo Cyanin Green
NIR: Near Infra Red
PPV: Positive Predictive Value
NPV: Negative Predictive Value

Introduction

In neurosurgery, indocyanine green (ICG) fluorescence has been widely utilized in the management of various conditions, including brain tumors, vascular anomalies, intracranial aneurysms, and spinal dural arteriovenous fistulas. The application of ICG in endoscopic pituitary surgery was first documented by Litvack et al. in 2012, who observed that pituitary adenomas exhibited reduced fluorescence compared to normal pituitary tissue under ICG imaging. Since then, studies have demonstrated that ICG endoscopy can aid in differentiating healthy pituitary gland from adenomatous tissue. These properties suggest that ICG fluorescence endoscopy could serve as a valuable adjunct to facilitate safer and more complete tumor resection during endoscopic transsphenoidal surgery (ETSS).

Despite these advantages, the optimal usage strategies and potential limitations of ICG fluorescence in ETSS are not fully established. In this study, we explored the utility of ICG endoscopy during ETSS for pituitary adenomas, focusing on its ability to distinguish tumors from critical structures such as the internal

carotid arteries (ICAs) and normal pituitary gland. We also examined practical considerations, including potential technical challenges and limitations, in using ICG as a real-time intraoperative imaging aid.

Typically, pituitary surgeries rely heavily on preoperative magnetic resonance imaging (MRI) for surgical planning. Intraoperatively, differentiation between tumor and normal tissue is usually based on subjective visual assessment of tissue characteristics, including color, consistency (e.g., soft, fibrous, or gelatinous), and capillary bleeding patterns. While techniques such as intraoperative frozen section diagnosis exist, they are technically demanding, time-intensive, and depend on additional personnel. As such, there remains a need for a straightforward, reliable, and real-time method for identifying tissue types during surgery that does not impede surgical visibility or instrument handling.

While intraoperative MRI has been introduced to improve the extent of tumor resection, its cost and procedural complexity limit widespread use. Fluorescent agents such as 5-aminolevulinic acid (5-ALA), ICG, and fluorescein have increasingly been adopted in neurosurgery as intraoperative contrast agents. Recently, their application in pituitary surgery has also been investigated. Various studies have evaluated the temporal fluorescence behavior of different anatomical and pathological structures, including the ICA, intercavernous sinus (ICS), pituitary gland, and tumors like adenomas, craniopharyngiomas, and meningiomas. Furthermore, ICG fluorescence has proven beneficial for assessing the patency of small vessels supplying the optic apparatus and pituitary stalk during and after tumor removal.

With endoscopic systems capable of delivering light sources directly into the sphenoid sinus and sella, the surgeon gains a wide-angle, high-resolution panoramic view. This enhanced visualization facilitates more extensive tumor resection compared to the narrower field and limited access provided by traditional microscopic approaches through sublabial or transnasal routes. Despite these advancements, no randomized controlled trials have yet compared outcomes of fully endoscopic versus microscopic approaches for pituitary tumor resection.

Materials and Methods

Study design: A prospective Observational study

Inclusion Criteria: Patients who are having pituitary adenoma and willing to take part in the study.

Exclusion criteria

1. Patient giving Negative consent
2. Pituitary Macroadenoma with apoplexy
3. Prior allergy to ICG dye

The ICG compound (25mg) {AUROGREEN}, was dissolved in 10ml of sterile water, and 5ml of the solution (12.5 mg of ICG) was injected into a peripheral vein as a bolus by the anesthetist (twice during the surgery), for flushing we used 10 ml of saline. The maximum absorption and emission wavelength of ICG in water are 780 nm and 805 nm, respectively; in plasma they are 800 nm and 825 nm.

Firstly, we will inject ICG (12.5mg) immediately after opening the dura, then we will inspect for the following

1. Identification of microadenoma
2. To identify the border between adenoma and normal pituitary
3. To identify the vital structures like ICA, cavernous sinus
4. To identify posterior pituitary

We do the dissection in white light only, we use NIR camera only if needed to identify the above mentioned structures and rest of the resection is done again carried out in white light only.

Second dose of ICG (12.5mg) is injected post resection before the skullbase reconstruction Post resection ICG is used to:

1. To identify the remnants those are left during the resection
2. To look for vasculature of Nasoseptal flap (But we didn't use ICG for this purpose)

AUROGREEN lyophilized powder (active ingredient indocyanine green ICG) i s a diagnostic dye used for ophthalmic angiography.

Results

We have done the study in 20 individuals who have undergone ETSS for Pituitary adenoma in the past two and half - three years in our Institute. The results are discussed here in the following headings

Age

Majority of the patients are in the age group between 50-60 years(n=6) and mean age is 52.25 years.

Sex

Out of the twenty subjects 10 were males and rest are females

Presenting complaints

Majority of the patients present with Headache (n=7), the next most common symptom is bitemporal field defect (n=6). Four patients had unilateral temporal field defects and three patients presented with hormonal disturbances.

Pre Operative MRI Findings

Majority of the patients had Pituitary macroadenoma and only one patient (Case no 5 in our master chart) had pituitary microadenoma (functional ACTH secreting adenoma causing Cushing's Disease).

Pre Op Hormonal Status of the Patient

Majority of the patients had normal preoperative hormonal status, two patients had Acromegaly (Case no 4 and 7 in our master chart) and one patient had Cushing's disease (case no 5)

Intra operative Identification of adenoma and other Vascular structures

Intra operative identification of pituitary adenoma and normal Pituitary gland is based on the Hypo fluorescence of adenoma when compared with normal pituitary, Though intra operatively adenoma shows hypofluorescence we could not identify the clear margin between Adenoma and normal pituitary gland due to following reasons (Figure 1)

A) Pooling of blood in the operative field: As there is pooling of blood in the operative field it obscures the margins of the tumor and the gland

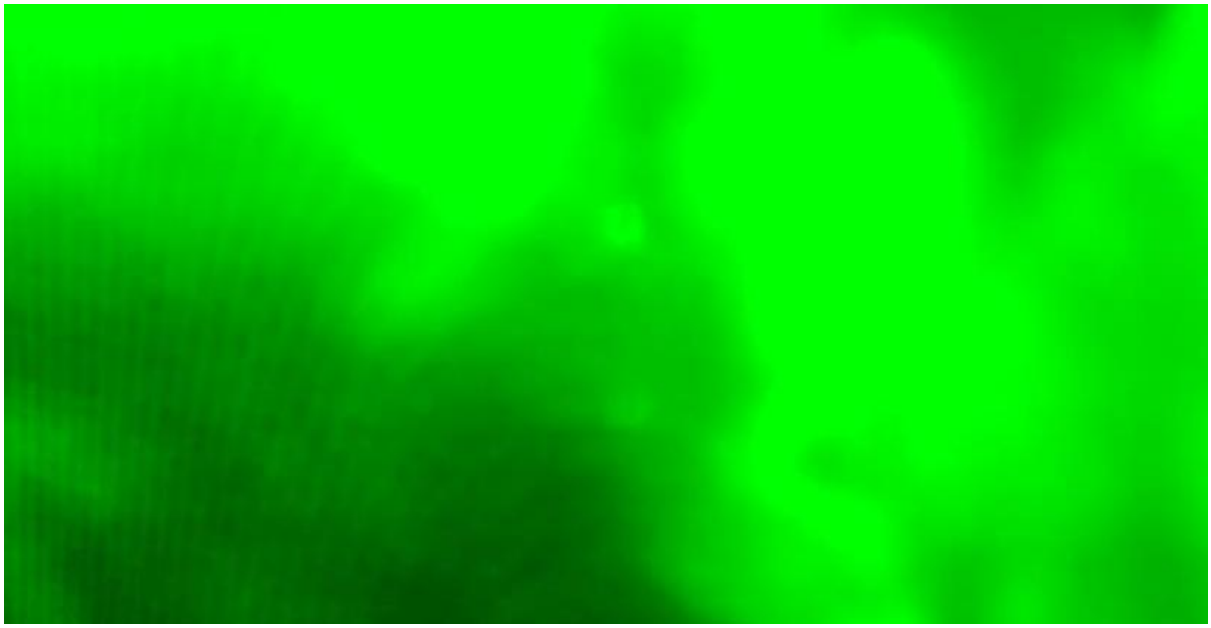


Figure 1. Image showing pooling of blood on operative field

B) Surrounding Vascular structures Obscuring the hypo fluorescence from the gland

Surrounding vascular structures like ICA and Cavernous sinus may obscure the hypofluorescence from gland and hence no distinct border could be made out between tumor and normal pituitary gland.

Identification of vascular structures

As mentioned earlier we can see the clear boundary and pulsation of ICA in ICG endoscopy and so it is very much useful in identification of vascular structures (Figure 2).

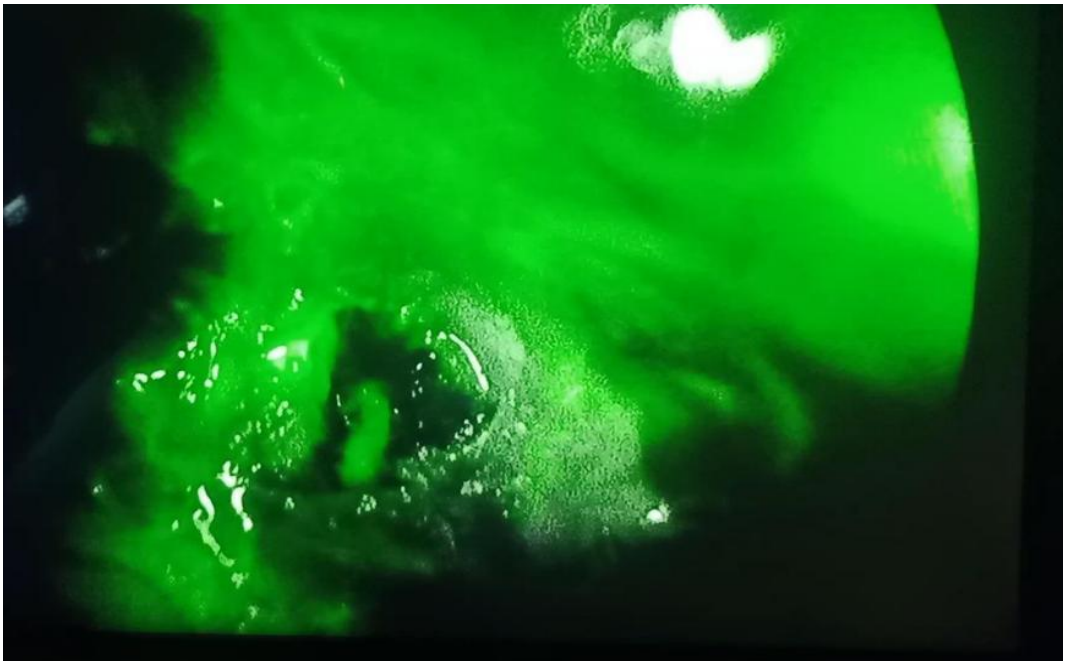


Figure 2. Image showing ICA near the lateral wall of Sella

ICA showing early hyper fluorescence immediately after ICG injection Identification of micro adenoma.

Postoperative CSF leak

Only Two patients had postOperative CSF leak, one patient (case no 1) managed conservatively with lumbar drain and other patient had undergone endoscopic CSF leak repair(Case no 4)

Postoperative Diabetes Insipidus

Out of 20 patients, 6 patients had postoperative transient diabetes insipidus. So with thus we conclude that the ICG is not useful in identifying the posterior pituitary (Table 1).

Table 1 Showing the observational finding and post op follow in patients who had undergone Intra Operative ICG endoscopy

S.NO	HOS.NO	Age	Sex	Complaints / Visual Filed Defect	MRI finding(in Cm)	Hormones	Tumour and vascualr identification	Post OP CSF leak	Post OP Transient DI	MRI after 6 months
1	899583	51	F	Bitemporal Hemianopia	2.9x1.6x2	Normal	Useful	present	Nil	Normal
2	904961	58	M	Headache,Fields Normal	2.4x1.8x1.2	Normal	Useful	Nil	Nil	Normal
3	921241	77	M	Bitemporal Hemianopia	1.7x2.6x2.2	Normal	Useful	Nil	Present	Small residue
4	924195	61	F	Right LR and Left 3rd palsy Acromegalic features	2.3x1.6x1.5	GH elevated	Useful	Present, repair done	Nil	Normal
5	936856	18	M	Obesity,HTN,Normal field	0.7x0.5x0.3	elevated ACTH	VERY useful	Nil	Present	Normal
6	947064	55	M	Bitemporal hemianopia	3.4x2.4x1.3	Normal	Useful	Nil	Nil	Normal
7	948440	24	F	Acromegalic features	1.6x2.6x1.6	Elevated GH	Useful	Nil	Present	Normal
8	951430	51	M	Head ache ,Field Normal	1.6x2.3x2.1	Normal	Useful	Nil	Nil	Normal
9	961373	74	M	Headache,Field Normal	2.4x2x3	Normal	Useful	Nil	Nil	Normal
10	992595	45	F	Headache,Field Normal	2.3x2x1.6	Normal	Useful	Nil	Nil	Normal
11	948716	59	F	Headache,field Normal	2.1x1.5x1.4	Normal	Useful	Nil	Nil	Normal
12	1004616	55	F	Bitemporal Hemianopia	3.2x1.7x1.5	Normal	Useful	Nil	Nil	Normal
13	1023366	61	M	Headache,Field Normal	1.5x1.5x1.9	Normal	Useful	Nil	Present	Normal
14	1030492	36	F	Right Temporal Hemianopia	1.6x1.4x1.2	Normal	VERY useful	Nil	Nil	Normal
15	956830	39	M	Left Superior Quadrantanopia **RECURRENCE**	1.8x1.7x1.7	Normal	Useful	Nil	Nil	Normal
16	1041590	63	M	Left Temporal Hemianopia	2x2x1.8	Normal	Useful	Nil	Nil	Normal
17	1000377	62	F	Bitemporal Hemianopia	1.9x1.9x2.6	Normal	Useful	Nil	Present	Normal
18	913883	69	M	Bitemporal hemianopia **RECURRENCE**	3.1x2.5x2.3	Normal	Useful	Nil	Nil	Normal
19	999510	49	F	Headache,Fields Normal	1.7x1.4x1.3	Normal	Useful	Nil	Nil	Normal
20	916384	38	F	Left Temporal Hemianopia	1.8x1.6x1.5	Normal	Useful	Nil	Present	Normal

Discussion

The introduction of endoscopic techniques into transsphenoidal surgery has significantly enhanced visualization by providing a wide-angle, panoramic view of the surgical field. The use of angled endoscopes offers multidirectional perspectives, allowing better understanding of the anatomical relationships between the sella and adjacent critical structures such as the internal carotid arteries (ICAs) and optic nerves. Despite these advancements, accurately distinguishing pituitary adenomas from surrounding tissues—particularly the normal pituitary gland and

vascular structures—remains challenging [1,2].

This distinction is especially vital in surgeries for functioning pituitary adenomas, where complete tumor removal is necessary to resolve hormonal imbalances and alleviate clinical symptoms. Achieving this requires real-time intraoperative tools capable of clearly identifying tumor boundaries while preserving normal tissues.

ICG fluorescence endoscopy has recently emerged as a valuable adjunct in this context. Endoscopes integrated with ICG video angiography help confirm the patency of vessels not readily visible with conventional microscopy or standard endoscopy. ICG is well-suited for vascular imaging due to its rapid hepatic clearance, strong binding to plasma proteins, and established safety profile. As noted in our study, ICG fluorescence enables intraoperative visualization of vascular and glandular structures in real time, supporting safer dissection and more complete resections [3].

However, optimal imaging with near-infrared (NIR) fluorescence requires a bloodless surgical field, as pooled blood can obscure fluorescence signals. Incomplete hemostasis or residual tumor burden can result in high background fluorescence, making it difficult to distinguish target structures. Additionally, repeated ICG administration within short intervals—less than 30 minutes—can interfere with tissue contrast, reducing imaging clarity. Thus, it is essential to determine in advance which structures are of most interest to the surgeon to maximize the diagnostic utility of ICG.

Although current ICG systems do not support simultaneous overlay of NIR and visible (white light) images, future developments in multimodal visualization—incorporating navigation systems and 3D imaging—may further enhance surgical precision and safety during ETSS [4].

Several technical and biological limitations also need to be considered. The current principle of ICG imaging relies on the delayed and reduced uptake of the dye by tumor tissue relative to normal pituitary gland. While this helps in identifying normal tissue, it would be even more effective if the tumor itself were selectively highlighted. The development of tumor-specific fluorescent tracers could improve the specificity of intraoperative visualization, allowing surgeons to resect only fluorescent, and therefore tumorous, tissue.

Additionally, the technique is prone to false-positive fluorescence in non-neoplastic tissues such as skin, nasal mucosa, and dura, possibly due to nonspecific binding of negatively charged ICG molecules. Moreover, endoscopic proximity to tissues can amplify fluorescence signals due to inverse-square intensity effects—bringing the scope too close can artificially enhance signal strength, leading to misinterpretation. Maintaining a consistent viewing distance is key to minimizing these errors [5].

A report by Sandow et al. highlighted a possible correlation between ICG signal patterns and clinical subtypes of pituitary adenomas. Notably, patients with Cushing's disease demonstrated early and distinct fluorescence, suggesting a possible link between tumor vascularity and fluorescence behavior. Previous studies have shown that the normal pituitary gland is highly vascularized, while adenomas typically display reduced microvascular

density (MVD), though this varies by tumor subtype [6].

The literature remains inconclusive on vascular differences among adenoma types. For instance, Niveiro et al. found higher MVD in thyrotroph adenomas compared to prolactinomas, and suggested that older patients may exhibit increased tumor vascularity. Conversely, Turner et al. reported lower MVD in ACTH-secreting tumors and microprolactinomas, while Jugenburg et al. found prolactinomas to have the highest MVD and GH-producing adenomas the lowest. To date, there are no studies directly comparing histological MVD assessments with intraoperative ICG imaging, which could provide valuable insights into adenoma angioarchitecture and the real-time applicability of ICG video angiography.

Interestingly, while Litvack et al. noted hypervascularity in cases of acromegaly and prolactinoma, and Sandow's series found hyperfluorescence in Cushing's disease, our findings differ. In our cohort, both acromegaly and Cushing's disease cases demonstrated hypofluorescence, even though the tumors were confirmed as corticotroph adenomas by a reputed national institution. These discrepancies suggest that additional research is necessary to elucidate how adenoma subtype, vascular characteristics, and tumor biology influence intraoperative fluorescence patterns [7,8].

Conclusion

Indocyanine green (ICG) fluorescence endoscopy holds significant potential as an intraoperative tool for distinguishing pituitary tumors from the normal gland and for identifying areas of dural invasion. With further refinement, ICG administration combined with endoscopic fluorescence-guided visualization could enhance tumor resection, ensuring better preservation of surrounding structures. This approach supports the development of fluorescence-guided resection techniques and encourages future prospective trials to confirm improved outcomes, such as the preservation of healthy tissue and more complete tumor removal. Given its promising capabilities, this technique could be applied to a variety of CNS tumors.

ICG is considered one of the most effective fluorophores for real-time imaging, especially in pituitary tumor dissection, including microadenomas. However, as noted in the literature, challenges remain, such as blood pooling in the surgical field, which can obscure the fluorescence signal, making it difficult to clearly differentiate between the tumor and normal pituitary tissue. Moreover, as Sandow et al. highlighted, there is a lack of conclusive data on the fluorescence characteristics of different types of pituitary adenomas. Therefore, further research is necessary to determine whether ICG fluorescence is truly effective in identifying adenomas and understanding the fluorescence patterns specific to various adenoma subtypes.

The outcomes of our study are summarized as follows

1. Is the ICG dye helpful in identifying the margin between tumor and normal pituitary gland? No it is not very much helpful in identifying the distinct border between tumor and normal pituitary gland. Limitations a) Pooling of blood b) Presence of vascular structures which shows hyperfluorescence.

2. Whether it is helpful in identifying vascular structures?

   Yes it is really helpful in identifying vascular structures

3. Whether it is helpful in identifying posterior pituitary?

   No it is not helpful in identifying posterior pituitary gland, we had more patients with transient DI in the postoperative period

4. Whether it is helpful in identifying functional micro adenoma (Cushing's, acromegaly)?

   Yes it is very much helpful in identifying functional microadenoma, in our study functional microadenoma showed hypofluorescence and we confirmed the adenoma with HPE and ICH markers.

5. Whether it is helpful is decreasing postoperative CSF leak?

   To some extent it is helpful in reducing postoperative CSF leak, but it may vary among surgeons depending upon their experience.

6. Whether it is helpful in preventing recurrence of Pituitary adenoma?

It is very much helpful in preventing recurrence, out of the twenty patients operated on, only one patient had a small residue and the patient is asymptomatic for more than 3 years and he is on follow-up.

As mentioned earlier we used ICG endoscopy after the resection of adenoma to ensure the completion of excision, it is also useful in recurrent pituitary adenoma cases. So to conclude ICG endoscopy is very much useful in above mentioned scenarios for surgery of pituitary adenoma. Limitation of ICG dye is already mentioned and as it is a small study (n=20), we need larger study samples and clearly published data to talk about fluorescence patterns of different kinds of adenomas. The fluorescence pattern interpretation also has inter observer variations and it also depends upon the distance from which the endoscope is used. So I conclude that ICG is a good tool for pituitary adenoma excision but we need further study and research in this subject.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

References

1. Akihiro Inoue, Takanori Ohnishi, Shohei Kohno, Naoya Nishida, Yawara Nakamura, Yoshihiro Ohtsuka, Shirabe Matsumoto, Shiro Ohue, "Usefulness of an Image Fusion Model Using Three-Dimensional CT and MRI with Indocyanine Green Fluorescence Endoscopy as a Multimodal Assistant System in Endoscopic Transsphenoidal Surgery", International Journal of Endocrinology, vol. 2015, Article ID 694273, 10 pages, 2015. https://doi.org/10.1155/2015/694273
2. Amano, K., Aihara, Y., Tsuzuki, S. et al. Application of indocyanine green fluorescence endoscopic system in transsphenoidal surgery for pituitary tumors. Acta Neurochir 161, 695–706 (2019). https://doi.org/10.1007/s00701-018-03778-0
3. Bongetta D, Tartara F, Pagella F, Somma T, Cavaliere M, Di Perna G,

Zenga F, Cofano F, Garbossa D, Zoia C. Fluorophores Use in Pituitary Surgery: A Pharmacokinetics and Pharmacodynamics Appraisal. Brain Sciences. 2021; 11(5):565. https://doi.org/10.3390/brainsci11050565

4. Hide T, Yano S, Shinojima N, Kuratsu J. Usefulness of the indocyanine green fluorescence endoscope in endonasal transsphenoidal surgery. J Neurosurg. 2015 May;122(5):1185-92. doi: 10.3171/2014.9.JNS14599.
5. McLaughlin N, Eisenberg AA, Cohan P, Chaloner CB, Kelly DF. Value of endoscopy for maximizing tumor removal in endonasal transsphenoidal pituitary adenoma surgery. J Neurosurg. 2013 Mar;118(3):613-20. doi: 10.3171/2012.11.JNS112020.
6. Cho SS, Salinas R, Lee JYK. Indocyanine-Green for Fluorescence-Guided Surgery of Brain Tumors: Evidence, Techniques, and Practical Experience. Front Surg. 2019 Mar 12;6:11. doi: 10.3389/fsurg.2019.00011.
7. Lee MH, Lee TK. Application of fusion-fluorescence imaging using indocyanine green in endoscopic endonasal surgery. J Clin Neurosci. 2022 Feb 4;98:45-52. doi: 10.1016/j.jocn.2022.01.023.
8. Sandow N, Klene W, Elbelt U, Strasburger CJ, Vajkoczy P. Intraoperative indocyanine green videoangiography for identification of pituitary adenomas using a microscopic transsphenoidal approach. Pituitary. 2015 Oct;18(5):613-20. doi: 10.1007/s11102-014-0620-7.