Original scientific paper

LIMITATIONS IN UTILIZATION OF SODIUM FLUORESCEIN AS A CONTRAST AGENT DURING BRAIN SURGERY

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Medicus 2025, Vol. 30 (3): 360-367

APSTRACT

Introduction: Although today's neurosurgery worldwide accepts the use of sodium fluorescein as a useful intraoperative contrast agent, there are several limitations and disadvantages of its utilization. Human medicine requires continuous research and development. Thus we made a clinical study that will provide useful information about some specific details about the use of sodium fluorescein intraoperative for brain tumors. In advance, we are looking forward in improving the fluorescent surgery and overcoming these disadvantages. Sodium fluorescein has a great potential as an intraoperative contrast agent and overcoming these limitations will lead to a more successful outcome.

Material and methods: Specific information about sodium fluorescein's characteristics was gained from 39 patients operated with its utilization during surgery of brain tumors. All of these patients were injected intravenously sodium fluorescein at a dose of 5mg/kg prior to skin incision. During surgery, operative microscope Zeiss Kinevo 900 with "white" (daylight) and "yellow" (with 560nm filter) was used. The data was collected during a period of 3 years from year 2022 to 2025. Details were discussed during surgery and notes were taken weather tumor margins are clear or blur. Patients' neurological status was assessed after surgery. Imagine methods such as MRI and CT scans pre and post operatively were compared in order to assess the extent of tumor resection. Days of hospital stay were used as an indirect indicator of postoperative complications. All this data was helpful in estimating surgical success using sodium fluorescein intraoperative. However, the goal of this study is to emphasise the problems and disadvantages that we encountered utilizing sodium fluorescein. Thus, the analytical part is of greater value, than the numerical.

Conclusion: Sodium fluorescein is useful adjunct for brain tumor surgery. However, in some specific cases and situations it can guide the neurosurgeon in wrong direction and cause unwanted damage. Therefore, every neurosurgeon who utilizes sodium fluorescein for tumor resection need to receive thorough education for its characteristics first. In the hands of skilled and experienced neurosurgeon these limitations can be overwhelmed and sodium fluorescein guided surgery can contribute to greater overall surgical success.

INTRODUCTION

Today, in modern neurosurgery, the use of sodium fluorescein during brain tumor surgeries is widely accepted as justified. This has been confirmed by numerous studies, most of which focus on patients with malignant brain tumors. However, the fact that sodium fluorescein does not bind within malignant cells raises some doubts about its precision. In contrast to 5-ALA, which is metabolized in the cytoplasm of malignant cells, sodium fluorescein accumulates in tumor tissue due to disruption of the blood-brain barrier. Guided by this fact, the aim of this paper is to present the limitations of sodium fluorescein use in various pathological brain processes. The affordable cost and easy availability of this contrast agent facilitate its application in everyday neurosurgical practice. Any institution equipped with a microscope featuring a 560 nm yellow filter can routinely perform brain tumor surgeries with intraoperative use of sodium fluorescein. In addition to malignant tumors, its application can also be extended to benign tumors (1), arteriovenous malformations, and cerebral aneurysms. This opens opportunities for numerous studies that could highlight both the advantages and disadvantages of sodium fluorescein. In this context, it is necessary to clearly define which tissues show a strong fluorescence and whether such tissue should actually be removed during surgery. Intracranial, there are physiological tissues that exhibit intense fluorescence, as well as tumor tissues that do not fluoresce under yellow light. This is due to the varying biological and pathological characteristics of intracranial processes, as well as individual patient differences. Our goal is to emphasize these specific features and to demonstrate situations in which the neurosurgeon should not rely solely on the tissue accumulation of sodium fluorescein. In the following sections, we will present and analyse specific clinical experiences and observations from our practice.

MATERIALS AND METHODS

To demonstrate the specific properties of sodium fluorescein, data were analyzed from both a prospective and retrospective study involving 39 patients aged between 9 and 86 years. All patients received an intravenous administration of 5 to 10 mg/kg of sodium fluorescein after induction of anesthesia and before the start of surgery. All surgical procedures were performed by the same operative team. The extent of tumor resection was assessed by comparing preoperative contrast-enhanced magnetic resonance imaging (MRI) with postoperative contrast-enhanced computed tomography (CT) scans. Although these are imaging modalities with different levels of precision, postoperative CT scans clearly display residual or recurrent tissue and can therefore serve as reliable evidence of the resection extent. The scans were performed within a short postoperative period of 2 to 5 days.The intracranial lesions included a variety of pathologies–both benign and malignant tumors with different grades of malignancy, as well as recurrent and metastatic tumors. Furthermore, the lesions were located in various intracranial regions, including the posterior cranial fossa, cerebral convexity, skull base, pontocerebellar area, parasagittal region, intralobar locations, and others. The wide range of tumor malignancy and anatomical diversity enabled us to obtain extensive data on the behaviour of sodium fluorescein under different conditions. All surgeries were performed using a Carl Zeiss Kinevo 900 microscope under both “white (standard)” and “yellow (560 nm filter)” light. The surgical procedures were video recorded, and additional images were captured, annotated, and presented in the following sections. Patients were monitored in the postoperative period, and their neurological status was evaluated. For simplicity, the outcomes were categorized into three groups: improved, unchanged, or worsened neurological status. However, the present study focuses on qualitative rather than quantitative data. The aim was to demonstrate the varying degrees of contrast agent accumulation within different intracranial tissues.

RESULTS

A total of 39 patients who underwent surgery for various types of brain tumors with intraoperative use of sodium fluorescein were evaluated. The statistical data obtained are presented in the table below (Table 1).

Table 1. Patients operated with the use of sodium fluorescein intraoperative.

Patient	Pathohistological diagnosis	Residual/recurrent tissue on postoperative CT or MRI with contrast	Hospital stay (days)	Neurological status	Demarcation
1	MS melanoma	+	27	Unchanged	Clear
2	Glioblastoma	-	8	improved	Clear
3	Meningeomaatypicumrecidivans	-	8	Unchanged	Unclear
4	MS colonis	+	90	Worsened Exituslethalis	Partial
5	Glioblastomarecidivans	+	7	Unchanged	Clear
6	Meningeoma	-	6	Worsened	Clear
7	Astrocytoma gr III	+	8	improved	Clear
8	Meningeoma	-	7	improved	Unclear
9	MS pulmo	-	7	improved	Clear
10	Glioblastoma	-	7	Unchanged	Unclear
11	Glioblastoma	-	7	Unchanged	Clear
12	Glioblastomarecidivans	-	12	improved	Unclear
13	Medulloblastoma	-	15	improved	Clear
14	Pylocitic astrocytoma	+	8	Unchanged	Partial
15	Sphenoid wing meningeoma	+	18	Worsened	Unclear
16	Ependymoma gr II	-	7	improved	Unclear
17	Astrocytoma gr IV	+	10	Unchanged	Partial
18	Glioblastoma	+	9	Worsened	Clear
19	Sagitalmeningeoma	-	8	improved	Partial
20	Meningeoma gr III	-	7	improved	Clear
21	Medulloblastoma	-	28	Worsened	Partial
22	MS	-	7	improved	Clear
23	Masson tumor	-	6	Unchanged	Partial
24	Glioblastoma	-	7	improved	Clear
25	Glioblastoma	-	6	Unchanged	Clear
26	Glioblastomarecidivans	-	9	Unchanged	Partial
27	Pylocitic astrocytoma	+	16	improved	Clear
28	Oligodendroglioma gr III recidivans	+	7	Unchanged	Clear
29	MS Pulmo	-	24	Worsened	Clear
30	Medulloblastoma	-	11	Unchanged	Clear
31	Pleomorphic xantoastrocytoma	-	6	improved	Unclear
32	Necrosis	-	11	Unchanged	Clear
33	MS melanoma	-	10	improved	Clear
34	Glioblastoma	-	21	Unchanged	Clear
35	MS melanoma	-	8	Unchanged	Partial
36	Astrocytoma gr III	-	11	Unchanged	Partial
37	Glioblastoma	-	6	improved	Partial
38	GBM recidivans	+	7	Unchanged	Partial
39	TuGlomusJugulare	-	8	Worsened	Partial

Legend

MS – Metastatic spread

+ – Presence of residual/recurrent tissue

– – No residual/recurrent tissue

Demarcation: Clear = distinct fluorescence boundary; Partial = partially visible boundary; Unclear = poor or absent boundary

Discussion

During the use of sodium fluorescein as a contrast agent in brain tumor surgeries, we encountered several situations that could potentially mislead the neurosurgeon during the operative course. These situations are discussed in the text below. Every neurosurgeon performing operations with the aid of sodium fluorescein should be aware of these details. When speaking about limitations, it generally refers to which tissues retain and which do not retain the contrast agent—that is, which structures exhibit strong fluorescence and which do not. According to the literature, several anatomical structures are known to accumulate sodium fluorescein and therefore produce strong fluorescence under the microscope's yellow light. The best-known such structure is the dura mater, which usually does not pose a significant problem due to its clear distinction from the surrounding tissue. However, in meningioma surgeries, confusion regarding the tumor–dura boundary can occasionally occur. In such cases, sodium fluorescein is not helpful, since there is no difference in fluorescence intensity under yellow-light illumination. Nevertheless, because it facilitates easier identification of tumor portions in less accessible regions, the use of sodium fluorescein remains justified even in surgeries of benign tumors.

In addition to the dura, it is important to note that arachnoid granulations (GA) also produce a strong fluorescence signal under yellow-light microscopy (Figure 1). These anatomical structures should be taken into consideration, particularly in parasagittal pathologies such as meningiomas, parietal glioblastomas, astrocytomas, and similar lesions. Although these structures can easily be identified without a microscope and under white light, during tumor resection under yellow-light illumination and from certain angles, they may create a false perception of tumorous tissue.

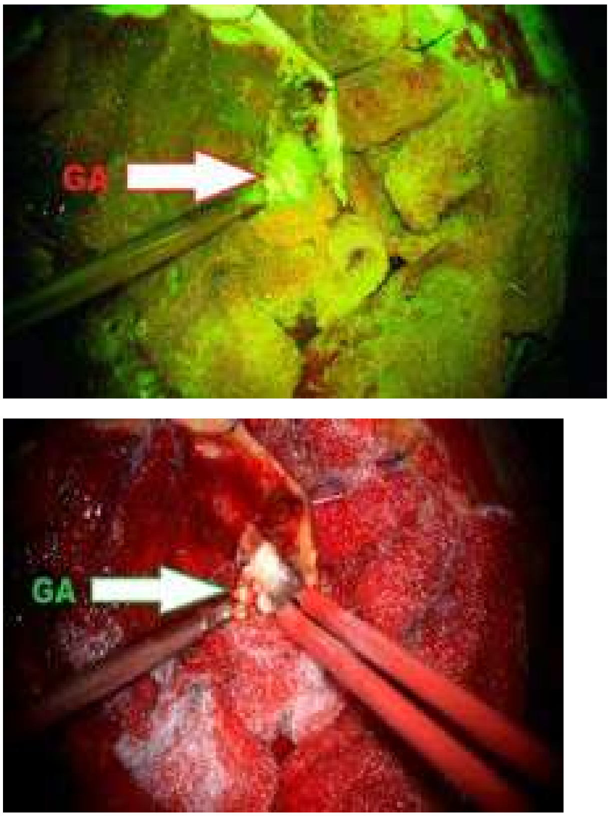

Figure 1. GA = Granulationes Arachnoidales.

The ependymal lining of the ventricular system accumulates a large amount of sodium fluorescein and exhibits fluorescence intensity comparable to that of the dura mater and tumorous tissue. This characteristic can, in certain situations, represent a disadvantage. Such examples include tumors located near or in communication with the ventricular system, such as intraventricular tumors, glioblastomas with ventricular infiltration, and lesions within the posterior cranial fossa.A particularly challenging situation arises due to the staining of the ependymal surface of the fourth ventricle, which covers the posterior wall of the brainstem during surgeries involving tumors in this region. After cerebrospinal fluid (CSF) drainage, both the tumor and the posterior aspect of the medulla oblongata may display nearly identical fluorescence (Figure 2). This may falsely guide the neurosurgeon and lead to inadvertent injury of the brainstem, which is especially vulnerable.Therefore, the use of sodium fluorescein in procedures involving the posterior cranial fossa should be approached with extreme caution and reserved for experienced neurosurgeons only.

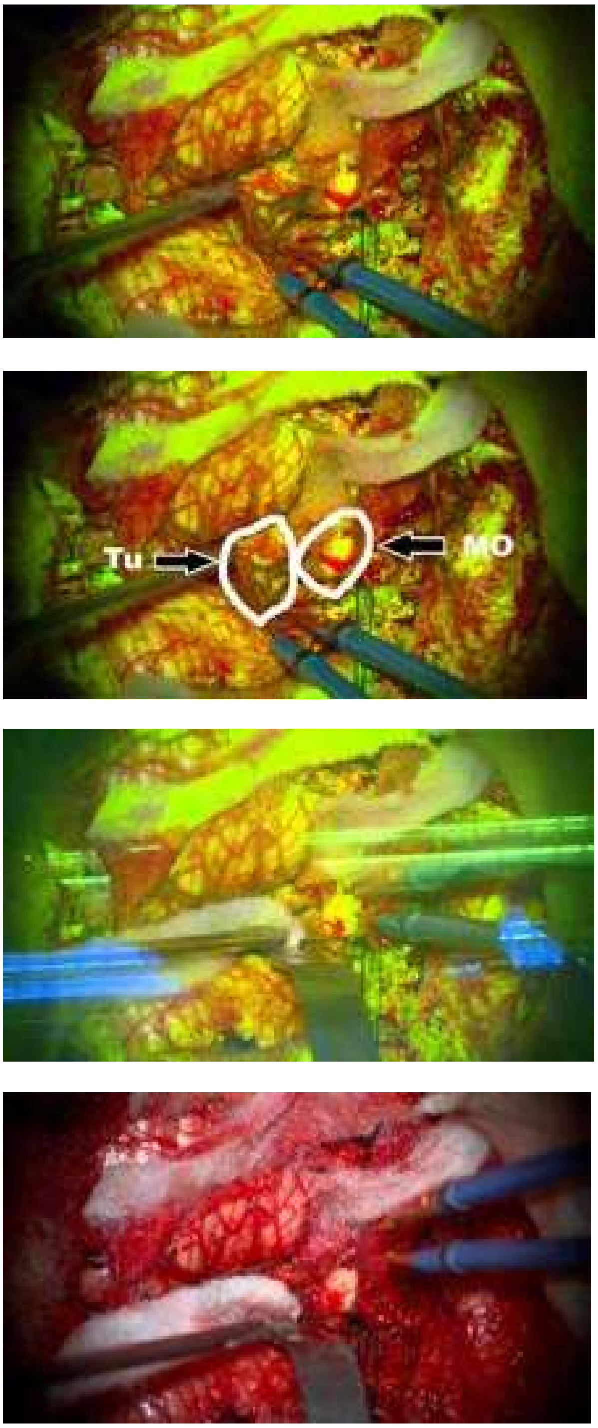

Figure 2.Tu = Tumor, MO = Medulla oblongata. The tumor and the brainstem may falsely give the impression of being in continuity, potentially misleading the neurosurgeon. The second image shows the marking of the tumorous tissue and the medulla oblongata for clearer differentiation. The third image demonstrates the strong fluorescence of the medulla oblongata under yellow light, while in the fourth image, it is clearly delineated from the surrounding structures.

Within the ventricular system, another structure exhibits strong contrast accumulation–the choroid plexus. Due to its rich capillary network, the plexus displays intense fluorescence under yellow light, similar to the previously mentioned arachnoid granulations and dura mater. This presents a potential problem when dealing with intraventriculartumors. Furthermore, the choroid plexus should be taken into consideration in cases where tumors are in close proximity to the ventricular system and where ventricular perforation occurs during tumor excision. After cerebrospinal fluid (CSF) drainage, the plexus may appear within the surgical field and falsely mimic tumorous tissue. Although the plexus is not as vulnerable as some other central nervous system structures, its injury can still result in undesirable postoperative consequences.

An especially important topic in contemporary neurosurgery is the accumulation of sodium fluorescein within peritumoral brain edema (Figure 3). Some authors argue that edematous tissue does not retain the contrast agent and therefore does not fluoresce, while others report the opposite. In our study, after completion of the resection, we frequently observed tissue that was partially stained with the contrast agent. The borders of this tissue could be clearly distinguished both from the tumor and from the surrounding healthy brain parenchyma. Based on its location, frequency of occurrence, and association with malignant (particularly metastatic) tumors, we believe this tissue represents peritumoral brain edema (Figure 4). From a pathophysiological standpoint, our interpretation appears consistent. In edematous tissue, a disruption of the blood-brain barrier and contrast agent attenuation are to be expected. This differentiates it from normal brain parenchyma, where the blood-brain barrier remains intact and contrast accumulation is absent. Conversely, the tumor causes far greater destruction of the blood-brain barrier, leading to higher contrast uptake. As a result, our conclusion is that peritumoraledema partially attenuates sodium fluorescein, producing weak fluorescence under yellow light. Nevertheless, further studies on this specific issue are necessary, since preservation and recovery of edematous brain tissue significantly contribute to better postoperative outcomes.

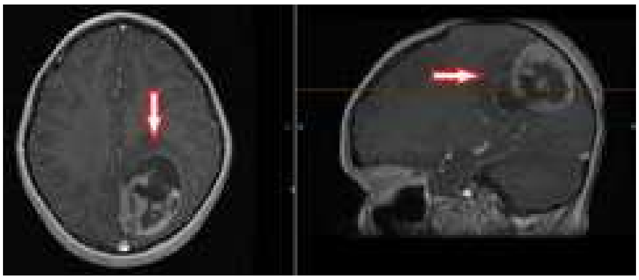

Figure 3.Perilesionaledema

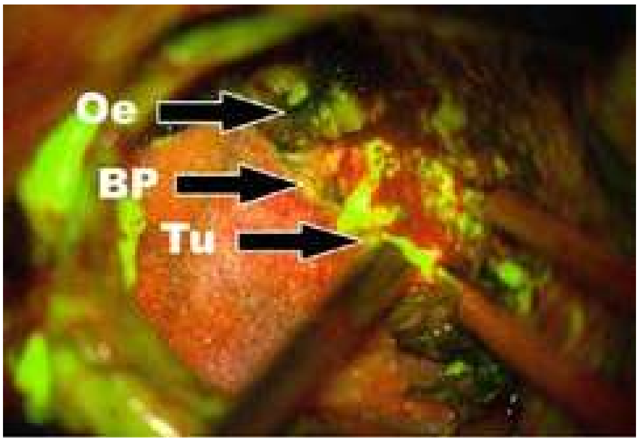

Figure 4.Oe = Edema, BP = Brain Parenchyma, Tu = Tumor. The tumorous tissue shows the strongest fluorescence, followed by the peritumoral brain edema, which demonstrates partial fluorescence. The healthy brain parenchyma does not retain the contrast agent and shows no fluorescence.

A particular challenge in neurosurgery is presented by operations on recurrent tumors. Adhesions, in addition to disrupting normal anatomy, also complicate the use and interpretation of sodium fluorescein. The literature contains very few references regarding the fluorescence characteristics of recurrent adhesions. From our experience, these adhesions exhibit a strong fluorescence under yellow light, comparable to that of the dura mater. This creates difficulties in identifying the true borders of the recurrent tumor. In our study, all five cases of recurrent tumors showed similar staining of both the tumor and the adhesions (Figure 5). This made it impossible to clearly determine the final tumor margins and to separate the lesion from the surrounding healthy brain parenchyma.

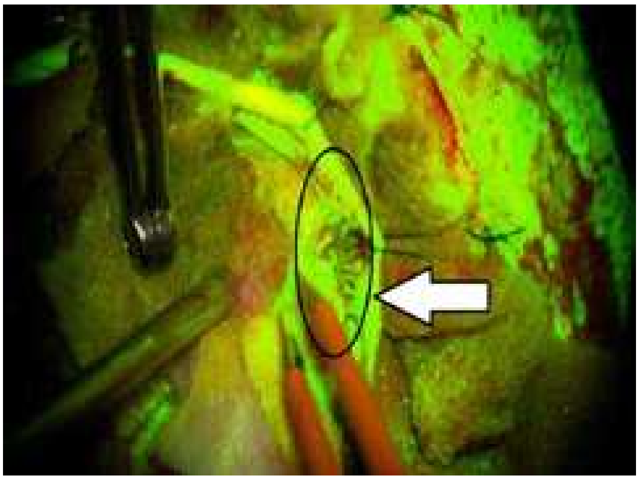

Figure 5. Adhesions strongly retain contrast and complicate the surgical process.

In addition to the undesired accumulation of sodium fluorescein in the anatomical structures mentioned above, a problem also arises from its absence in certain tumors. In our study, we encountered both malignant and benign tumors in which, despite the expected staining under yellow light, the tumor tissue did not fluoresce and appeared inert. Although it is generally accepted that glioblastomas accumulate contrast, in one case from our study, the tissue appeared grayish in color with a friable consistency, clearly demarcated from the surrounding healthy parenchyma (Figure 6). Histopathological analysis confirmed the diagnosis of glioblastoma, validating our intraoperative suspicion.This raises the question: why did sodium fluorescein fail to accumulate in this tumor tissue? This uncertainty prevents the surgeon from relying fully on the degree of contrast accumulation as a marker for tumor tissue. Upon further analysis, one possibility considered was that the tissue might be necrotic. However, whether the tissue represents tumor or radionecrosis, we would generally still expect strong fluorescence, since sodium fluorescein accumulates in tissues where the blood-brain barrier is disrupted. In the results described above, there is one example of a patient in whom histopathology confirmed necrosis. In this case, the necrotic tissue accumulated contrast and fluoresced similarly to tumor tissue. The distinction from healthy parenchyma was clear, and intraoperatively the process was treated as malignant, leading to an excellent postoperative outcome. Therefore, further studies with detailed explanations of such situations are necessary to increase understanding of the specific behavior of sodium fluorescein.

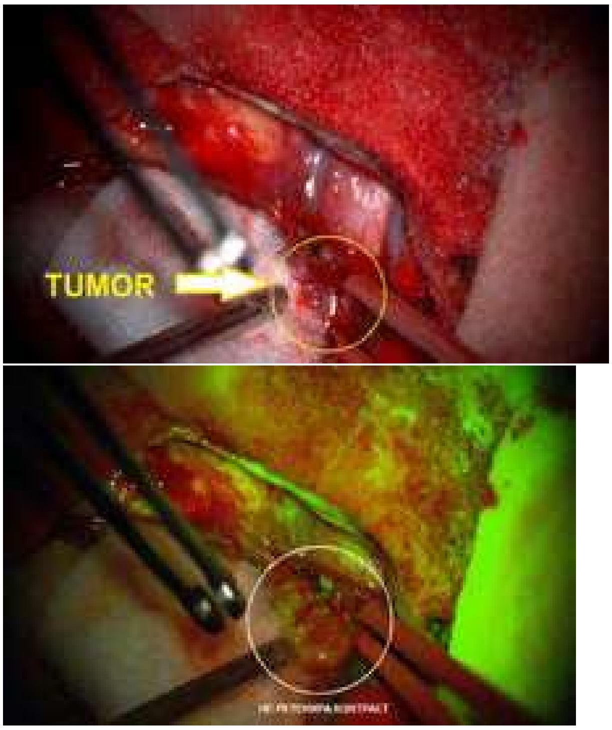

Figure 6.Tissue highly suspicious for glioblastoma, which does not fluoresce under yellow light in the microscope.

Tumors that did not accumulate sodium fluorescein have also been reported in the study by Christian Ott and colleagues, where three cases involving tumors in the posterior cranial fossa showed only weak fluorescence. Their study was compared with the study by Bat and collaborators, in which no contrast agent was used for tumor resection in the posterior cranial fossa, and it was concluded that the extent of resection was not significantly different. One contributing factor to this finding is the tendency of tumors in the posterior cranial fossa to infiltrate vital anatomical structures. Therefore, it is emphasized that microsurgical procedures under white light should remain the standard, while fluorescent-guided tumor resection can be used as a helpful adjunct. The diversity of tumors and patients in our study complicates classification and percentage-based presentation of results. Nevertheless, some conclusions can be drawn from detailed analyses. To provide a clearer overview, patients were grouped according to operative success into three categories (Table 2).

Excellent outcome: Patients with improved neurological status and no postoperative residual tumor or recurrence on imaging studies.

Good outcome: Patients in whom the surgical goal was achieved, and overall treatment was satisfactory, considering the circumstances and complex nature of the pathology.

Poor outcome: Patients who experienced postoperative deterioration, severe complications, incomplete tumor resection (voluntarily or involuntarily), and/or fatal outcomes.

Table 2. Tabular presentation of operative success in patients undergoing surgery with intraoperative use of sodium fluorescein.

Operative outcome	Number of patients
Excellent	18
Good	16
Poor	5

It is important to note that the numerical data in our study have limited statistical significance, as the primary goal is to highlight the characteristic properties of sodium fluorescein and present specific clinical situations related to its use. Gender and age were omitted from the table, as they are not relevant to the properties of sodium fluorescein. The purpose of classifying operative success is to provide a clearer picture of whether intraoperative use of sodium fluorescein is justified. From Table 2, it can be observed that undesirable outcomes occurred in only 5 out of 39 patients, indicating a generally solid operative success. Postoperative residual tumor or recurrence occurred in 28% of patients (11 out of 39). The mean length of hospitalization was 12.4 days. Postoperative neurological deterioration was recorded in 7 patients (18%). Based on these results, it can be concluded that, despite the aforementioned limitations, sodium fluorescein is of significant benefit in the surgical management of intracranial lesions.

CONCLUSION

Sodium fluorescein is a valuable tool in neurosurgery which, when used correctly, can contribute to safer, more precise, and successful surgical interventions. The aim of this study was to illustrate specific situations and dilemmas encountered during intraoperative use of sodium fluorescein, which may lead to misinterpretation by the surgeon. Therefore, comprehensive theoretical and practical training is essential before its clinical application. In conclusion, the intraoperative use of sodium fluorescein by a surgeon with adequate experience and knowledge of its properties contributes to overall improved operative success.

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