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Original Research Article

Assessment of Surgical Success in Benign Neoplasms of Neural Origin using Sodium Fluorescein as an Intraoperative Fluorescent Technique

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Abstract

The use of sodium fluorescein intraoperatively in benign tumors of the brain and spinal column is still in the process of research and proving. There is not enough number of studies about its possible positive effect in the world literature. Theoretical knowledge indicates the usefulness of fluorescence techniques in tumors with rapid growth and greater destructiveness of nervous tissue, such as malignant tumors. Here, the accumulation in the pathological tissue allows better differentiation from the healthy brain parenchyma. In the case of benign tumors of the brain and spinal column, the anatomy allows a clearer distinction and the usefulness of fluorescence techniques is not taken into account. However, the distinction is only one of the many intraoperative problems and challenges that the neurosurgeon faces when removing benign tumors. Some of these issues can be overcome by using fluorescent agents such as sodium fluorescein. According to the presented clinical study, conclusions were drawn based on a comparison between a control group of patients operated on without the use of sodium fluorescein and a test group of patients operated on with the use of sodium fluorescein intraoperatively. The surgical success and percentage were based on neurological status postoperatively, control images from magnetic resonance imaging (MRI) and computed tomography (CT) with contrast postoperatively, days of hospital stay, and the number of fatal outcomes and intraoperative notes on the degree of tumor resection. The patients were operated on by the same surgical team over a period of nine years (from 2016 to 2025) in two hospitals. Neurological status was evaluated during the postoperative stay. Imaging methods were taken during a wide postoperative period starting from the days of hospitalization postoperatively to control examinations several years after the surgical treatment. The days of hospitalization were taken as an indicative measure of postoperative recovery and complications. Only those fatal outcomes that occurred during the postoperative hospital stay were recorded. The intraoperative note on the degree of tumor resection was based on the individual assessment of the neurosurgeon during the surgery performed using microsurgical technique under the Haag Streit and Zeiss Kinevo 900 operating microscope, using 'white' (daylight) and 'yellow' (adapted for fluorescent recognition) light with a 560nm filter. After mentioning all above, we came to a conclusion that sodium fluorescein (SF) should be used for benign brain and spine tumors in every possible situation. Although it has no influence on the recurrence rate, it can be used as a helpful adjunct for doubtable situations during surgery, can increase the operator's confidence and influences survival rate.

Keywords: Benign brain and spine tumor, Neoplasm of neural tissue, Neurosurgery, Sodim Fluorescein

INTRODUCTION

The use of fluorescent techniques during surgical procedures appeared in general medicine back in 1946, when sodium fluorescein was used under violet light to distinguish diseased from healthy tissue during resection

of gastric carcinoma (1). Over the years, sodium fluorescein emerged as a useful fluorescent method in operations in gynecology, ophthalmology, general and neurological surgery. In 2003, a study from Shinoda et al. was published in the global medical literature, where 105 patients operated on for glioblastoma received intraoperative sodium fluorescein intravenously at a dose of 20 mg/kg and were operated under 'white' light. A GTR rate of 84.4% could be achieved in the FL group in contrast to only 30.1% in the non-FL group (1). Since then, numerous studies have been published confirming the usefulness of using sodium fluorescein, primarily in malignant tumors. One of them is the study of 279 patients by Naoto Falco and colleagues, in which it was proven that sodium fluorescein fluorescent staining technique is a safe and effective technique to improve visualization and resection of different CNS tumors and conditions (2). The same study also described cases where the use was proven beneficial in low-grade (grade 2) tumors. The main goal for using sodium fluorescein is to increase tumor resection while preserving healthy brain parenchyma. When administered intravenously, it accumulates in the pathological tissue where the blood-brain barrier is disrupted. In recent decades, it has been useful in a larger dose as a contrast agent (about 20 mg/kg) to observe accumulation in pathological tissue under 'white' light. With modernization in neurosurgical technology, newer operating microscopes use a 560 nm filter to better differentiate tissue in which sodium fluorescein is retained. This also allows for significantly smaller doses of the contrast agent during surgery and the same to be properly seen in pathological tissue under 'yellow' light. Although the exact mechanism of sodium fluorescein accumulation and dosing is not yet 100% defined, the global neurosurgical community agrees that the fluorescent staining technique is useful for precise resection of malignant tumors at doses of 5 mg/kg. In contrast, there are fewer published studies on the use of sodium fluorescein during operations on benign brain and spinal cord tumors. One such study involved 11 patients by Krasimir Minkin and his colleagues, in which sodium fluorescein was shown as a useful fluorescent technique for better delineation of tumor boundaries. In that study, a high dose of 20 mg/kg was used in pilocytic astrocytomas and neuroglial tumors that poorly retain contrast both during radiological imaging and during surgery itself (3). In a thorough analysis regarding the use of contrast fluorescent agents in surgeries for meningiomas by Bianca M. Dijkstra and her collaborators, it was concluded that these agents do not affect the surgical outcome and survival (4). All these facts were the motivation to create a study that would provide a larger amount of information regarding the use of sodium fluorescein in benign brain and spinal tumors, and which would help determine the more precise application during surgical procedures.

MATERIALS AND METHODS

In the study, the conclusions were drawn by comparing two groups of patients. One is the control group and the other is the experimental group.

The control group consists of 60 patients operated on for benign brain and spinal cord tumors, without the use of sodium fluorescein, during the period from 2015 to 2020, at the City General Hospital (CGH) “8th of September.” A Haag Streit surgical microscope with white (daylight) illumination was used for precise microsurgical technique.

The other group consists of 20 patients also operated on for benign brain and spinal cord tumors, with the use of sodium fluorescein, during the period from 2022 to 2025, at the Private Healthcare Institution Acibadem Sistina Clinical Hospital. In the second group, a Zeiss Kinevo 900 surgical microscope was used, with white (daylight) and yellow (with a 560nm filter) light that vividly displays the fluorescent staining. For all patients, a histopathological examination and diagnosis were established. The percentage distribution of the diagnoses is presented in Tables and Diagrams 1 and 2.

It can be observed that the majority of benign brain and spinal cord tumors fall into the group of meningiomas. For this reason, they are categorized according to their grades in order to gain a better understanding of the recurrence rate. The type of benign tumor was selected to allow for a more precise comparison with the examined group, due to the varying timeframes for recurrence. In general, all are characterized by slow growth, a solid component, a longer period before recurrence, and the potential for complete recovery through total surgical resection.

The neurological status of each patient was carefully evaluated before and after surgery. In this study, it serves as an indicator of the patient's condition following the operation. Only changes that occurred during the postoperative hospital stay were considered as changes in neurological status. For easier comparison between the groups, neurological status is marked as: improved, unchanged, and worsened. Patients whose neurological deficits—persisting before surgery due to tumor growth—resolved postoperatively are considered to have an “improved neurological status.” If neurological deficits or symptoms related to tumor growth persist even after surgical treatment, those patients are marked as having an “unchanged neurological status.” Meanwhile, patients who developed new neurological issues or complications related to the surgical treatment are recorded as having a “deteriorated neurological status.” More specifically, the category “deteriorated neurological status” includes patients who postoperatively experienced paresis of the facial nerve (n. facialis), lower limb paraparesis, dysphasia, dysphagia, psychotic behaviour, hemiparesis, oculomotor nerve (n. oculomotorii) paresis, epileptic

Table 1. Diagnosis for patients operated without utilization of Sodium Fluorescein intraoperatively.

Diagnosis	Number of patients	Percentage (%)
Meningioma gr I (WHO)	32	53.3
Meningioma gr II (WHO)	4	6.7
Ependymoma low grade	5	8.3
Astrocytoma low grade	3	5.0
Neurinoma	10	16.7
Hemangioblastoma	1	1.7
Dermoid Cyst	2	3.3
Haemangioma	1	1.7
Chordoma	2	3.3

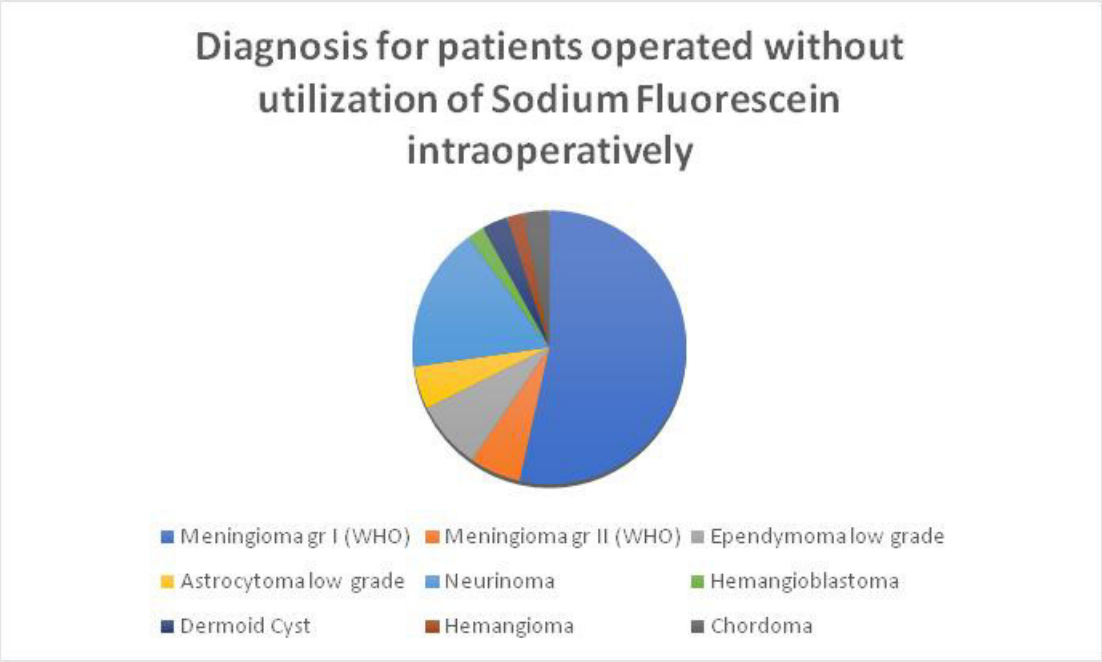


Diagram 1

Table 2. Diagnosis for patients operated **with** the utilization of Sodium Fluorescein intraoperatively.

Diagnosis	**Number of patients**	**Percentage (%)**
Meningioma gr I (WHO)	7	35
Meningioma gr II (WHO)	3	15
Ependymoma low grade	2	10
Astrocytoma low grade	3	15
adenoma	2	10
Hemangioblastoma	1	5
Oligodendroglioma low grade	2	10

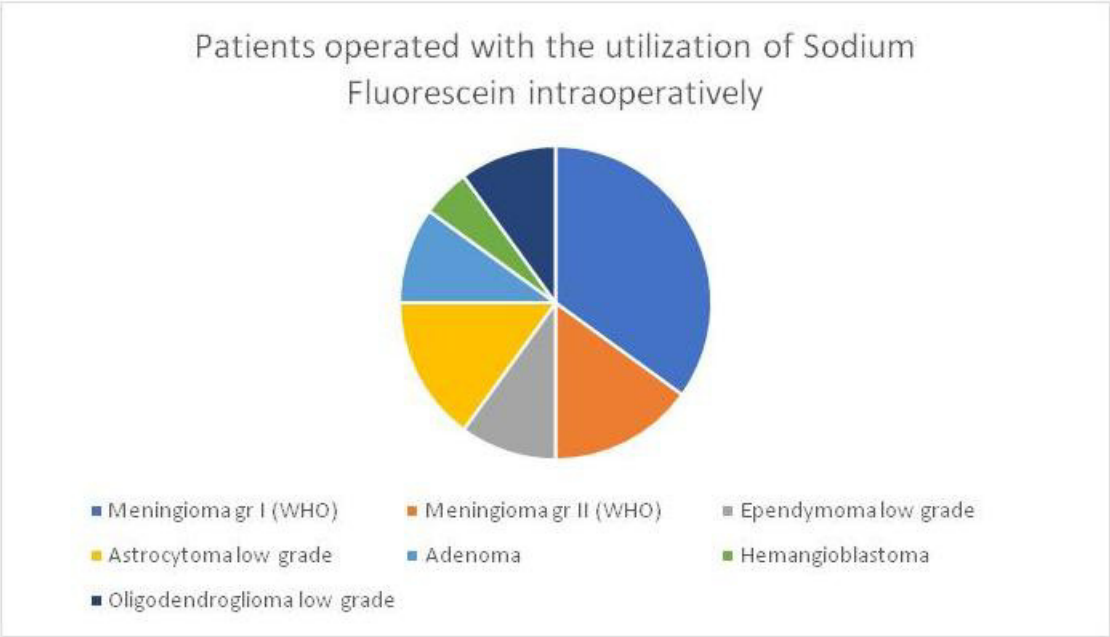


Diagram 2.

Table 3. Evaluated neurological status for postoperative period of patients operated **without** utilization of sodium fluorescein.

Postoperative neurological status	Number of patients	Percentage (%)
Improved	16	26.7
Unchanged	24	40.0
Deteriorated	15	25.0
Exituslethalis	5	8.3

Table 4. Evaluated neurological status for postoperative period of patients operated **with** utilization of sodium fluorescein.

Postoperative neurological status	Number of patients	Percentage (%)
Improved	11	55
Unchanged	6	30
Deteriorated	3	15
Exituslethalis	0	0

seizures, and cardiopulmonary insufficiency. It is important to note that most postoperative neurological deficits are transient and tend to improve or disappear over time. However, some may remain permanent. Our interest lies solely in documenting the patient's condition after surgery, which is why all postoperative complications are classified under "deteriorated patients," regardless of whether the deterioration is temporary or permanent. Thus, the neurological status in the form of statistical data for patients operated on with and without sodium fluorescein is presented in Tables 3 and 4 and Diagram 3.

The extend of tumor resection, amount of residual pathologic tissue and the time for recurrent tumor growth is estimated with radiological imagine methods postoperatively. Magnetic resonance (MRI) with contrast and computer tomography (CT) with contrast were the methods of choice. Although, MRI is a superior method over CT, both of them are sufficient in showing residual or recurrent tumor tissue especially for non-neural origin tumors. Most of the patients are followed up for several years and performed contrast MRI regularly. Those who lack data for long term follow up, were assessed by the postoperative contrast CT scan. Postoperative MRI is performed within the period of three months to three years after surgery. For a more specific comparison, postoperative imagine method were categorised in two time-dependent groups. The first group consists of patients who preformed MRI or CT scan with contrast within the first six months. The second group consists of

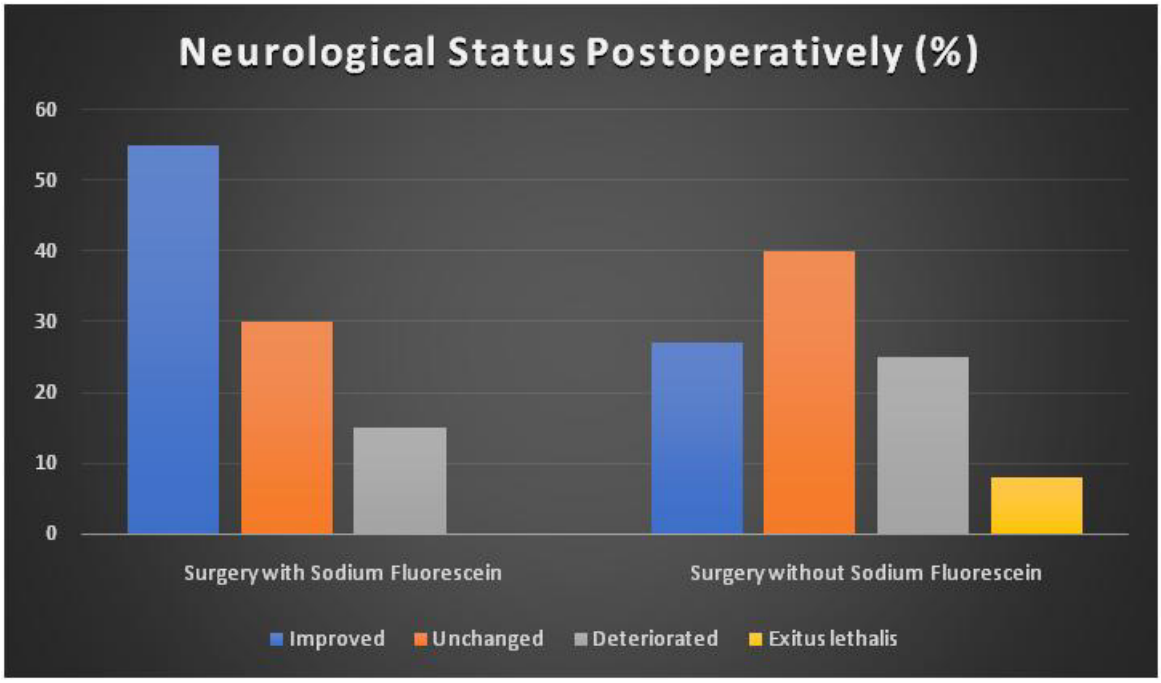


Diagram 3

Table 5. Patients operated without the use of sodium fluorescein during surgery. The sum of patients (in numbers and percentage) is taken for comparison with the examination group.

Residual/Recurrent pathological tissue on postoperative imagine method (MRI or CT with contrast)	Imagine method performed within the first 6 months	Imagine method performed after 6 months	Sum	Percentage from the sum up (%)
Positive (Present)	1	12	**13**	**31.7**
Negative (Absent)	9	19	**28**	**68.3**

Table 6. Patients operated with the use of sodium fluorescein during surgery. The sum of patients (in numbers and percentage) is taken for comparison with the examination group.

Residual/Recurrent pathological tissue on postoperative imagine method (MRI or CT with contrast)	Imagine method performed within the first 6 months	Imagine method performed after 6 months	Sum	Percentage from the sum up (%)
Positive (Present)	4	2	**6**	**30.0**
Negative (Absent)	2	12	**14**	**70.0**

patients who performed the same imagine methods after six months. Furthermore, the patients were categorized weather the imagine methods were positive for residual or recurrent contrast enhancing pathological tissue, or not. The data for patients operated with and without utilization of sodium fluorescein is presented in table 5 and 6 and diagram 4. For simpler comparison we took into consideration only weather the residual/recurrent tumor tissue was present on postoperative MRI/CT scan, or absent. Some data lacks due to discontinued follow up.

Hospitalization days were also taken into account. This serves as an indirect indicator of the patients' condition and surgical success. A shorter hospital stay is associated with a lower number of complications, more precise tumor resection, and quicker return to daily activities. On the other hand, a longer stay is most often due to postoperative complications (systemic and

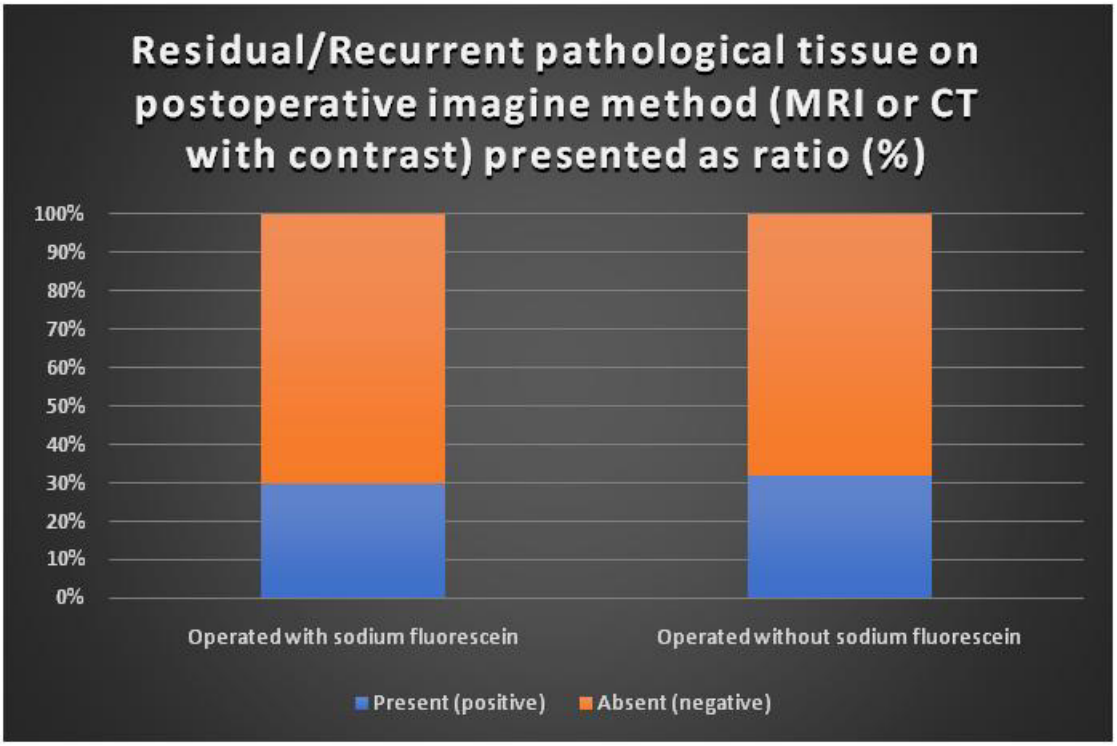


Diagram 4.

Table 7. Days of hospital stay for patients operated without the use of sodium fluorescein during surgery

Hospital days	Sum	Mean value
11,8,6,10,7,7,8,6,7,16,8,7,9,10,7,6,8,8,20,11	180	**9.0**

Table 8. Days of hospital stay for patients operated without the use of sodium fluorescein during surgery.

Hospital days	Sum	Mean value
6,8,9,17,9,9,9,11,11,11,9,9,9,14,8,15,14,25,10,14, 8,9,10,16,10,20,12,7,40,10,9,21,15,17,9,27,10,10,8, 13,28,14,24,20,14,18,9,12,17,20,14,10,12,13,15,20, 29,10,29,13.	849	**14.1**

neurological), problems with residual pathological tissue or damage to healthy brain parenchyma, the need for additional procedures to improve the condition (such as: lumbar drainage, V-P shunt, external drainage, puncture for fluid evacuation, etc.), and the inability of the patient to independently return to daily routines. The number of hospitalization days is presented individually and then summarized as a total and average value (Table 7 and 8 and diagram 5). For simpler comparison between patients operated on with and without sodium fluorescein, only the average value is used.

The last feature for assessing sodium fluorescein usefulness is the operator's opinion of weather it helped in delineating and showing precise tumor's margins allowing him to remove it completely. Although this is a subjective feature, it helped us collect valuable notes during surgery, as each case has specific characteristic. To simplify the notes and make it possible for a statistic comparison we choose to categorise the patients into two groups, depending on weather the sodium fluorescein helped the operator to remove the whole tumor and delineate it precisely, or not. In the first group of patients the surgeon stated that the fluorescent agent helped him continue with tumor resection to the margins and was regarded as useful. The other group of patient is the one where the surgeon did not find sodium fluorescein useful, and could not completely resect the tumor. In that group of patients, the utilization of sodium fluorescein was marked as Not useful. The level of resection of the benign tumors correlates directly with the presents of residual

Diagram 5

Table 9. Notes on usefulness in utilizing sodium fluorescein during surgery according to neurosurgeon's statement for patients operated without fluorescent contrast.

Surgeon's point of view during surgery	Number of patients	Percentage (%)
Useful (complete resection)	11	**73.0**
Not useful (incomplete resection)	4	**26.7**

Table 10. Notes on usefulness in utilizing sodium fluorescein during surgery according to neurosurgeon's statement for patients operated with fluorescent contrast.

Surgeon's point of view during surgery	Number of patients	Percentage (%)
Useful (complete resection)	37	**64.9**
Not useful (incomplete resection)	20	**35.1**

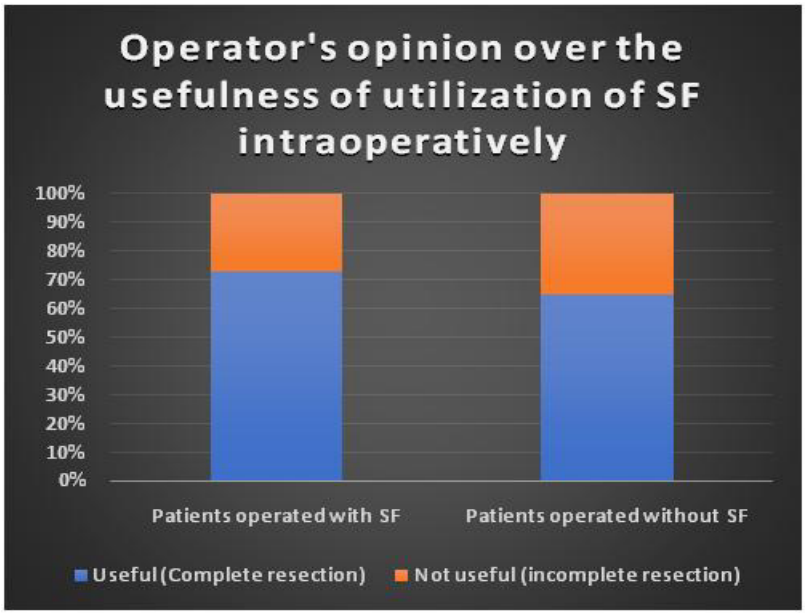


Diagram 6.

tumor tissue on post operative imagine, as well as with the time required for a recurrent tumor to occur. It has also direct impact on the neurological status of the patient, weather is improved, did not change or was worsened. Statistically the usefulness of the utilization of sodium fluorescein from the surgeon's point of view is presented in tables 9 and 10 and diagram 6. Data for

some patients lack due to uncertainty of the neurosurgeon.

DISSCUSION

The postoperative imagine techniques did not show valuable difference between the two groups. Meaning, patients who were applied SF intraoperatively had the same recurrent rate and residual tumor tissue findings as the ones who did not receive contrast agent. In the controlled group data for some patients is lost due to discontinuity of follow up. Another factor that may influence data is the fact that these postoperative images are not performed at the exact same time after surgery. Many of them vary in months or years. Furthermore, CT scan was generally performed for patients who went though some form of postoperative complication. Others were advised to perform MRI six months or one year following surgery. For the ones who did not performed MRI, CT scans were included in the data as a alternative imagine method. From the available data we can conclude that the utilization of SF intraoperatively for benign tumors does not improve the success of surgery and the life expectancy of the patients.

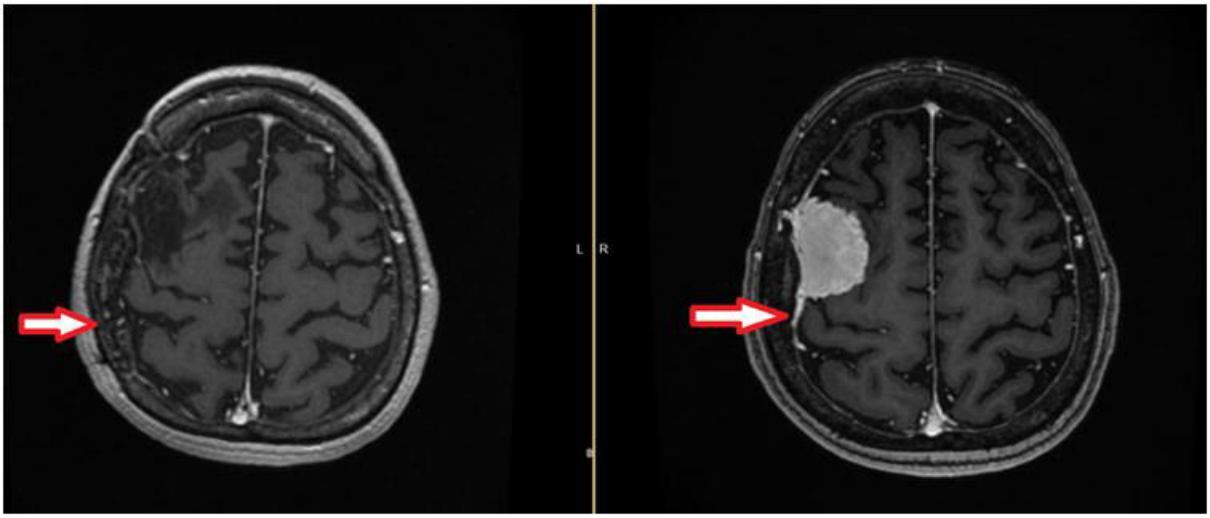
The postoperative neurological status showed improvement with the utilization of SF during surgery. The neurological status depends on the level of resection, timing of surgery, preservation of healthy neurological tissue, damaging surrounding neurovascular structures and residual tumor tissue. All mentioned above can be improved using SF intraoperatively. This is proved by overcoming some unexpected and specific problems for complete tumor removal during surgery. By helping removing the dural tail in meningiomas, delineating tumor margins in low grade astrocytomas and oligodendrogliomas; and finding enhancing residual tissue in ependymomas, sodium fluorescein positively influences the neurological outcome of patients. All these features are described below. It is important to note that in the group of “deteriorated” neurological status we placed patients that showed new neurological abnormalities after surgery. Many of then were temporarily, while others stayed permanently. Examples of such abnormalities are mentioned above in the “methods and materials”.

The days of hospital stay are indirect marker for the operative success. In our clinical study we found significant difference between the hospital stay of patients who were operated with and without the use of SF intraoperatively. The length of stay depends on the overall patient health, postoperative complications, postoperative neurological status, imagine methods and the pathohistological type of the lesion. Patients that underwent complete tumor removal with little or no damage to brain tissue are likely to have less postoperative complications and better neurological status, hence stay fewer days in hospital. By comparing the mean value of hospitalization in both groups we can state that SF improves surgical success rate.

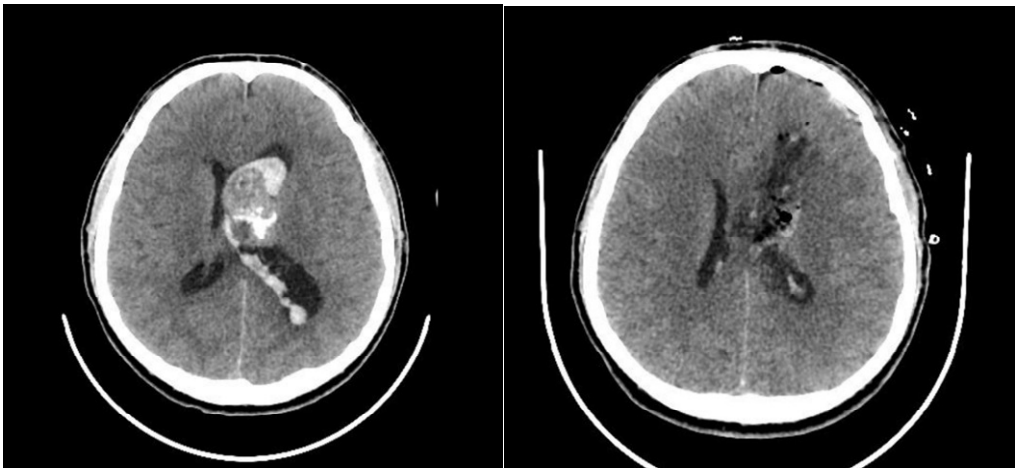
The last feature used in this study for rating level of tumor removal and surgical success is the operator’s opinion on the usefulness in utilizing SF intraoperatively. Although this is a subjective feature and depends directly on the operator’s statements, we believe it helps us get better perspective for the use of the contrast agent during surgery of benign brain and spinal tumors. In order to be able to compare the two groups, we categorized them as a group of patients in which tumor removal was considered complete and group of patients in which residual tumor tissue was suspected. Mostly, the operator has a true perspective for the level of tumor removed or left over due to well established margins of benign tumors (for example meningiomas). Therefore, the operator’s notice during surgery is considered credible. In other words, he can precisely tell whether the SF was useful during surgery and helped to remove the tumor completely, or was not useful and residual tissue persists. When compared statistically, minor difference was found (table 10). Meaning, the neurosurgeon was confident for tumor resection with or without using SF in a similar fashion. Therefore, we conclude that this feature shows no difference in surgical success rate and tumor removal with or without SF.

According to the world literature we have so far SF is considered as a useful fluorescent method only for malignant brain and spine tumors. However, an increasing number of studies which show the positive impact of SF utilization for benign lesions over the operative success are been published. Most of the benign neural lesions are well delineated and easily recognisable. The tumor capsule additionally makes differentiation simple. Nevertheless, as each case varies, each neurosurgical treatment of benign tumors as its own characteristics. Meaning, during surgery many times the neurosurgeon is experiencing unexpected problems with complete tumor removal, which has a direct impact over the residual tissue and time required for a recurrency to occur. One example of such challenge is the meningiomas’ tail removal. As we can see from the results most od our benign lesions were meningiomas (50% and 60% of operated patients with and without SF, respectively). Most meningiomas include dural tail which is adherent to the surrounding dura and difficult to identify during surgery. If not removed, it is a solid ground for a recurrent tumor to occur. In our study we noticed that tail enhancing after SF administration helps the neurosurgeon to maximise resection (Picture 1). This was confirmed by the operator during surgery and meningioma removal. This specific problem we encountered was published in the clinical study of Carlos Eduardo da Silva et al. in which they presented 5 cases of falx meningioma with dural tail enhancement (6). In all cases resection was extended and tumor removal completed.

Although we had only two cases low grade ependy-



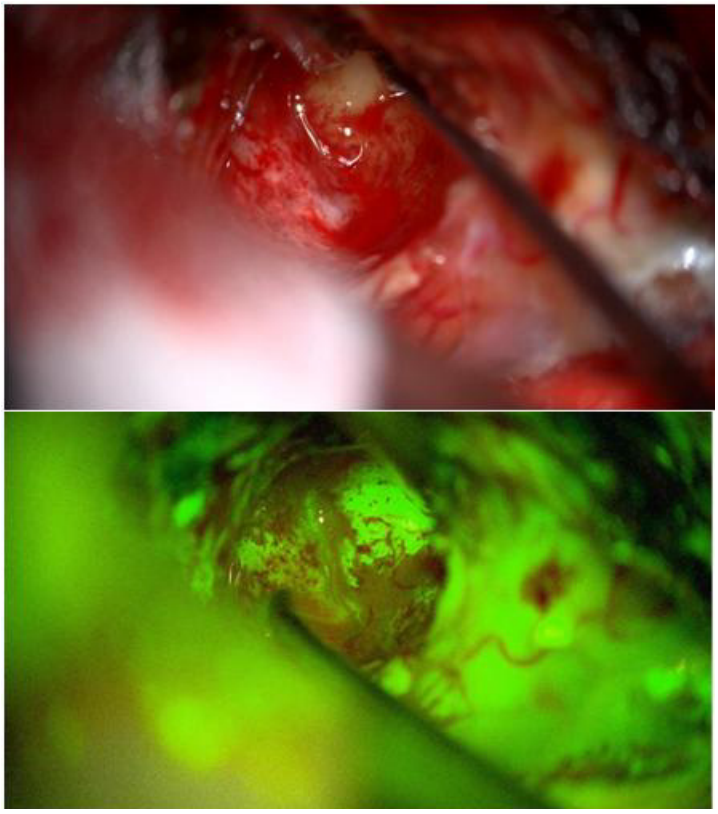
Picture 1. Postoperative and Preoperative MRI of a patient operated from convexity meningioma. The arrow shows dural tail completely resected using SF intraoperatively.



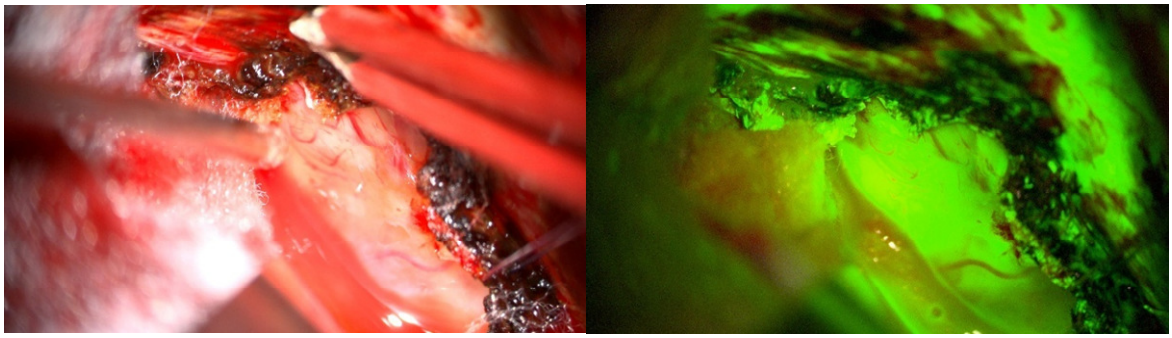
Picture 2. Pre and postoperative CT scan with contrast for patient operated from Ependymoma gr II. Complete resection is achieved using SF intraoperatively

momas, they were sufficient to show that SF helped in finding residual tissue and maximizing surgical resection. In the literature studies, such as the one from Boschi Andrea et al. also prove that SF is useful for the treatment of ependymomas especially in the posterior fossa. One factor that contributes to this is the fact that ependymomas do not have firm capsule and their soft tissue often can be hidden by the anatomical structures of the posterior fossa. Thus we state that SF should be considered in all cases of ependymomas, especially in the posterior fossa (Picture 2).

Low grade astrocytomas can be well delineated and maximally resected using SF intraoperatively. They tend to have similar morphologic tissue as the brain and are sometimes difficult to distinguish. Their shape is commonly irregular with margins curvilinear. In these cases, dying tumor tissue is of big help for the operator. In the control group we encountered difficulties removing the tumors completely, deteriorated neurological status postoperatively and residual/recurrent tumor on post-operative imagine techniques. More specifically, two out of three cases had deteriorated neurological status with residual tissue on postoperative MRI and longer stay in hospital (11+20). The same number of patients with low grade astrocytoma were evaluated in the cohort. Two out of three cases had extended resection as a result of enhancing tumor tissue after SF application. Both cases had improved neurological status and no residual tissue on postoperative MRI (Picture 3 and 4). In the third case of pilocytic astrocytoma residual tissue was left over due to its firm adherence to critical neural structures. This residual tissue however, was clearly visualized and could



Picture 3. Enhancement of residual pilocytic astrocytoma tissue.



Picture 4. Enhancement of sodium fluorescein delineates boundaries of low grade astrocytoma

be resected if not damage to medulla oblongata was in danger. Days of hospital stay were also shorter in the cohort (8+16+8; compared to 11+20+12). Delineation was improved as well.

Important fact to note is enhancing of brainstem. We regard this fact as a disadvantage utilizing SF intraoperatively due to the danger of confusing tumor with critical structures such as the brain stem. Therefore, SF should be carefully used when for surgeries of fossa posterior astrocytomas. Although some studies recommend high dosages od SF for low grade astrocytomas (3), we achieved satisfactory results applying standard 5mg/kg dose intravenously prior to dural opening.

Lastly the fatal outcome should be taken into consideration. The results show that all patients operated with the use od SF intraoperatively survived, whereas 5 patients in the control group passed away postoperatively. These statistics support the use od SF during surgery for benign tumors. However other factors should be taken into account when fatal outcome is discussed. All of the patients who passed away following extirpation od benign brain tumors had many comorbidities and late diagnosis. Furthermore, all patients died of systemic postoperative complications (pulmonary embolus, cardiac arrest, renal failure and et.).

Theoretically, utilization of SF could save more time during tumor extirpation and lower the risk for systemic complications. In any case, our results support utilization od SF for benign tumor resection whenever it is possible.

CONCLUSION

After mentioning all above, we came to a conclusion that sodium fluorescein (SF) should be used for benign brain and spine tumors in every possible situation. Although it has no influence on the recurrence rate, it can be used as a helpful adjunct for doubtable situations during surgery, can increase the operator's confidence and influences survival rate. So far, no significant adverse effect of utilization of SF intraoperatively are published in the literature and can be therefore regarded as a very safe procedure. We believe that patients operated for benign brain and spine tumors should receive a standard dose (5mg/kg) of SF. The precise dosage for tumor delineating vary in the literature and further clinical studies are required for more standardize value. Further studies are required to prove whether sodium fluorescein should be considered as a standard operative feature for benign tumors in neurosurgery. Utilization of sodium fluorescein intraoperatively also depends on the experience of the neurosurgeon with this fluorescent agent.

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