Skull Base Meningiomas and Cranial Nerves Contrast Using Sodium Fluorescein: A New Application of an Old Tool

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Abstract

Objective The identification of cranial nerves is one of the most challenging goals in the dissection of skull base meningiomas. The authors present an application of sodium fluorescein (SF) in skull base meningiomas with the purpose of improving the identification of cranial nerves.

Design A prospective study within-subjects design.

Setting Hospital Ernesto Dornelles, Porto Alegre, Brazil.

Participants Patients with skull base meningiomas.

Main Outcomes Measures Cranial nerve identification.

Results The group of nine meningiomas was composed of one cavernous sinus, three petroclival, one tuberculum sellae, two sphenoid wing, one olfactory groove, and one temporal floor meningioma. The SF enhancement in all tumors was strong, and the contrast with cranial nerves clearly evident. There were one definite olfactory nerve deficit, one transient abducens deficit, and one definite hemiparesis. All lesions were resected (Simpson grades 1 and 2). The analysis of the difference of the delta SF wavelength between the meningiomas and cranial nerve contrast was performed by the Wilcoxon signed rank test and showed $p = 0.011$.

Conclusions The contrast between the enhanced meningiomas and cranial nerves was evident and assisted in the visualization and microsurgical dissection of these structures. The anatomical preservation of these structures was improved using the contrast.

Keywords
- cranial nerves
- fluorescent markers
- fluorescent-guided surgery
- meningiomas
- sodium fluorescein

Introduction

The identification of cranial nerves is one of the most challenging tasks during the dissection of a skull base meningioma. In fact, a favorable outcome depends on the preservation of the vascular structures and the function of the cranial nerves. Neurophysiologic monitoring and the use of neuronavigation devices during the surgery improve the localization and preservation of the nerves. Even so, the identification of the displacement of the cranial nerves and their encasement by large skull base meningiomas remains very difficult in some cases. In this article, the authors present an application of sodium fluorescein (SF) in nine skull base meningiomas and perform a digital analysis of the visual

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contrast between cranial nerves and the enhanced meningiomas. Simpson grade resection and morbidity of the series are also discussed.

Methods

A prospective study within-subjects design was performed. This study included nine patients with skull base meningiomas who were operated on between January 2010 and October 2011. The criteria for inclusion in the series were those patients who presented tumors with radiologic criteria for meningiomas located in the anterior, medial, or posterior cranial base, and those whose lesion involved at least one cranial nerve. These patients were informed about the intraoperative use of SF with the objective of better viewing the tumors during the surgical procedure. After being informed, written consent was obtained before the procedure. The study was submitted and approved by the ethical committee of the Pontifícia Universidade Católica do Rio Grande do Sul, document code/number CEP 11/05729.

The initial dissections were performed, and after exposing the tumors and their relation to the cranial nerves, a dose of 1 g of SF 20% was injected into a peripheral vein. A digital photo was taken through the optical lens of the microscope 10 minutes after the SF injection. The digital camera used was a SONY DSC-W90, 8.1 megapixels, with macro activation on and internal flash off. The light source of the pictures was the same xenon lamp of the surgical microscope that generated the images visualized by the surgeon, thus making the use of special filters or mechanical adaptations unnecessary.

Digital Analysis

To validate the clinical impression of the contrast between SF-enhanced meningiomas and cranial nerves, a digital image analysis was performed. The pictures were saved in JPEG format with minimal compression. A mask was applied using Adobe Photoshop CS6 (Adobe Systems Incorporated, San Jose, California, United States), isolating the tumors and the cranial nerves from other tissues. Images were then analyzed by the IMAGE PRO PLUS 4.5.1 program (Media Cybernetics, Silver Spring, Maryland, United States). The SF postinjection image was submitted to the program for analysis first, the tumor and cranial nerve separately. In the area of interest, different colors were selected manually using level 4 sensitivity (range: 1–5). A false red color was used to highlight the area stained at the wavelength (WL) of the SF in the image. The area enhanced by SF was saved, and the program calculated the total area of the picture showing the SF staining area both in the tumors and cranial nerves. The absolute value obtained by such a statistical analysis of the program was then saved on an Excel (Microsoft, Redmond, Washington, United States) spreadsheet. Finally, the same process was performed for pre–SF-injected images of tumors and cranial nerves. The specific SF wavelength of the postinjection picture was recorded by the program and applied to the selected area of the cranial nerve. The program then calculated the area presenting the SF staining. Data were saved for statistical analysis on the Excel spreadsheet.

Statistical Analysis

Data from both groups of measurements, tumors and cranial nerves, measured by the software were then evaluated. Then the percentage change of SF staining area for tumors and cranial nerves was calculated using the following equation:

$$\%\ \text{Change} = \text{post-value} - \text{pre-value} / \text{pre-value} \times 100$$

The relative percentage change (delta) was calculated for both tumors and cranial nerves groups, demonstrating the real impact of the SF enhancement on the structures.

The following equation was applied:

$$\text{Relative}\ \%\ \text{Change (delta)} = (\text{post-value} + 0.5) + (\text{pre-value} + 0.5) / (\text{pre-value} + 0.5) \times 100$$

To overcome zero values in the percentage calculation, we utilized Agreste's correction, adding 0.5 to each value during operations.

The Wilcoxon signed rank test was used to assess the significance of the difference among the relative percentage change of tumors and cranial nerves.

Results

The group of nine meningiomas was composed as follows: one cavernous sinus, three petroclival, one tuberculum sellae, two sphenoid wing, one olfactory groove, and one temporal floor.

►**Table 1** presents the values of SF staining area in the tumors and cranial nerves both pre- and post-SF injection measured by Image Pro Plus. ►**Table 2** presents the difference between delta relative SF staining enhancement in tumors and cranial nerves. ►**Table 3** presents the relationship to tumor site, size, Simpson grade resection, and neurologic deficits.

►**Fig. 1** illustrates the clinical effects observed under the surgical microscope in six examples.► **Figs. 2** and **3** illustrate

Table 1 Absolute values of the sodium fluorescein staining area

Meningioma site	TU pre SF SA	TU post SF SA	CN pre SF SA	CN post SF SA
CS	174	3798	0	0
OG	358	44,405	4345	7060
PC1	85	6196	2274	13,284
PC2	1492	4753	154	645
PC3	10	3311	177	638
SW1	510	66,992	37,816	95,420
SW2	0	3535	0	0
TF1	464	5457	2014	2712
TS1	71	55,170	15	5014

Abbreviations: CN, cranial nerve; SA, staining area; SF, sodium fluorescein; TU, tumor.

Table 2 Value of the delta relative sodium fluorescein staining enhancement in tumors and cranial nerves

Meningioma site	▲ relative TU	▲ relative CN
CS	2077	1
SW 2	707,000	1
TF	1075	35
OG	12,286	62
SW 1	13,023	152
PC 3	31,438	260
PC2	218	318
PC 1	7147	484
TS	77,062	32,252

Abbreviations: CN, cranial nerve; TU, tumor.

the dissection of the sixth cranial nerve passing through the middle of a petroclival meningioma. ►**Fig. 4** illustrates the final result after the tumor removal and preservation of the cranial nerves. ►**Fig. 5** illustrates the graphic representation of the delta SF staining area in the tumors and cranial nerves.

Discussion

Moore et al first investigated SF in neurosurgery.[1] Other authors tested the applicability of SF during surgical removal of glioblastoma and metastatic disease.[2–6] The application of SF during cranial base tumors was first described in 2010.[7] In the former study, the clinical effect of the enhancement of skull base tumors using SF was very positive. The application of SF during skull base meningiomas surgery making it possible to observe the contrast between the tumors and cranial nerves is an extension of the previous study using SF in skull base tumors.[7]

Meningiomas are the most common tumor lesion in the cranial base, and they involve critical neural and vascular structures in most cases. Surgical removal, as radical as possible, is still the recommended treatment for most of these lesions. A curative procedure is the goal for both patient and physician. Advances in surgical techniques, neuronavigational systems, and neurophysiologic monitoring have shown a progressive improvement in resections.[8–25] Even so, concern about the morbidity related to dissections around the cranial nerves and arterial and venous vessels remains during the surgical management of skull base meningiomas and represents a limitation for the aggressive removal of such tumors.[22–30]

The use of SF in skull base meningiomas was first investigated in a introductory series that presented promising results in terms of SF enhancement of the mass.[7] The cranial nerves, however, were considerably less affected by the SF intravascular application. The contrast between SF-enhanced meningiomas and involved cranial nerves create a favorable environment for dissection and neural preservation (►**Figs. 1–4**).

All tumors were resected to obtain Simpson grade 1 and 2[30] (►**Table 3**). Definite morbidity involving a cranial nerve occurred only in a giant olfactory groove meningioma (11%) that presented definite anosmia in the postoperative neurologic examination. Transient sixth nerve palsy (11%) was observed in patient with a recurrent temporal fossa meningioma with cavernous sinus involvement, but the patient had completely recovered at the 3-month follow-up. One hemiparesis, secondary to venous obliteration in a petroclival meningioma, was also observed in the present series. This had no relation to the SF contrast between tumors and nerves.

The meningiomas showed a marked enhancement by gadolinium on magnetic resonance imaging (MRI), and this aspect could explain the strong SF captured by the tumors. Blood-brain barrier (BBB) disruption plays a role in the gadolinium enhancement of lesions on MRI.[2–7]

SF is also present in the cerebrospinal fluid (CSF), specifically in the first hour. Constant irrigation and suction to clean the surgical field makes the tumor and cranial nerve contrast effective and more evident.

A wide range of the simple arithmetic sum of the SF staining area was demonstrated by the software (►**Table 1**). This probably occurred as a result of the variability of light

Table 3 Morbidity related to meningiomas resection

Meningioma site	Size, cm	Simpson grade	CN definitive deficit	CN transient deficit	Other deficits
Olf. groove	> 3	1	Olfactory		
Tub. sellae	< 3	1			
Cav. sinus	> 3	2			
Temporal fossa	> 3	2		Abducens	
Petroclival	< 3	2			
Petroclival	> 3	2			
Petroclival	> 3	2			Hemiparesis
Sphenoid wing	> 3	1			
Sphenoid wing	> 3	1			

Abbreviations: Cav, cavernous; CN, cranial nerve; Olf, olfactory; Tub, tuberculum.

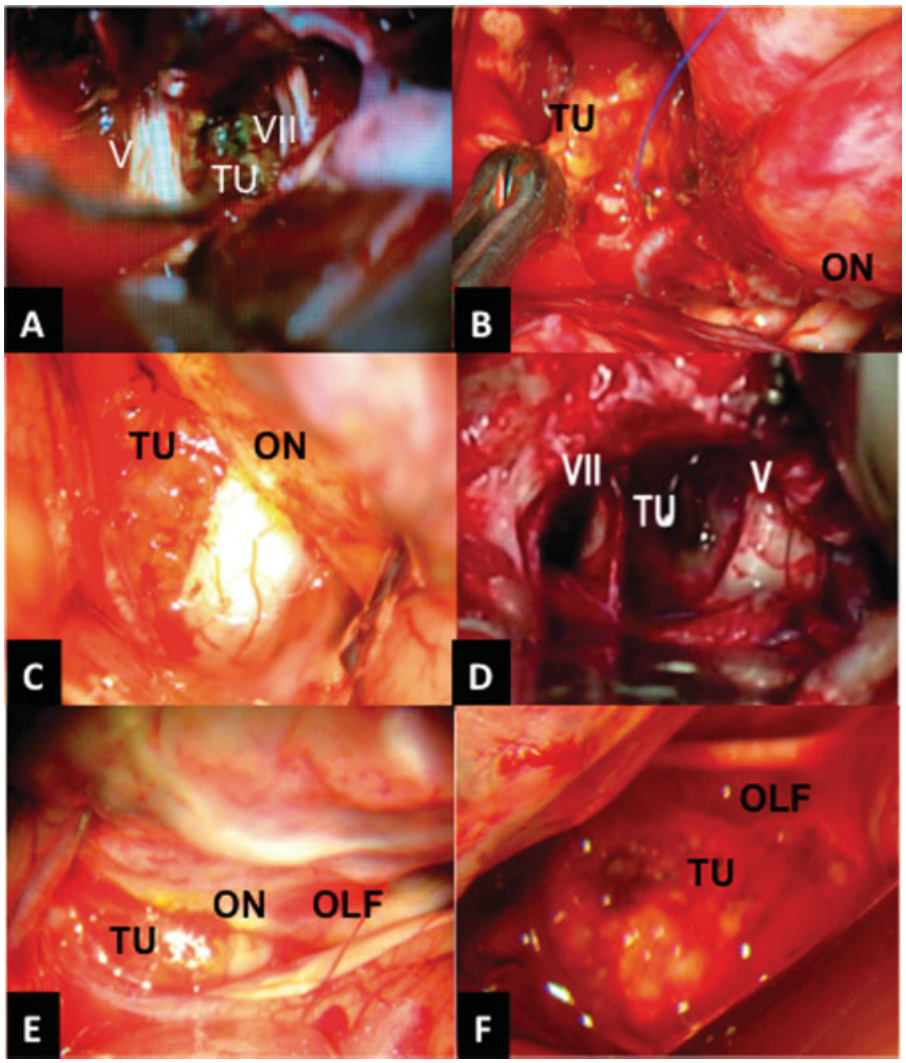

Fig. 1 Post–sodium fluorescein enhanced meningiomas and cranial nerves. (A) Tuberculum sellae. (B) Left anterior clinoid. (C) Left cavernous sinus. (D) Right petroclival. (E) Right sphenoid wing. (F) Left sphenoid wing. OLF, olfactory nerve; ON, optic nerve; TU, tumor; VII, facial nerve.

while taking the pictures using the ocular lens of the microscope, but the difference between cranial nerve SF WL and meningiomas SF WL remained unaltered, even with external light variations. All cases but one, a petroclival meningioma (►**Fig. 1D**), presented a wide difference in the digital analysis between the tumors and cranial nerves enhancement, with strong predominance in meningiomas (►**Fig. 2**). This exception was probably due to less tumor contrast and the CSF enhancement around the nerves, which could have played a significant role in the result. We chose to include the original picture to illustrate this finding, but during the surgical removal, the washing of the subarachnoid space, the dye effect was completely removed in the cranial nerves.

The dye was evident after 10 minutes of SF injection and persisted during the tumor dissection for several hours,

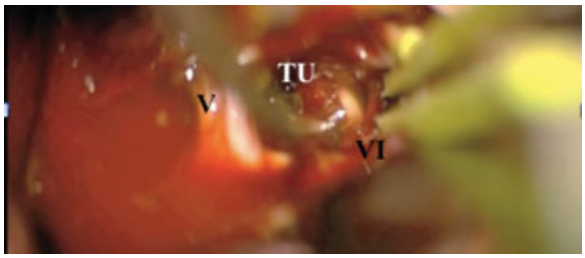

Fig. 2 Initial exposure of the sixth cranial nerve inside a petroclival meningioma. TU, tumor; V, trigeminal nerve; VI, abducens nerve.

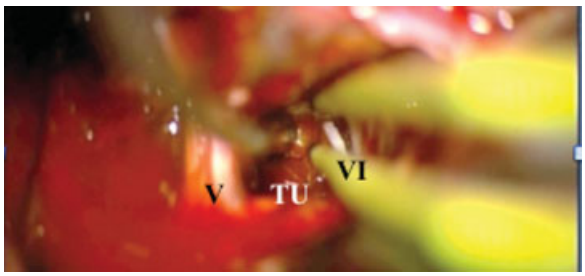

Fig. 3 Dissection of the sixth cranial nerve. Observe the contrast between the tumor and the fifth and sixth cranial nerves. TU, tumor; V, trigeminal nerve; VI, abducens nerve.

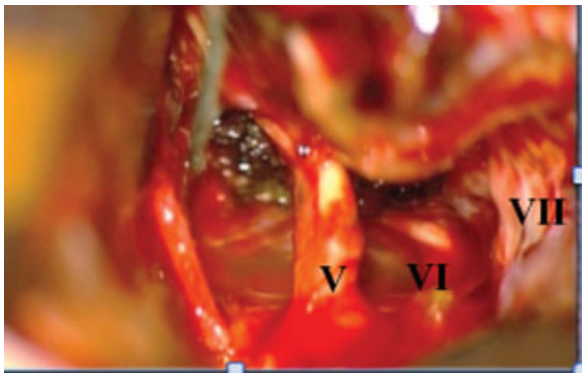

Fig. 4 Petroclival meningioma removed with preservation of fifth, sixth, and seventh cranial nerves. TU, tumor; V, trigeminal nerve; VI, abducens nerve; VII, facial nerve.

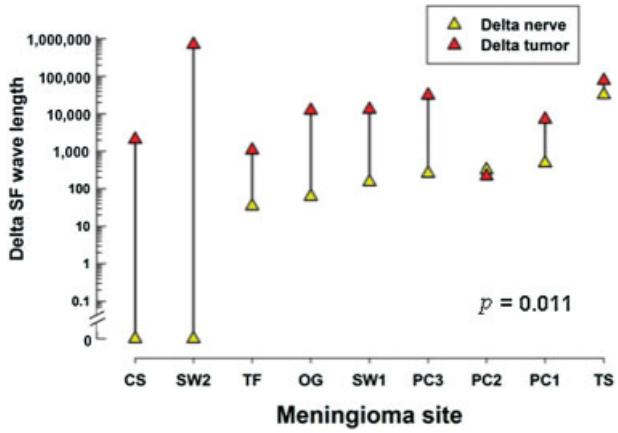

Fig. 5 Graphic representation of the differences between tumors and cranial nerves with SF enhancement. CS, cavernous sinus; OG, olfactory groove; PC, petroclival; SW, sphenoid wing; TF, temporal floor; TS, tuberculum sellae.

which made it possible to observe the contrast with the cranial nerves during the procedures.[1,5]

The patients included in the series presented no adverse reaction to SF application. The dye was eliminated in ~ 36 hours through urine.

Digital and statistical analyses were included with the objective of using a quantitative method to corroborate a qualitative application. Clinical impression was evident, and the Wilcoxon signed rank test presented a significant difference ($p = 0.011$) among the delta relative changes, both pre- and post-SF enhancement of the meningiomas and the cranial nerves.

The series presents petroclival and cavernous sinus cases, in which the contrast between meningiomas and cranial nerves could be more interesting for neural preservation (►**Fig. 1**). The dissection around the fourth through twelfth cranial nerves was helped by the contrast between nerves and tumors, emphasized by the SF enhancement of meningiomas. Actually, the CN nerves passing through the tumors, as the sixth cranial nerve into the petroclival meningioma illustrated in ►**Figs. 2–4**, were equally contrasted by the SF enhancement of the meningioma. This aspect indicates that the technique is promising for cranial nerve identification even if the nerves are stretched or displaced by tumors. Other cases of the anterior fossa were also included to observe and measure such differences in SF enhancement. Special attention was paid to the optic nerve.

The technique also helped in the dissection of distorted and thinned out cranial nerves. The SF enhancement of the meningiomas probably occurs as a result of the vascular supply and BBB disruption inside and around the tumors. Cranial nerves severely thinned and stretched out over a tumor present some vascular restriction, especially when cranial nerve deficits are observed, and this aspect could be an explanation for the contrast between meningiomas and such distorted nerves.

One important aspect is that the contrast was observed using a standard xenon light microscope. This method can be reproduced in any department with low-cost digital cameras without special devices or adaptations. However, specific filters that could reinforce the SF visualization should be tested in future studies.

SF was previously used in skull base for CSF identification, but the application of an intraoperative tumor contrast was a new application of this tool. SF has a low cost, high safety, and is universally available. It is a particularly interesting dye for use in skull base surgery.

Conclusion

The SF did not enhance cranial nerves with the same intensity as the skull base meningiomas. The contrast between the enhanced meningiomas and nerves was strong and assisted with the microsurgical dissection and the anatomical preservation of these structures. Further studies with larger series should be performed to confirm SF as a possible tool for cranial nerve preservation during the removal of skull base meningiomas.

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