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ORIGINAL ARTICLE - PERIPHERAL NERVES

Extracapsular dissection in peripheral nerve schwannoma surgery using bright light and fluorescein sodium visualization: case series

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Abstract

Background Schwannomas are the most frequent peripheral nerve sheath tumors and are treated by surgical resection when symptomatic. Tumor removal is performed by intraneural dissection and enucleation. In order to safely remove the tumor from the nerve, the use of sodium fluorescein has recently been proposed to distinguish the tumor from the adjacent normal nerve fibers, before incision of the tumor pseudocapsule and during intraneural tumor dissection.

Methods We report a consecutive case series of 5 peripheral nerve schwannomas operated in 4 patients, in which we evaluate the usefulness of sodium fluorescein compared to usual visual landmarks, at each step of the surgical procedure.

Results After exposition of the schwannoma, sodium fluorescein helped with the localization of intracapsular en passant nerve fascicles in only one case. Hence, the definition of a safe entry zone for capsular incision relied mainly on nerve monitoring and direct visualization of en passant nerve fascicles under microscope. During intraneural dissection, there was a sharp contrast between the fluorescent tumor and the non-fluorescent adjacent pseudocapsule in most cases but the colorimetric variation between tumor and normal tissue induced by fluorescence did not outperform the natural contrast between the yellow true capsule and the gray-red layers of the pseudocapsule.

Conclusion Based on these results, we consider that the limited additional value of sodium fluorescein in primary peripheral nerve schwannoma surgery does not warrant its use in daily clinical practice. Additional studies are needed to assess its usefulness during the surgery of recurrences and tumors which are intertwined with several fascicles of origin such as neurofibromas.

Keywords Peripheral nerve sheath tumors · Schwannoma · Sodium fluorescein · NF2

Introduction

Schwannomas are the most frequent peripheral nerve sheath tumors and represent 5% of all soft tissue tumors [9]. They are slow-growing neoplasms that almost never undergo malignant transformation and are therefore treated by surgical resection only when symptomatic. Tumor removal is performed by intraneural dissection and enucleation of the tumor [13]. To achieve excellent neurological outcome, surgery must focus on avoiding iatrogenic nerve injury during dissection in order to preserve neurological function. As neurological deficits often result from fascicular manipulation or transection during dissection from the tumor capsule, the definition of the correct surgical plane is paramount to preserve function. Indeed, permanent neurological deficits are not uncommon after peripheral nerve schwannoma surgery, ranging from 7.5 to 36.7% of cases [1, 4, 5, 7, 8].

In order to achieve gross-total resection of the tumor while preserving nerves fascicles embedded in the tumor pseudocapsule, the correct visualization of the dissection plane may be facilitated by recently described "color cues." In direct light, Stone and Spinner observed that the correct dissection plane corresponding to the tumor "true capsule" was a thin, translucent, and shiny membrane covering the predominantly

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Table 1 Patient characteristics

Patient number	Sex	Age at surgery	Sporadic/ NF2	Preoperative symptoms	Localization	Affected nerve	Tumor size (cm^3)	Tumor resection	Post-operative symptoms
1	F	43	Sporadic	Local pain, irradiated pain in the hand	Left arm	Branch of the musculocutaneous nerve at the biceps	12.3	Total	Pain resolution, no deficits
2	F	61	Sporadic	Pain along the ulnar nerve, paresthesias of the 4th and 5th digits	Axilla	Ulnar nerve	4	Total	Pain resolution, no deficits
3	F	27	NF2	Local pain	Left arm	Radial nerve	0.9	Total	Pain resolution, no deficits
				Local pain	Left hand	Digital nerve	0.3	Total	Pain resolution, no deficits
4	F	67	Sporadic	Ascending sciatic pain, foot numbness	Left ankle	Tibial nerve	11.8	Total	Complete pain resolution, mild heel numbness

yellow tumor and they defined this "first yellow layer" as the landmark for dissection [12]. Using fluorescein sodium and newly developed microscope filters, Pedro et al. showed that peripheral nerve schwannomas displayed increased fluorescence compared to adjacent normal nerve tissue, allowing for a better definition of the dissection plane and reducing the risk of tumor remnants [10]. Following these two publications, we decided to evaluate the two techniques of tumor dissection in a prospective case series of peripheral nerve schwannomas.

Methods

This study was conducted by a single surgeon (M.P) on consecutive schwannoma cases operated on between February and April 2019. The basic principles of peripheral nerve schwannoma surgery, including fascicular mapping, intraneural dissection, and en-bloc tumor enucleation, were respected. All tumors were operated with the use of neuromonitoring (I.B) to localize motor nerve fibers in the tumor pseudocapsule. Adult patients with a preoperative suspicion of schwannoma were included. Informed consent covering application of SF (Fluorescein Sodium 10%, SERB, France) was obtained from all patients prior to surgery. SF was injected intravenously during anesthetic induction at a previously reported dose (0.5 mg/kg body weight) [10]. Each case was performed using a specific fluorescence filter YELLOW 560 on the Zeiss Kinevo Microscope©. Pictures of the tumor dissection were recorded during surgery, and the collected material was retrospectively analyzed. All image analyses were performed using the GIMP© Software. A standardized ROI (4500 pixels) was used to record the red, green, blue (RGB) values of the specific anatomic regions of each

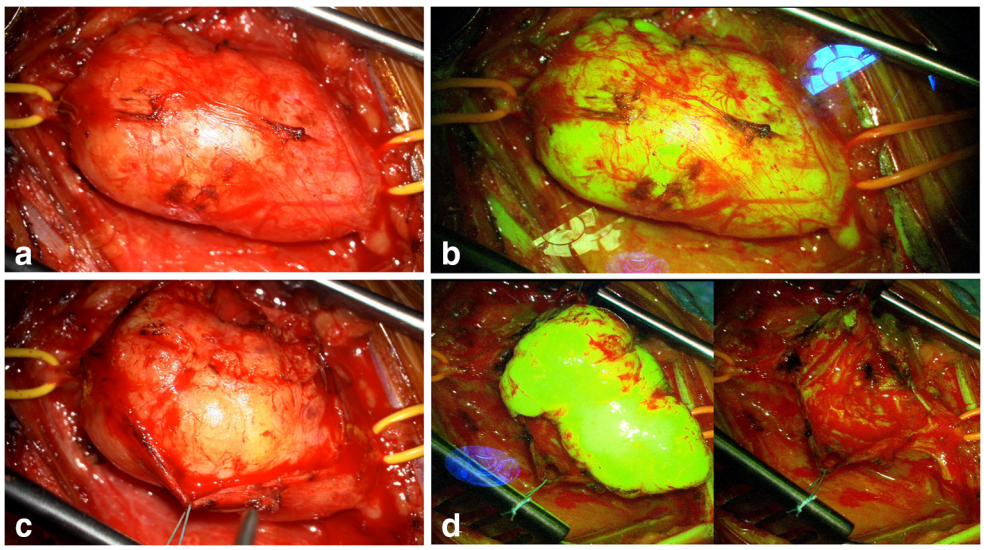

Fig. 1 Patient 1. **a** Exposition of the tumor. **b** Application of fluorescence filters allows the correct visualization of the tumor and the affected nerve but does not highlight passing nerve fascicles inside the tumor capsule. **c** After capsular incision, the yellow color of the tumor "true capsule" is visible. **d** The enucleated tumor displays high fluorescence (left panel) while no fluorescent tumor remnant can be seen on the dissected nerve (right panel)

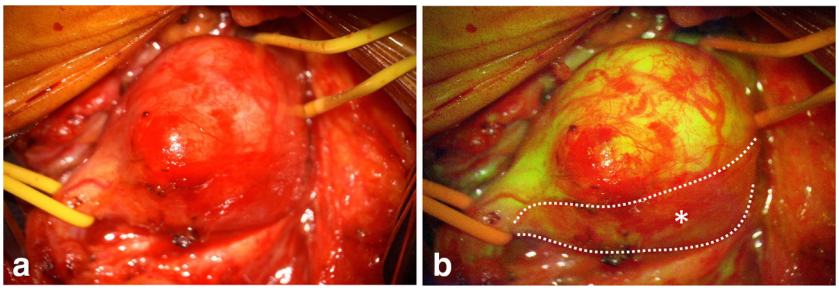

Fig. 2 Patient 2. **a** Exposition of the ulnar nerve schwannoma. **b** Fluorescence allows the visualization of passing nerve fascicles at the lower part of the tumor capsule (asterisk)

procedure: tumor capsule, corresponding to the tumor surface before incision of the capsule; adjacent nerve, corresponding to the adjacent dissected normal nerve; and tumor, corresponding to the tumor surface after enucleation.

Case series

Patient characteristics are described in Table 1. The cohort consisted of 4 women with a mean age at surgery of 49 years (27–67 years). One patient had neurofibromatosis type 2 (NF2) and harbored two peripheral nerve schwannomas while all other tumors were sporadic. Tumor volumes ranged from 0.3 to 12.3 cm^3. All tumors were resected en-bloc. Based on previous reports [10], all patients were operated using the smallest dosage of fluorescein sodium (0.5 mg/kg). No side effects of fluorescein injection were reported. Adjacent nerve tended to be less fluorescent than the tumor itself (Fig. 1) but nerve fascicles embedded in the tumor capsule were only visible in one case (Fig. 2) (Table 2). Incision of the tumor capsule was therefore made using electric mapping of nerve fibers and based on the location of adjacent normal nerve.

During tumor dissection, the goal is to divide the pseudocapsule until the thin, shiny, and translucent layer corresponding to the tumor true capsule is found. If correctly identified, the plane of the true capsule allows a simple blunt dissection around the tumor to perform enucleation. If significant resistance is encountered, further layer-by-layer attempts at deepening pseudocapsular dissection are sometimes needed. When using sodium fluorescein, we observed that the high fluorescence of the tumor concealed the multiple layers of the pseudocapsule and the thin layer of the true capsule was also less easily identified (Fig. 1c, d). Conversely, the use of white light under high magnification allowed a better visualization of the different layers of the pseudocapsule (Fig. 3c) and the identification of the first yellow layer that forms the true capsule of the tumor (Fig. 4e, f) [12]. After tumor removal, the affected nerve was either fluorescent (Fig. 3) or not (Fig. 1), making it hazardous to look for possible tumor remnants. In matched images, the yellow color observed after capsule incision under bright light tended to perfectly match the green color found under fluorescence (Fig. 4). On image analysis, value of green color intensity was higher in schwannomas compared to the adjacent normal nerve without reaching statistical significance ($P = 0.06$) (Fig. 5). Values of red and blue intensity were not different in the capsule and the adjacent affected nerve. Value of yellow color, obtained after conversion of RGB into CMYK pictures, was only slightly higher in schwannomas compared to the tumor capsule (less than 50% increase in yellow intensity in all cases).

Discussion

Peripheral nerve schwannoma enucleation has become a standardized technique to obtain gross-total resection without harming nerve fascicles embedded in the tumor pseudocapsule and therefore avoiding neurological deterioration. In order to perform tumor enucleation safely, there are two critical steps: 1—identification of normal nerve fibers at the surface of the tumor; 2—identification of the right dissection plane between the tumor pseudocapsule and its true capsule during intraneural dissection.

Table 2 Subjective evaluation by the surgeon of the fluorescence of the different anatomical structures during surgery

Patient number	Tumor fluorescence	Adjacent nerve fluorescence	Intracapsular fascicles fluorescence	Nerve fluorescence after total tumor resection
1	High	Low	Mild	Low
2	High	Low	Not visible	Low
3-1	High	High	High	High
3-2	High	Low	Not visible	Low
4	High	Low	Low	Low

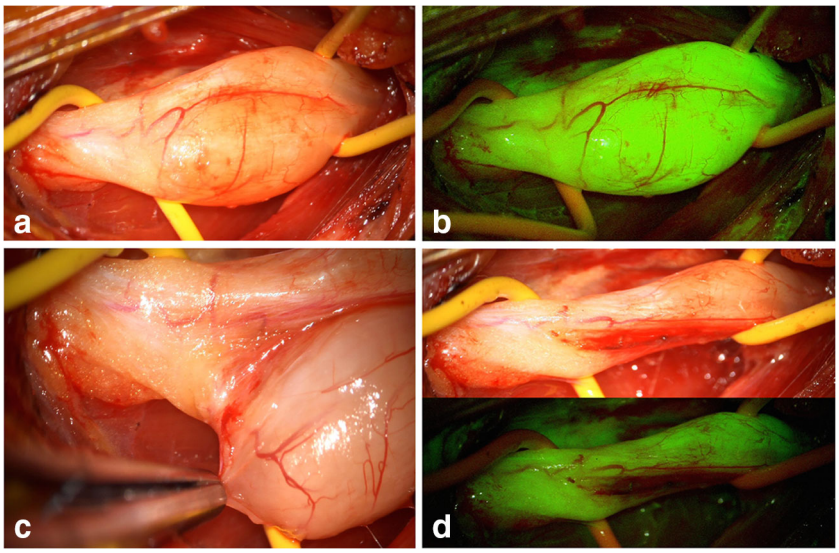

Fig. 3 Patient 3—radial nerve tumor. **a** In this case, the normal nerve fascicles were easily identified next to the schwannoma. **b** Fluorescence did not allow the differentiation of the tumor from adjacent normal nerve. **c** Under high magnification, the different planes surrounding the tumor "true capsule" are identified. **d** After tumor enucleation, normal radial nerve remains fluorescent

In order to open the pseudocapsule in a fascicle-free zone, intraoperative neuromonitoring should ideally be performed. When unavailable or negative, normal fascicles are sometimes easily visualized entering and exiting the tumor like in patient 3. Recently it has been suggested that the use of intraoperative sodium fluorescein could enhance tissue differentiation during this first step. In our small case series, we found only one case in which fluorescence allowed correct visualization of the position of passing nerve fascicles at the surface of the capsule (patient 1).

The identification of the right dissection plane is usually aided by visual and sensory cues: a change in color with the

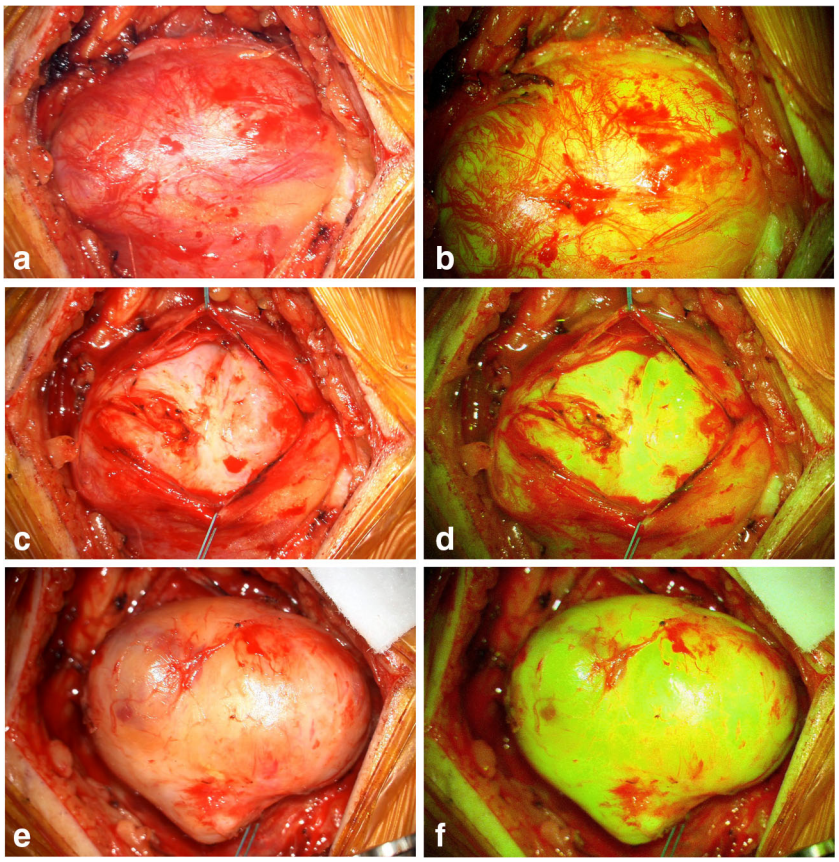

Fig. 4 Patient 4. Comparison of visual landmarks during peripheral nerve schwannoma surgery under bright light (**a**, **c**, **e**) and fluorescence (**b**, **d**, **f**). At each step, the yellow color of the tumor "true capsule" mirrors the fluorescence at exposition (**a**, **b**), capsule incision (**c**, **d**), and after enucleation (**e**, **f**). Of note, the bright fluorescence of the tumor (**f**) conceals the details of vascularization and structure of the true capsule seen under bright light (**e**)

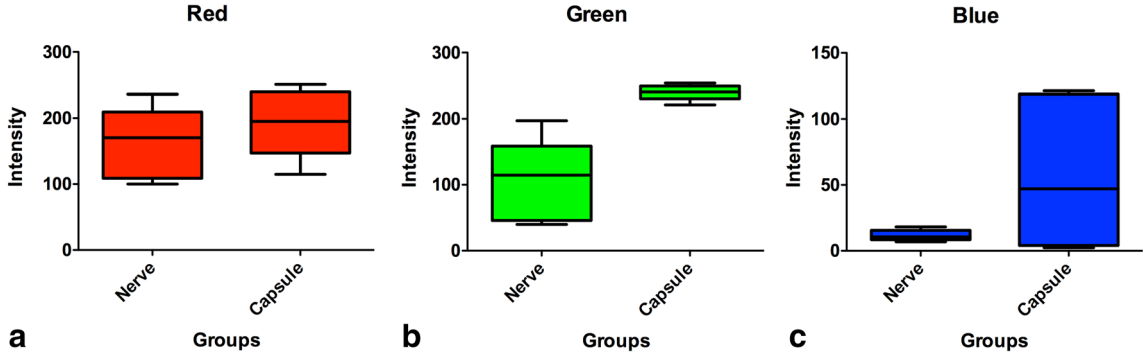

Fig. 5 Box-plot diagrams showing the distribution of intensity scores for red (**a**), green (**b**), and blue (**c**) means of the tumor capsule and the adjacent non-affected nerve

identification of a yellow layer and a relative decrease in the resistance needed to continue this yellow layer plane around the tumor mark the tumor true capsule [12]. We tried to evaluate in this small case series the added value of intraoperative sodium fluorescein to perform this surgical step. While we acknowledge the clear-cut difference of fluorescence between the pseudocapsule and the tumor itself, as already described [10], we believe that this technique is not reliable and specific enough to advocate for its standardized use in peripheral schwannoma surgery. There is otherwise a good sensitivity as all schwannomas in our series were fluorescent. Nonetheless, the high contrast between the tumor and the adjacent nerve under fluorescence may impair the correct visualization of the different planes of the pseudocapsule during surgery, as demonstrated in patient 3. The use of the "yellow layer" hint may therefore be as useful as the fluorescence signal to identify the true capsule, while allowing a better visualization of the different layers of the pseudocapsule under bright light. Intraoperative sodium fluorescence may nonetheless prove helpful during surgery at relapse when dissection planes are less easily identified [10]. Similarly, sodium fluorescein might prove helpful to perform the dissection of tumors more closely intertwined with nerve fibers, such as neurofibromas [6].

There are of course limitations to our exploratory study, the first of them being the small number of patients. Sporadic and NF2-related schwannomas may also display different fluorescence patterns as reflected by the high fluorescence of the radial nerve before and after dissection in our third case. This observation might be related to the underlying pathological nature of macroscopically normal nerves in NF2, as already demonstrated by MRI [2, 11] and pathology, with the presence of Schwann cell tumorlets in otherwise normal peripheral nerves [3]. Additional and larger studies are therefore needed to address these questions more precisely. However, the additional value of fluorescence is merely to improve the safety and not the extent of resection. It could therefore prove difficult to demonstrate its usefulness in a dedicated trial. In terms of vision improvement, our opinion is that sodium fluorescein, although rather sensitive, does not enhance comfort and safety of surgery enough to support its cost in this restricted indication and has therefore no place in primary peripheral nerve schwannoma surgery.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Pitié-Salpêtrière research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent All four patients have consented to the submission of the case reports to the journal.

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