CHAPTER FIVE

Fluorescein-guided surgery for spinal gliomas: Analysis of 220 consecutive cases

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Abstract

Objective: Sodium fluorescein (FL) is widely used as a fluorescent tracer for brain tumor resection. However, FL-guided resection of spinal gliomas has been reported only occasionally. To evaluate the safety, characteristics, and usefulness of FL-guided surgery in the resection of spinal glioma.

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Methods: Between January 2015 and December 2018, 220 consecutive patients with 227 spinal gliomas underwent FL-guided resection using the Zeiss Pentero 900 surgical microscope with an integrated YELLOW 560 filter. FL evaluation and clinical outcomes were analyzed.

Results: No FL-related complications occurred in this series. Entire tumor fluorescence was observed in 161 (70.93%) gliomas, nodular fluorescence in 46 (20.26%) tumors, and no fluorescence in 20 (8.81%) tumors. The intraoperative fluorescence of 217 (95.59%) gliomas was highly correlated with preoperative contrast-enhancing magnetic resonance imaging, except in eight ependymomas, one pilocytic astrocytoma, and one diffuse midline glioma. Gross-total resection was achieved in 78.85% (179/227) of spinal gliomas, including 94.30% (149/158) ependymal tumors and 43.48% (30/69) astrocytic and oligodendroglial tumors. At the final clinical follow-up, the spinal function of 75 (33.04%) patients showed significant improvement, 105 (46.26%) showed stabilization, and 47 (20.70%) showed deterioration.

Conclusion: FL is a safe and useful real-time tool that could enhance tumor borders or residual tumors and hence increase the gross-total resection rate in cases with contrast-enhanced tumors.

Abbreviations

5-ALA 5-aminolevulinic acid
BBB blood–brain barrier
EOR extent of resection
FL fluorescein
GTR gross-total resection
MRI magnetic resonance imaging
PR partial resection
STR subtotal resection

1. Introduction

Spinal gliomas are rare in the central nervous system. Although the extent of resection (EOR) is regarded as a prognostic factor, gross-total resection (GTR) of glioma is challenging for neurosurgeons (Garcés-Ambrossi, McGirt, Mehta, et al., 2009; Li, Chu, Xu, et al., 2014; Wostrack, Ringel, Eicker, et al., 2018; Zou, Sun, Zhou, et al., 2018). It is difficult to balance maximum cytoreduction with the preservation of healthy spinal cord tissue because of the infiltrative nature of some tumors.

Fluorescence-guided surgery with sodium fluorescein (Acerbi, Broggi, Schebesch, et al., 2018; Acerbi, Cavallo, Schebesch, et al., 2017;

Roberts & Olson, 2017; Suero Molina & Stummer, 2018) (FL, a passive targeting agent) or 5-aminolevulinic acid (Inoue, Endo, Nagamatsu, et al., 2013; Millesi, Kiesel, Woehrer, et al., 2014; Stummer, Pichlmeier, Meinel, et al., 2006) (5-ALA, a metabolic targeting agent) has been increasingly used to distinguish tumors from the normal brain or spinal cord tissue thus improving surgical resection. FL was the first fluorophore used for brain tumor surgery and was introduced in 1948 (Moore, Peyton, et al., 1948); low-dose FL was later widely applied for resection of brain tumors using a novel YELLOW filter system (Carl Zeiss Co., Oberkochen, Germany) in 2013 (Schebesch, Proescholdt, Höhne, et al., 2013) and of spinal gliomas in 2017 (Acerbi et al., 2017). 5-ALA was first reported for locating brain tumors in 1998 (Stummer, Stocker, Wagner, et al., 1998) and spinal glioma in 2006 (Shimizu, Utsuki, Sato, et al., 2006). Unlike 5-ALA, FL, as an inexpensive and biosafe fluorophore that is easily administered and can accumulate in the intracellular space and mark regions of blood–brain barrier (BBB) disruption. However, to our knowledge, FL-guided resection of spinal glioma has been reported only occasionally (Acerbi et al., 2017; Suero Molina & Stummer, 2018).

This is the first study to systematically analyze the safety, characteristics, and usefulness of fluorescence guidance for spinal glioma surgery with the aim of determining the following: (1) the role of fluorescein-guided techniques in removing spinal gliomas; (2) the relationship between intraoperative fluorescence staining and preoperative contrast-enhanced magnetic resonance imaging (MRI); and (3) whether fluorescein-guided surgery can be helpful in the resection of nonenhancing gliomas.

2. Materials and methods

2.1 Patient selection

The Institutional Review Board of our hospital approved this study and written informed consent was obtained from all of the patients. We retrospectively reviewed the data obtained in 220 consecutive patients with 227 spinal gliomas resected with the assistance of FL between January 2015 and December 2018. The clinical data are summarized in Tables 1 and 2.

2.2 Operative protocol

Patients were placed in the lateral prone posture. FL (3–5 mg/kg, Guangzhou Baiyunshan Mingxing Pharmaceutical Co., China) was

Table 1 Summary of the clinical characteristics of 220 patients with 227 spinal gliomas.

Variables	Total ($n = 227$)	Ependymal tumors ($n = 158$)	Astrocytic and oligodendroglial tumors ($n = 69$)
Age, yrs	37.80 ± 15.37	41.40 ± 13.13	29.55 ± 16.98
Male:Female	116:111	75:83	41:28
Duration of symptoms, month	12 ± 32	15.5 ± 33	10 ± 21
No. of glioma/lesion level	3/7	3/6	4/7
Symptoms (%)			
Sensory deficits	187 (82.38)	128 (81.01)	59 (85.51)
Motor deficits	149 (65.64)	91 (57.59)	58 (84.06)
Pain	123 (54.19)	86 (54.43)	37 (53.62)
Bladder/bowel dysfunction	97 (42.73)	62 (39.24)	35 (50.72)
Preoperative treatment (%)			
No	169 (74.45)	127 (80.38)	42 (60.87)
Biopsy or resection	30 (13.22)	21 (13.29)	9 (13.04)
Corticosteroid therapy	26 (11.45)	11 (6.96)	15 (21.74)
Radiotherapy	4 (1.76)	1 (0.63)	3 (4.35)
Chemotherapy	3 (1.32)	0	3 (4.35)
Extent of resection (%)			
Gross-total resection	179 (78.85)	149 (94.30)	30 (43.48)
Subtotal resection	30 (13.22)	5 (3.16)	25 (36.23)
Partial resection	18 (7.93)	4 (2.53)	14 (20.29)
Spinal function at follow-up (%)			
Improvement	75 (33.04)	56 (35.44)	19 (27.54)
Stabilization	105 (46.26)	83 (52.53)	22 (31.88)
Deterioration	47 (20.70)	19 (12.03)	28 (40.58)
Duration of follow-up, months	20 ± 24	22 ± 24	18 ± 22.5

Table 2 MRI and fluorescence characteristics of spinal gliomas.

F L	MRI					
	Ependymal tumors ($n = 158$)			Astrocytic and oligodendroglial tumors ($n = 69$)		
	Whole tumor enhanced ($n = 129$)	Nodular ($n = 24$)	No enhanced ($n = 5$)	Whole tumor enhanced ($n = 39$)	Nodular ($n = 21$)	No enhanced ($n = 9$)
Entire tumor fluorescence (%)	124 (96.12)	0	0	37 (94.87)	0	0
Nodular fluorescence (%)	2 (1.55)	21 (87.50)	0	2 (5.13)	21 (100)	0
No fluorescence (%)	3 (2.33)	3 (12.50)	5 (100)	0	0	9 (100)

FL, fluorescein; MRI, magnetic resonance imaging.

intravenously administered after anesthesia induction and skin test. Laminoplasty or laminectomy was performed via a midline posterior approach and was followed by a durotomy and myelotomy. Microsurgical procedures were performed by one senior doctor (G.H.W.) under monitoring by electromyography, somatosensory and motor-evoked potentials. For visualization, a Zeiss Pentero 900 surgical microscope (Carl Zeiss Co., Oberkochen, Germany) with an integrated YELLOW 560 filter was used. Generally, the senior doctor (G.H.W.) resected the tumor under white light illumination and the microscope could be switched from white light to fluorescent illumination during resection. After tumor resection, a final examination under fluorescence was performed to determine whether tumor tissue remained.

2.3 Data collection and analysis

Data were collected and analyzed by three doctors (Z.X.S., L.K.J., and J.W.). All patients underwent pre- and postoperative spinal MRI (3.0T, GE, America), and the MRI data were reviewed to determine the tumor location (Fig. 1) and evaluate the enhancement of the tumor (classified as whole tumor enhancement, nodular enhancement, and nonenhancement), tumor level, lesion level (including tumor, edema, syrinx, and cyst), and EOR (Fig. 2). The EOR was classified as GTR (resection of all visible tumor), subtotal resection (STR, residual tumor $\leq$20% of the initial size), and partial resection (PR, residual tumor >20% of the initial size) according to pre- and postoperative MRI. Under a YELLOW 560 filter, the fluorescence of the tumor was classified as entire tumor fluorescence, nodular fluorescence, or no fluorescence.

The neuropathologist was blinded to the intraoperative fluorescence status when obtaining an independent histopathological diagnosis following World Health Organization 2016 criteria. The spinal function was assessed

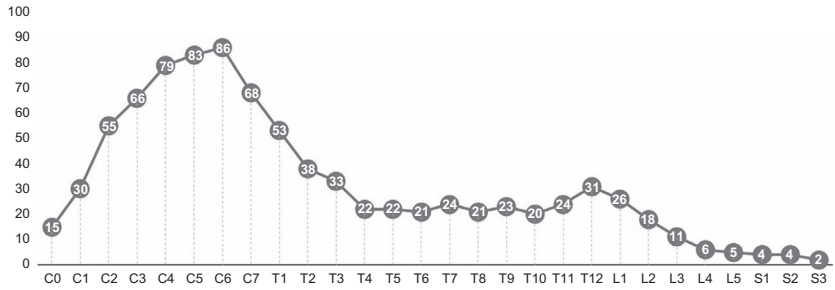

Fig. 1 The location of spinal gliomas. C0 indicates a tumor located above the C1 level.

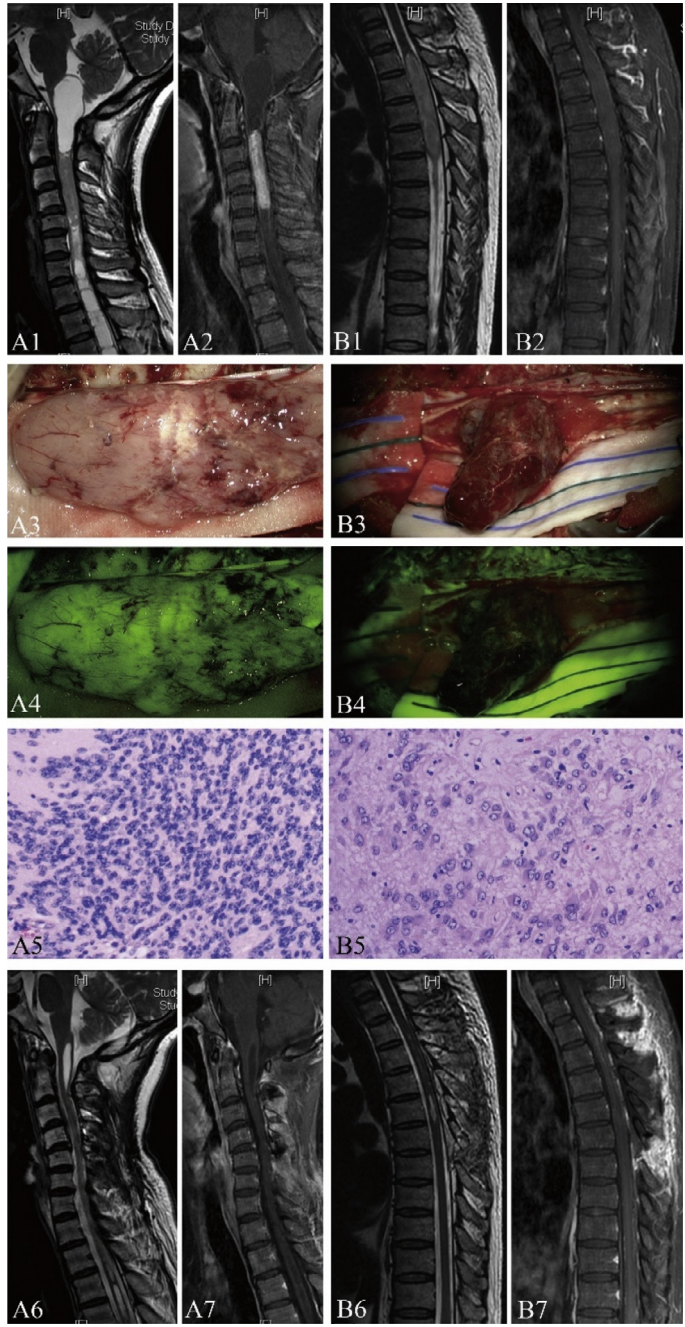

Fig. 2 Magnetic resonance imaging (MRI) and intraoperative fluorescein staining. A1–A7: Preoperative T2-weighted (A1) and contrast-enhanced T1-weighted (A2) sagittal MRI showing an enhanced tumor at the C2–C5 levels. Fluorescein (FL)-guided resection under inspection with white (A3) and fluorescent (A4) light. Histopathological examination confirmed the final diagnosis of ependymoma (A5). Postoperative MRI confirmed complete tumor resection (A6 and A7). B1–B7: Preoperative MRI showing a non-enhancement tumor at the T2–T5 levels (B1 and B2). FL-guided resection under inspection with white (B3) and fluorescent (B4) light. Postoperative histopathological examination confirmed the final diagnosis of ependymoma (B5). Postoperative MRI confirming complete tumor resection (B6 and B7).

and classified as "improvement," "stabilization," or "deterioration (including death)" according to the McCormick scale both before surgery and at the final clinical follow-up.

3. Results

3.1 Patient-related characteristics

Two hundred twenty patients with 227 spinal gliomas underwent fluorescein-guided resection. Multiple gliomas were resected in one procedure in four patients, and three patients underwent microsurgery twice because of tumor recurrence.

The mean age was 37.80 ± 15.37 years old, and 116 males and 110 females were included. The mean duration of symptoms was 12 ± 32 months. The most common clinical presentation was sensory deficits (82.38%). Other symptoms included motor deficits (65.64%), pain (54.19%), and bowel and bladder dysfunction (42.73%). The median tumor level was three spinal segments, and the median lesion level was seven spinal segments. The locations of gliomas are presented in Fig. 1 and were most commonly the cervical cord followed by the upper thoracic cord.

Prior to resections reported in this study, 197 (86.78%) gliomas were newly diagnosed and unresected, 30 (13.22%) gliomas underwent biopsy or resection, 26 (11.45%) tumors underwent preoperative corticosteroid therapy, four (1.76%) gliomas was performed with radiotherapy, and three (1.32%) gliomas underwent chemotherapy.

3.2 Fluorescence and treatment-related characteristics

No fluorescein-related complications occurred. Using a Zeiss Pentero 900 surgical microscope with an integrated YELLOW 560 filter, we observed entire tumor fluorescence in 161 (70.93%) out of 227 spinal gliomas (Fig. 2A1–A7), nodular fluorescence in 46 (20.26%) tumors (Fig. 3), and no fluorescence in 20 (8.81%) tumors (Fig. 2B1–B7). Intraoperative fluorescence was, among the 217 (95.59%) gliomas, highly correlated with the preoperative contrast-enhancing MRI data except in eight ependymomas, one pilocytic astrocytoma, and one diffuse midline glioma (Table 2).

According to MRI data, GTR was achieved in 78.85% (179/227) of spinal gliomas, STR in 13.22% (30/227), and PR in 7.93% (18/227). The mean clinical follow-up was 20 ± 24 months. At the final clinical follow-up, the spinal function of 75 (33.04%) patients showed significant

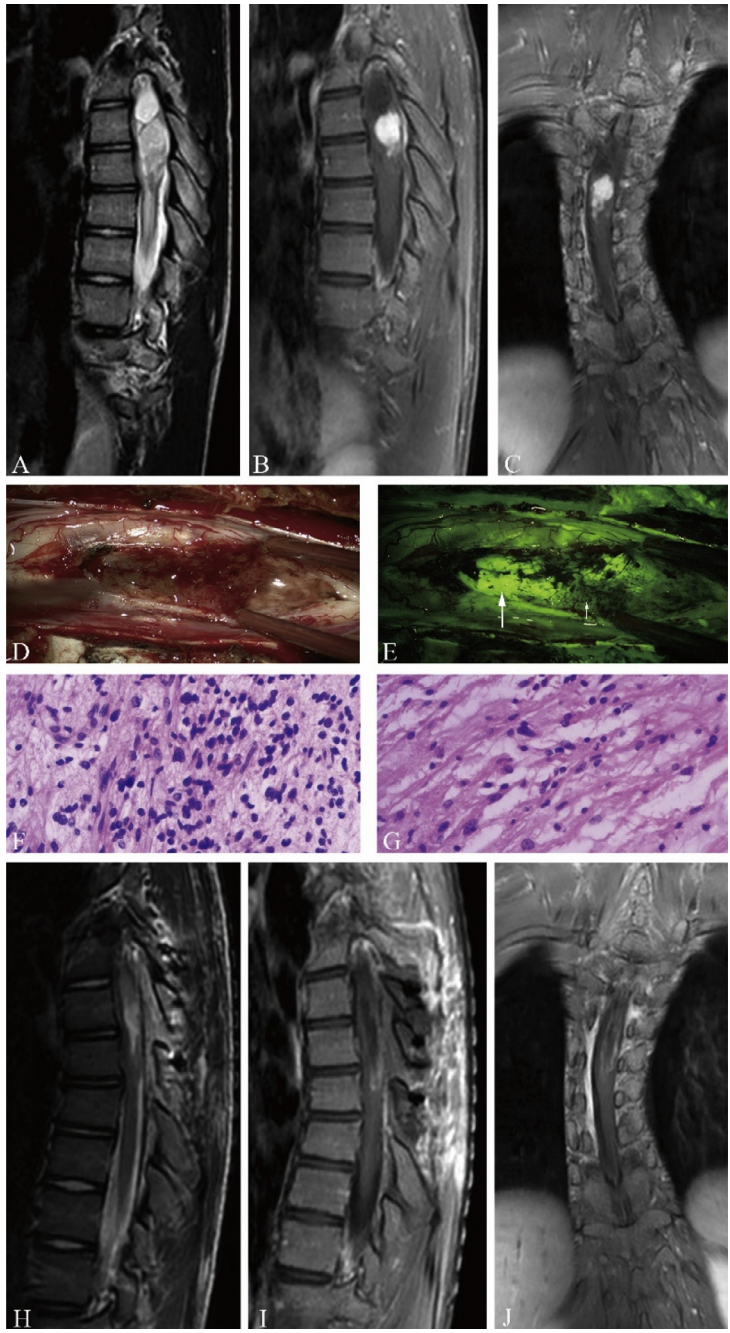

Fig. 3 Preoperative T2-weighted (A) and contrast-enhanced T1-weighted (B and C) MRI showing a nodular enhanced tumor at the T5–T7 levels. FL-guided resection under inspection with white (D) and fluorescent (E) light. Histopathological examination confirmed the final diagnosis of diffuse astrocytoma (F: large arrow in E, and G: small arrow in E). The fluorescent area (large arrow) had greater tumor cell density than the region with no fluorescence (small arrow). Postoperative MRI confirming complete tumor resection (H–J).

improvement, 105 (46.26%) showed stabilization, and 47 (20.70%) showed deterioration (18 patients died: eight with glioblastomas, four with anaplastic astrocytoma, two with anaplastic oligoastrocytoma, one with diffuse midline glioma, one with diffuse astrocytoma, one with anaplastic ependymoma, and one with ependymoma).

Based on the WHO classification of central nervous system tumors, there are 158 (69.60%) ependymal tumors, 69 (30.40%) astrocytic and oligodendroglial tumors (Table 2).

4. Ependymal tumors

One hundred fifty-eight ependymal tumors were resected using a Zeiss Pentero 900 surgical microscope with an integrated YELLOW 560 filter, and Patient and treatment-related characteristics were summarized in Table 1.

Entire tumor fluorescence occurred in 98 (78.40%) ependymomas, 21 (95.45%) myxopapillary ependymomas, and five (45.45%) anaplastic ependymomas. Nodular fluorescence was observed in 17 (13.60%) ependymomas, five (45.45%) anaplastic ependymomas, and one (4.55%) myxopapillary ependymoma. No fluorescence was present in 10 (8.00%) ependymomas and one (9.09%) anaplastic ependymoma. However, the region of fluorescein staining was smaller in eight ependymomas, which was not completely in accordance with the enhancing region observed on the preoperative contrast-enhancing MRI.

GTR was achieved in 94.30% (149/158) of ependymal tumors, STR in 3.16% (5/158), and PR in 2.53% (4/158). At the final clinical follow-up, the spinal function of 56 (35.44%) patients showed significant improvement, 83 (52.53%) showed stabilization, and 19 (12.03%) showed deterioration.

4.1 Astrocytic and oligodendroglial tumors

Sixty-nine astrocytic and oligodendroglial tumors were resected using a Zeiss Pentero 900 surgical microscope with an integrated YELLOW 560 filter, and Patient and treatment-related characteristics were summarized in Table 1.

Seven (43.75%) diffuse astrocytomas, seven (77.78%) glioblastomas, six (46.15%) pilocytic astrocytomas, six (50.00%) anaplastic astrocytomas, five (62.50%) diffuse midline gliomas, three (75.00%) anaplastic oligoastrocytomas, two (100%) oligoastrocytomas, and one (100%) pleomorphic

xanthoastrocytoma showed entire tumor fluorescence. Five (38.46%) pilocytic astrocytomas, five (41.67%) anaplastic astrocytomas, four (25.00%) diffuse astrocytomas, four (100%) oligodendroglioma, three (37.50%) diffuse midline gliomas, one (11.11%) glioblastoma, and one (25.00%) anaplastic oligoastrocytoma showed nodular fluorescence. Five (31.25%) diffuse astrocytomas, two (15.38%) pilocytic astrocytomas, one (8.33%) anaplastic astrocytoma, and one (11.11%) glioblastoma revealed no fluorescence. However, one pilocytic astrocytoma and one diffuse midline glioma showed nodular fluorescence despite whole tumor enhancement on a preoperative MRI.

GTR was achieved in 43.48% (30/69) of ependymal tumors, STR in 36.23% (25/69), and PR in 20.29% (14/69). At the final clinical follow-up, the spinal function of 19 (27.54%) patients showed significant improvement, 22 (31.88%) showed stabilization, and 28 (40.58%) showed deterioration.

5. Discussion

Microsurgical resection plays a key role in the management of spinal gliomas and could help patients relieve symptoms and improve prognosis. However, in some patients, total tumor resection may be difficult because of the tumor's infiltrative nature. Several intraoperative imaging technologies, such as neuronavigation, fluorescence-guided surgery, intraoperative MRI and ultrasound, are increasingly used to distinguish tumors from normal brain tissue, thus improving surgical resection. However, those technologies are scarcely used in the resection of spinal gliomas. To our knowledge, this is the first study to systematically evaluate the safety, characteristics, and usefulness of FL in the resection of spinal gliomas.

FL is a biosafe fluorophore with a low rate of severe complications (1/1900) and death (1/222,000); the rate of complications is related to the dose of FL (Moosbrugger & Sheidow, 2008; Yannuzzi, Rohrer, Tindel, et al., 1986). Only two studies have reported FL-related complications in resection of brain tumors using high-dose FL (20 mg/kg), including anaphylactic reactions with severe hypotension and bradycardia (Dilek, Ihsan, & Tulay, 2011; Tanahashi, Lida, & Dohi, 2006). However, when using the YELLOW 560 filter, low-dose FL-guided surgery (3–5 mg/kg) eliminates the occurrence of severe FL-related complications. In addition, patients were not maintained in darkened surroundings because of potential

skin phototoxicity, which occurs in patients after 5-ALA administration. In our series, intravenous FL (3–5 mg/kg) was injected after the skin test, and no FL-related complications occurred.

FL is an intraoperative fluorescent agent that can accumulate in the extracellular space via a disrupted BBB (Diaz, Dios, Hattab, et al., 2015). The majority of spinal gliomas showed some degree of contrast-enhancement at preoperative MRI. Therefore, the region of FL staining is theoretically in accordance with the preoperative contrast-enhanced areas (Fig. 2) (Kobayashi, Ando, Kato, et al., 2018; White, Miller, Layton, et al., 2007). Acerbi et al. (2017) retrospectively reviewed the clinical and intraoperative data obtained in seven patients with spinal gliomas and found that five ependymomas and one pilocytic astrocytoma displayed fluorescence, and one astrocytoma showed no fluorescent staining, completely in accordance with the preoperative contrast-enhanced MRI data. In the present study, 168 (74.01%) gliomas presented whole tumor contrast enhancement, 45 (19.82%) showed nodular enhancement, and 14 (6.17%) showed no enhancement on preoperative contrast-enhanced T1-weighted MRI (Table 2). However, the intraoperative fluorescence of 10 (4.41%) tumors was markedly different from that observed in the preoperative MRI. Two patients with ependymoma or pilocytic astrocytoma received preoperative corticosteroid therapy, and one patient with ependymoma underwent surgical resection and radiotherapy at another hospital. Corticosteroids may lead to the restriction of FL accumulation in the extracellular space and thereby reduce FL staining because of the tightening effect on the BBB (Grabb & Gilbert, 1995). However, we were unable to determine any correlation between the corticosteroids and intraoperative fluorescence.

Some studies have also reported that fluorescein staining could be present not only in contrast-enhanced regions on preoperative MRI but also in nonenhancing regions (Bowden, Neira, Gill, et al., 2018; Neira, Ung, Sims, et al., 2017; Zhang, Tian, Huang, et al., 2017). Zhang et al. (2017) obtained and analyzed the nonenhancing regions of 10 fluorescein stained biopsies, including two malignant gliomas, seven gliosis or tumor cell infiltrations, and one normal cerebral tissue. Bowden et al. (2018) reported that 10 of 13 (76.92%) tumors that presented nonenhancement and T2/fluid-attenuated inversion-recovery hyperintense showed patchy fluorescence, and a diagnosis of glioma was achieved in 19 (19/20, 95%) tissue samples obtained from these areas. The reason for FL staining in nonenhancing regions may be related to the differential permeability profiles of gadolinium (Omniscan®, GE Healthcare, Ireland) and FL according to their different

molecular weights (gadolinium, 573.66 and FL, 376.28) and the pathological characteristics of tumors (e.g., high cell density and proliferative activity) (Bowden et al., 2018; Neira et al., 2017; Zhang et al., 2017). However, no nonenhancing region of tumor in the present study presented the entire tumor or nodular fluorescence.

Several studies have used a YELLOW 560 filter and suggested that resection with low-dose FL could detect tumors with a sensitivity of 82.20–94.40% and a specificity of 88.60–95.00%, improve the rates of GTR and further improve survival (Acerbi et al., 2018, 2017; Acerbi, Broggi, Eoli, et al., 2014; Catapano, Sgulò, Seneca, et al., 2017; Hamamcıoğlu, Akçakaya, Göker, et al., 2016; Katsevman, Turner, Urhie, et al., 2019). Katsevman et al. (2019) compared the clinical outcomes of patients who underwent neurosurgery with FL vs those who did so without FL and found that low-dose FL increased the rates of gross- or near-total resection (47/64, 73.44% vs 21/40, 52.50%) and improved median survival (78 weeks vs 60 weeks). Acerbi et al. (2017) resected seven spinal gliomas under YELLOW 560 filter visualization and reported that GTR was obtained in five ependymomas and one pilocytic astrocytoma, while STR was obtained in one astrocytoma. In the present study, we resected spinal gliomas using both fluorescence and white light mode. After presumed GTR was obtained under white light, we checked for potential residual tumors using a fluorescence module and detected residual tumors with fluorescein staining in tumors that were resected. Similar to previous studies, our results showed that 78.85% of the patients achieved GTR, 13.22% achieved STR, and 7.93% achieved PR. In addition, the GTR rate of ependymal tumors was higher than astrocytic and oligodendroglial tumors (94.30% vs 43.48%).

FL is a useful tool for the resection of spinal gliomas and the detection of potential residual tumors, especially for high-grade gliomas. However, fluorescence guidance is not "useful" only for gliomas. Peritumoral spinal cord edema and cystic components may also display fluorescence, and fluorescein extravasation can be observed in the tumor cavity after surgical injury. The necrotic portion of the tumor did not stain with fluorescein. Therefore, neurosurgeons should improve their ability to evaluate the information comprehensively, thus avoiding the risk of over-resection, which can potentially be even more catastrophic than in cranial surgery.

The major limitations of this study are its retrospective and observational nature. Unfortunately, the lack of approval has limited the use of 5-ALA, and this study focuses on the value of clinical and neuroimaging data related

to FL in spinal gliomas. Admittedly, the normal spinal cord cannot be biopsied during surgery, and we did not compare the fluorescence and non-fluorescent samples at the boundaries of the tumors. It is also necessary to investigate methods to obtain objective measurements rather than individual impressions.

6. Conclusions

This is the first study to systematically analyze the safety, characteristics, and usefulness of FL-guided resection for spinal glioma surgery. Intraoperative fluorescence of gliomas was highly correlated with the preoperative contrast-enhancing MRI. FL is a safe and useful real-time tool that could enhance tumor borders or residual tumors and thereby increase the GTR rate in cases with contrast-enhanced tumors. However, FL-guided surgery was not helpful for the resection of nonenhancing tumors.

Acknowledgment

None.

Disclosure

The authors report no conflict of interest concerning the material or methods used in this study or the findings specified in this paper.

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