The impact of fluorescence guidance on spinal intradural tumour surgery

Sven O. Eicker · Frank W. Floeth · Marcel Kamp ·
Hans-Jakob Steiger · Daniel Hänggi

Received: 7 June 2012 / Revised: 12 November 2012 / Accepted: 2 January 2013 / Published online: 10 January 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract

Purpose 5-Aminolevulinic acid (5-ALA)-based fluorescence-guided surgery was shown to be beneficial for cerebral malignant gliomas. Extension of this technique for resection of meningiomas and cerebral metastasis has been recently evaluated. Aim of the present study is to evaluate the impact of fluorescence-guided surgery in spinal tumor surgery.

Methods Twenty-six patients with intradural spinal tumors were included in the study. 5-ALA was administered orally prior to the induction of anesthesia. Intraoperative, 440 nm fluorescence was applied after exploration of the tumor and, if positive, periodically during and at the end of resection to detect tumor-infiltrated sites.

Results Tumors of WHO grade III and IV were found in five patients. In detail intra- or perimedullary metastasis of malignant cerebral gliomas was found including glioblastoma WHO grade IV ($n = 2$), anaplastic astrocytoma WHO grade III ($n = 1$), anaplastic oligoastrocytoma WHO grade III ($n = 1$). In addition, one patient suffered from a spinal drop metastasis of a cerebellar medulloblastoma WHO grade IV. Tumors of WHO grade I were diagnosed in 18 patients: Eight cases of meningioma (two recurrences), six cases of neurinoma, one neurofibroma, two ependymoma and one plexus papilloma. At least, benign pathologies were histologically proven in three patients. All four spinal metastasis of malignant glioma (100 %),

seven of eight meningiomas (87.5 %) and one of two ependymoma (50 %) were found to be ALA-positive.

Conclusion The present study demonstrates that spinal intramedullary gliomas and the majority of spinal intradural meningiomas are 5-ALA positive. As a surgical consequence, especially in intramedullary gliomas, the use of 5-ALA fluorescence seems to be beneficial.

Keywords Fluorescence-guided surgery · 5-Aminolevulinic acid (ALA) · Spinal intradural tumor · Spinal meningioma · Spinal glioma · Spinal neurinoma

Objective

Spinal intradural tumors are rare tumors of the central nervous system. While the majority of primary extramedullary tumors are benign, intramedullary neoplasms are usually malignant [1]. In the majority, microsurgical resection is the established treatment in extramedullary spinal tumors. In meningiomas and neurinomas this is more or less easy to perform depending on the dural attachment and on adhesions to the spinal cord or the nerve rootlets. Maximum safe cytoreductive treatment is widely accepted in malignant intramedullary tumors. Clear visualization of solid tumor tissue, identification of tumor borders and safe differentiation of normal neuronal tissue in extra- and intramedullary gliomas, recurrent or infiltrative meningiomas and extra- and intramedullary ependymomas can be challenging.

5-Aminolevulinic acid (5-ALA)-based fluorescence-guided surgery is well established in cytoreductive surgery of malignant cerebral gliomas and is accompanied by improved extent of tumor resection and progression-free survival [26, 28, 29]. 5-ALA induced fluorescence is not

S. O. Eicker (✉) · M. Kamp · H.-J. Steiger · D. Hänggi
Department of Neurosurgery, Heinrich-Heine-University,
Moorenstraße 5, 40225 Düsseldorf, Germany
e-mail: eicker.s@mac.com

F. W. Floeth
Department of Spine and Pain, St.-Vinzenz-Hospital,
Düsseldorf, Germany

seen in malignant gliomas only. Visualization and photodynamic therapy with 5-ALA of bladder, lung or gastrointestinal tumors has been established and for other cerebral intradural pathologies such as meningiomas, metastasis and medulloblastomas it has been recently explored [5, 7, 12, 14, 15, 18, 30].

Extension of this technique to spinal intradural pathologies is documented in only four case reports [3, 9, 20, 21].

The aim of the present prospective study was to evaluate: (1) the 5-ALA fluorescence in spinal cord tumors, (2) its usefulness according to the surgical strategy.

Clinical materials and methods

Patients

From the 48 patients suffering from symptomatic intradural, extra- or intramedullary spinal cord tumors who presented in the clinic between February 2011 and December 2011, 26 patients were included in this prospective single center study.

All patients underwent pre- and postoperative T1 and T2 weighted magnetic resonance imaging (MRI) of the spine $\pm$ contrast in axial, sagittal and coronal planes and in some cases additional computerized tomography (CT) was performed. Patients were examined pre- and postoperatively (day 7 after surgery) by ASIA impairment scale [6].

Patient characteristics are illustrated in Table 1. Informed consent was obtained from the patients regarding surgery and the off-label application of 5-ALA.

Treatment

Indication for surgery was discussed with each patient. Especially in malignant glioma metastasis the palliative treatment character was disclosed.

Three hours before induction of anesthesia a freshly prepared solution of 5-ALA (20 mg/kg body weight) was administered orally [25]. All patients were operated under general anesthesia with continuous neuromonitoring (somatosensory and motor evoked potentials and in some cases D-wave recording) in prone position. For level localization intraoperative fluoroscopy or preoperative computed tomography-guided placement of a hooked-wire needle system as described before was used [23].

The operation was carried out using a neurosurgical microscope (Pentaro with fluorescence kit, Carl Zeiss Surgical GmbH, Oberkochen, Germany), which allows the surgeon to switch from white xenon illumination to violet-blue excitation light.

All tumors were subjected to standard histological classification based on formalin-fixed and paraffin-embedded tissue sections.

Results

A total of eleven men (42 %) and fifteen women (58 %), mean age of 56.2 years (range 27–82 years) were included in the study. Of those, 3 spinal tumors were located in the cervical spine, 11 in the thoracic spine, 4 at the conus medullaris, 6 at the cauda equina and 2 within the canalis sacralis (Table 1).

High grade spinal tumors were histologically proven in five patients: four patients suffered from intra- or perimedullary gliomas arising from primary cerebral disease. Two of them presented with metastasis of glioblastoma (WHO grade IV), one with metastasis of an anaplastic astrocytoma (WHO grade III) and one with a metastasis of an oligoastrocytoma (WHO grade III), respectively. In one patient, a drop metastasis of a cerebellar medulloblastoma (WHO grade IV) was diagnosed. In two cases, the tumor was located intra and extramedullary (cases 18 and 19), two were located extramedullary (cases 16 and 23) and one intramedullary (case 17).

Low grade tumors of WHO grade I were found in 18 patients: in eight patients the space occupying lesions turned out to be a meningioma (all WHO grade I); therefrom two were recurrences (cases 4 and 6). All meningiomas were located extramedullary. In six patients a neurinoma and in one a neurofibroma (all WHO grade I) was diagnosed (extramedullary). Two patients were treated with ependymomas (extramedullary) and one patient with an extramedullary drop metastasis of a ventricular plexus papilloma (all WHO grade I).

Benign lesions were diagnosed in three patients: one patient suffered from an epidermoid cyst (extramedullary), one from an intramedullary lipoma and in one patient the assumed intramedullary lesion was proven to be a demyelinating disease.

After exposing the dura, the normal white light mode showed no suspicious changes in structure or color of the thecal sac. The microscope was switched to violet-blue excitation light, whereupon also no suspect area could be detected in the external sheet of the dura in all 26 cases.

After durotomy and exposure of the pathology seven meningiomas (88 %), including the two recurrent tumors, showed broad fluorescence (Figs. 1, 2). On the base of this fluorescence signal differentiation between tumor and cicatrize was possible which was proven by histological examination (Fig. 2). Tissue samples from 5-ALA positive areas showed clear meningioma tissue whereas in samples from the 5-ALA negative area cicatrize was diagnosed. In

Table 1 Study population characteristics

Case no.	Age (year)/sex	Medical history	Location	Surgical procedure	Neurological grade [6] preop./postop.	Specifics	Simpson grade [22]	WHO grade, type [17] or pathology	Fluorescence
Meningiomas									
1	67/F	Pain syndrome	L4/5 and L4	Interlaminar approach	E/E	–	2	Grade I, meningothelial	Positive
2	72/F	Pain syndrome	T11	Interlaminar approach	E/E	Identification of remaining tissue under fluorescence	2	Grade I, psammomatous	Negative
3	47/F	Pain syndrome	T9	Interlaminar approach	E/E	–	2	Grade I, meningothelial	Positive
4	62/F	Gait disturbance, pain syndrome	C7–B5	Laminoplasty	D/D	Recrudescence with cicatrices	2	Grade I, meningothelial	Positive
5	70/F	Numbness of left leg	T5	Hemi-laminectomy	D/D	–	2	Grade I, transitional	Positive
6	55/F	Progressive ataxia	T2/3	Re-Hemi-laminectomy	D/D	Recrudescence with cicatrices	1	Grade I, transitional	Positive
7	82/F	Progressive gait disturbance	T1	Interlaminar approach	C/D	–	2	Grade I, transitional	Positive
8	62/F	Pain syndrome	C3	Laminoplasty	E/E	Identification of remaining tissue under fluorescence	2	Grade I, metaplastic	Positive
Neurinomas/neurofibromas									
9	39/M	Incidental finding	L2/3	Interlaminar approach	E/E	–		Grade I, neurinoma	Negative
10	71/M	Gait disturbance, pain syndrome	C2	Hemi-laminectomy	D/D	Extensive dura attachment		Grade I, neurofibroma	Negative
11	46/F	Pain syndrome	T11	Laminoplasty	E/E	Three nodular lesions		Grade I, neurinoma	Negative
12	62/F	Pain syndrome	S1	Laminoplasty	E/E	–		Grade I, neurinoma	Negative
13	35/F	Numbness of right leg, Gait disturbance	L2/L3	Interlaminar approach	D/D	–		Grad I, neurinoma	Negative
14	48/M	Pain syndrome	C5–7	Laminoplasty	E/E	–		Grad I, neurinoma	Negative
15	76/M	Pain syndrome	L3/4	Laminoplasty	E/E	–		Grad I, neurinoma	Negative
Gliomas									
16 [20]	31/M	Recurrent cerebral anaplastic oligoastrocytoma	L5	Laminectomy	D/D	Mediastinal malignant glioma manifestation		Grad III, anaplastic oligoastrocytoma	Positive
17 [20]	70/M	Cerebral glioma grad IV	T3/4	Laminectomy	D/D	Refused adjuvant treatment; died 9 month after initial diagnosis		Grad IV, glioma	Positive
18 [9]	27/F	Recurrent spinal glioma	T12/L1	Laminectomy	A/A	Corpectomy to relief patient of pain		Grad III anaplastic astrocytoma	Positive
19	54/M	Cerebral glioma grad IV	T12/L1	Laminoplasty	D/C	Partial resection for pain relief		Grad IV, glioma	Positive

Table 1 continued

Case no.	Age (year)/sex	Medical history	Location	Surgical procedure	Neurological grade [6] preop./postop.	Specifics	Simpson grade [22]	WHO grade, type [17] or pathology	Fluorescence
Other diseases									
20	73/M	Urinary dysfunction, pain syndrome	T12/L1	Laminoplasty	D/D	Distinct improvement of pain syndrome		Grade I, myxopapillary ependymoma,	Negative, autofluorescence
21	47/F	Pain syndrome	T12/L1	Laminoplasty	E/E	–		Grade I, myxopapillary ependymoma	Positive
22	52/M	Urinary dysfunction, pain syndrome	L1–3	Laminoplasty	D/D	Regressive numbness of the leg		Epidermoid cyst	Negative, autofluorescence
23	47/M	Cerebellar and spinal medulloblastoma	T4	Hemi-laminectomy	D/D	Second small lesion T1		Grade IV, medulloblastoma	Negative
24	46/M	Pain syndrome, cerebral plexus-papilloma	S2	Laminoplasty	D/D	Persistent urinary dysfunction		Grade I, metastasis of plexus-papilloma	Negative
25	68/F	Spastic paraparesis	T9–10	Laminectomy	C/D	Persistent ataxia		Intramedullary lipoma	Negative
26	52/F	Progressive ataxia	T5–7	Laminoplasty	D/D	Lesion mimicking tumor		Demyelinating disease	Negative

Neurological grade preop./postop. in accordance with the five categories of the ASIA impairment scale [6]. *A* no motor or sensory function is preserved in the sacral segments S4–S5, *B* sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5, *C* motor function is preserved below the neurological level, but more than half of the key muscles below the neurological level have a muscle strength of less than three, *D* motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle strength of three or more, *E* motor and sensory functions are normal

two cases (cases 4 and 6), remaining tumor tissue was identified under fluorescence after supposed complete resection. One ependymoma and, as expected, glioma tissue of all 4 patients with drop metastasis of a cerebral malignant glioma (100 %) was also 5-ALA positive. Visualization of doubtful tumor areas with clearly positive fluorescence after switching to violet-blue excitation light was helpful to determine the tumor border and thus to achieve a complete resection.

One of the eight meningiomas, one of two ependymomas, all seven neurinomas and all remaining intradural pathologies (one medulloblastoma, one plexus papilloma, one epidermoid cyst, one lipoma and one demyelinating lesion) displayed no fluorescence signal. Like in cerebral ALA-supported surgery the operation time was not influenced because of the real-time nature of the procedure that makes uninterrupted surgery possible even during visualization of fluorescence.

Throughout the procedures SEP and D-wave recordings remained unaltered (except cases 18 and 19), whereas a transient loss of MEPs was observed in cases 16 and 17. In case 19, only a partial resection was performed due to abnormal neurophysiological recordings.

Postoperative MRIs confirmed complete resection of the lesions or contrast-enhanced tumors (except cases 19 and 26).

The postoperative course was uneventful. A transient motor dysfunction in cases 16, 17 and 23 was reversible during the following postoperative days. Only case 19 showed a persistent aggravation of neurological deficit.

Discussion

The study demonstrates that the application of 5-ALA can be useful for specific intradural spinal pathologies. The aim was to evaluate in which spinal tumor entities 5-ALA accumulates and thereby improves visualization of tumor tissue and potentially serves as a helpful tool for surgery. Though 5-ALA has been employed for the visualization of various tumors, there are only a few reports on 5-ALA fluorescence in spinal intradural pathologies [3, 9, 20, 21].

This prospective study detected broad fluorescence in 88 % of spinal meningiomas ($n = 8$) and 100 % of spinal gliomas ($n = 4$), as well as in one ependymoma WHO grade I ($n = 2$).

Fig. 1 Primary spinal meningioma. MRI (T1-weighted image, sagittal (a) and transversal (b) view with contrast) studies of upper thoracic spine (case 7). Clear positive fluorescence after opening the

dura (c). Xenon illumination (d) and *violet-blue* excitation light (e) of the prepared meningioma. Xenon illumination (f) and *violet-blue* excitation light (g) after complete tumor resection

The findings suggest that 5-ALA is a safe and useful real-time tool to identify tumor borders or remaining tumor tissue in meningiomas and gliomas and may be at least in some ependymomas.

First limitation of the study is the unknown uptake mechanism of 5-ALA in spinal tumor tissue. 5-ALA is a natural precursor for the heme biosynthesis [11]. After metabolization into the fluorescent molecule protoporphyrin IX (PpIX) strong fluorescence could be detected in malignant gliomas after illumination with violet-blue excitation light. In these tumors, the hydrophilic 5-ALA is able to pass the disrupted blood–brain barrier (BBB) with an abnormal accumulation in the mitochondria and a tumor-specific porphyrin fluorescence [27, 28]. Several additional mechanisms of PpIX accumulation in malignant glioma cells like reduced activity of ferrochelatase or decreased outflow of PpIX from the cells are reported [8, 19].

In intramedullary metastasis of malignant gliomas it could be assumed that the mechanism is similar to that in cerebral malignant gliomas.

In extramedullary tumors like meningiomas and neurinomas crossing of the BBB is probably of low relevance and the fast and efficient uptake in spinal meningioma tissue remains unknown. It can be hypothesized, that in this tissue enzymatic processes like reduced activity of ferrochelatase lead to the accumulation of 5-ALA.

Wherefore spinal neurinomas never show fluorescence is particularly ambiguous due to the fact that Schwann-cells are the glia of the peripheral nervous system like the astrocytes in the brain, which show, in terms of malignant transformation a broad fluorescence in most cases.

Second limitation is the unknown pharmacokinetic of 5-ALA in spinal pathologies after oral administration. According to the procedure described by Stummer et al. [26] 5-ALA was given 2–4 h before the induction of anesthesia.

Fig. 2 Recurrent Meningioma. MRI (T1-weighted image, sagittal (a) and transversal (b) view with contrast) studies of thoracic spine (case 6). Doubtful tumor area after opening the dura (c) with clearly positive fluorescence after switching to violet-blue excitation light (d) on the left side *plus* and cicatrize on the right side *asterisk*

Third, because of the small patient cohort, statistic significant conclusion could not be drawn although the results from spinal meningioma and glioma fluorescence suggest a quite reliable 5-ALA uptake and fluorescence in these tumor entities.

In this study, we do not present detailed clinical and neuroimaging data due to the fact, that this manuscript focuses on the evaluation in which spinal tumor entities 5-ALA accumulates.

Spinal metastasis of malignant gliomas

Spinal metastasis of malignant gliomas is rare although Ferreira et al. [10] described in a series of 67 cerebral gliomas spinal metastasis in 20 %. On the other hand, it can be assumed that the improved treatment of cerebral gliomas and subsequently the prolonged overall survival lead to an increased frequency of symptomatic spinal metastasis due to cerebrospinal fluid (CSF) seeding [13]. In most of these cases, treatment is restricted to incomplete resection or

biopsy and the prognosis is devastating [2, 4, 9]. Maximum safe cytoreductive treatment using 5-ALA is an accepted cornerstone in the therapy of cerebral malignant gliomas with a benefit onto the progression-free survival [26]. This study demonstrates that the technique also can be applied in spinal metastasis of gliomas. 5-ALA seems to be a useful tool for identifying solid tumor tissue during resection and for controlling the resection borders. How far this fluorescence-guided cytoreductive surgery can improve patient's life quality (prevention of paraplegia) and increase the overall survival has to be proven in further studies. Especially in comparison with well established treatment options after biopsy and palliative treatment.

Spinal meningioma

Resection of most spinal meningiomas is easy to perform due to their usually well circumscribed extramedullary location. In en plaque and infiltrative growing meningiomas or recurrent spinal meningiomas complete resection can be challenging depending on the infiltration of the dura, arachnoid scarring and spinal cord tethering.

Recurrence rates reported in the literature are between 6 and 14.7 % [16, 24]. In widespread recurrent or en plaque growing meningiomas with distinct arachnoid scarring and spinal cord infiltration the exact differentiation between vital tumor tissue, scar tissue of the dura and the arachnoid membrane and healthy neuronal tissue of the myelon and the nerve rootlets is crucial. Remaining cicatrizes with spinal cord adhesion but without compression after tumor removal can be left to prevent loss of neurologic function. In our study, differentiation between tumor and cicatrize was possible after the administration of 5-ALA which was proven by histological examination (cases 4 and 6).

But also in primary infiltrative meningiomas or for exact identification and subsequent complete coagulation of the dural attachment area the administration of 5-ALA may be useful to achieve a resection Simpson grade II which has a lower recurrence rate than incomplete resection [21]. No difference could be observed whether the tumor matrix has been coagulated (Simpson grade II) or resected (Simpson grade I) [16].

It remains unclear, why the histological subtype of a psammomatous meningioma (WHO grade 1) in case two showed no fluorescence. It might be possible that the time interval between application and the operative procedure was too long because of adjournment due to an emergency (in this case 7 h) and therefore the accumulation within the tumor cells was already low. According to other experiences, this subtype showed a broad fluorescence in cerebral meningiomas as described by Coluccia et al. [5].

Ependymoma

Only one of the two ependymomas in this study group exhibited fluorescence, therefore the value of 5-ALA in this entity cannot be estimated and further studies have to evaluate this phenomenon with focus on tumor pharmacokinetic. Theoretically, the advantages of a better delineation of vital tumor tissue, normal neuronal tissue and cicatrize can be beneficial in ependymoma surgery—if they show fluorescence. Especially in intramedullary ependymomas as well as in filum terminals ependymomas with adherence to the conus medullaris and tumor recurrences 5-ALA could be an additional useful tool to minimize damage to the normal neuronal tissue and optimize tumor resection to prevent local recurrences.

Conclusion

In this study, of 26 intradural spinal pathologies the vast majority of meningiomas and all gliomas showed a broad fluorescence after the administration of 5-ALA. 5-ALA fluorescence is a safe and useful intraoperative tool to identify vital tumor tissue and the resection borders in intramedullary or infiltratively growing extramedullary spinal tumors like gliomas, ependymomas and infiltrative meningiomas. In meningiomas coagulation of tumor matrix can be verified and in recurrent meningiomas differentiation between tumor tissue and cicatrize is possible.

However, the advantage of this technique remains to be supported by prospective investigations with a larger patient cohort, focus on intramedullary tumors, detailed clinical data, postoperative examination and neuroimaging and long-term clinical and radiological follow up.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Aghayev K, Vrionis F, Chamberlain MC (2011) Adult intradural primary spinal cord tumors. *J Natl Compr Canc Netw* 9:434–447
2. Alvisi C, Cerisoli M, Giulioni M (1984) Intramedullary spinal gliomas: long-term results of surgical treatments. *Acta Neurochir (Wien)* 70:169–179
3. Arai T, Tani S, Isoshima A, Nagashima H, Joki T, Takahashi-Fujigasaki J, Abe T (2006) Intraoperative photodynamic diagnosis for spinal ependymoma using 5-aminolevulinic acid: technical note. *No Shinkei Geka* 34:811–817
4. Ciappetta P, Salvati M, Capoccia G, Artico M, Raco A, Fortuna A (1991) Spinal glioblastomas: report of seven cases and review of the literature. *Neurosurgery* 28:302–306
5. Coluccia D, Fandino J, Fujioka M, Cordovi S, Muroi C, Landolt H (2010) Intraoperative 5-aminolevulinic-acid-induced fluorescence in meningiomas. *Acta Neurochir* 152:711–719
6. Dittunno JF, Donovan WH, Maynard FMASIAS, Dittunno JF (eds) (1994) Reference manual for the international standards for neurological and functional classification of spinal cord injury. ASIA, Chicago
7. Eicker S, Sarikaya-Seiwert S, Borkhardt A, Gierga K, Turowski B, Heiroth HJ, Steiger HJ, Stummer W (2011) ALA-induced porphyrin accumulation in medulloblastoma and its use for fluorescence-guided surgery. *Cen Eur Neurosurg* 72:101–103
8. El-Sharabasy MM, El-Waseef AM, Haffez MM, Salim SA (1992) Porphyrin metabolism in some malignant diseases. *Br J Cancer* 65:409–412
9. Ewelt C, Stummer W, Klink B, Felsberg J, Steiger HJ, Sabel M (2010) Corpectomy as final treatment option for diffuse intramedullary malignant glioma using 5-ALA fluorescence-guided resection. *Clin Neurol Neurosurg* 112:357–361
10. Ferreira NF, Barbosa M, Amaral LL, Mendonça RA, Lima SS (2004) Magnetic resonance imaging in 67 cases of glioblastoma multiforme and occurrence of metastases. *Arq Neuropsiquiatr* 62: 695–700
11. Fotinos N, Campo MA, Popowycz F, Gurny R, Lange N (2006) 5-Aminolevulinic acid derivatives in photomedicine: characteristics, application and perspective. *Photochem Photobiol* 82:994–1015
12. Hautmann H, Pichler JP, Stepp H, Baumgartner R, Gamarra F, Huber RM (2007) In vivo kinetics of inhaled 5-aminolevulinic acid-induced protoporphyrin IX fluorescence in bronchial tissue. *Respir Res* 8:33
13. Hübner F, Braun V, Richter HP (2001) Case reports of symptomatic metastases in four patients with primary intracranial gliomas. *Acta Neurochir (Wien)* 143:25–29
14. Hungerhuber E, Stepp H, Kriegsmair M, Stief C, Hofstetter A, Hartmann A, Kneuchel R, Karl A, Tritschler S, Zaak D (2007) Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. *Urology* 69:260–264
15. Kamp MA, Grosser P, Felsberg J, Sloty PJ, Steiger HJ, Reifemberger G, Sabel M (2012) 5-Aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study. *Acta Neurochir (Wien)* 154:223–228
16. Klekamp J, Samii M (1999) Surgical results for spinal meningiomas. *Surg Neurol* 52:552–562
17. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 114:97–109
18. Moesta KT, Ebert B, Handke T, Nolte D, Nowak C, Haensch WE, Pandey RK, Dougherty TJ, Rinneberg H, Schlag PM (2001) Protoporphyrin IX occurs naturally in colorectal cancers and their metastases. *Cancer Res* 61:991–999
19. Peng Q, Berg K, Moan J, Kongshaug M, Nesland JM (1997) 5-Aminolevulinic acid-based photodynamic therapy: principles and experimental research. *Photochem Photobiol* 65:235–251
20. Rapp M, Klingenhöfer M, Felsberg J, Steiger HJ, Stummer W, Sabel M (2012) Fluorescence-guided resection of spinal metastases of malignant glioma: report of 2 cases. *J Neurol Surg A Cent Eur Neurosurg* 73:103–105
21. Shimizu S, Utsuki S, Sato K, Oka H, Fujii K, Mii K (2006) Photodynamic diagnosis in surgery for spinal ependymoma. Case illustration. *J Neurosurg Spine* 5:380
22. Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment. *J Neurol Neurosurg Psychiatry* 20:22–39
23. Sloty P Jr, Kröpil P, Klingenhöfer M, Steiger HJ, Hänggi D, Stummer W (2010) Preoperative localisation of spinal and peripheral pathologies for surgery by computed tomography-guided placement of a specialized needle system. *Neurosurgery* 66:784–787

24. Solero CL, Fornari M, Giombini S, Lasio G, Oliveri G, Cimino C, Pluchino F (1989) Spinal meningioma: review of 174 operated cases. *Neurosurgery* 25:153–160
25. Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ (2000) Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid induced porphyrins: a prospective study in 52 consecutive patients. *J Neurosurg* 93:1003–1013
26. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, ALA-Glioma Study Group (2006) Fluorescence guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 7:392–401
27. Stummer W, Stocker S, Novotny A, Heimann A, Sauer O, Kempski O, Plesnila N, Wietzorrek j, Reulen HJ (1998) In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. *JPhotochem Photobiol B* 45:160–169
28. Stummer W, Stocker S, Wagner S, Stepp H, Fritsch C, Goetz C, Goetz AE, Kieffmann R, Reulen HJ (1998) Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. *Neurosurgery* 42:518–525
29. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, ALA-Glioma Study Group (2008) Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery* 62:564–576
30. Sultan SM, El Doray AA, Hofstetter A, Abdel-Gawad O, El Mahdy A, Khoder W (2006) Photodynamic selectivity of 5-aminolevulinic acid to prostate cancer cells. *J Egypt Natl Canc Inst* 18:382–386