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ORIGINAL ARTICLE - TUMOR - MENINGIOMA

Fluorescence imaging of meningioma cells with somatostatin receptor ligands: an in vitro study

Stefan Linsler[1] · Ralf Ketter[1] · Joachim Oertel[1] · Steffi Urbschat[1]

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Abstract

Background The use of five-aminolevulinic acid (5-ALA) in the staining of malignant glioma cells has significantly improved intraoperative radicality in the resection of gliomas in the last decade. Currently, there is no comparable selective fluorescent substance available for meningiomas. There is however a demand for intraoperative fluorescent identification of, e.g., invasive skull base meningiomas to help improve safe radical resection. Meningiomas show high expression of the somatostatin receptor type 2, offering the possibility of receptor-targeted imaging. The authors used a somatostatin receptor-labeled fluorescence dye in the identification of meningiomas in vitro. The aim of this study was to evaluate the possibility of selective identification of meningioma cells with fluorescent techniques.

Methods Twenty-four primary human meningioma cell cultures were analyzed. The tumor cells were incubated with FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide). As a negative control, four human dura tissues were cultured as well as a mixed cell culture in vitro and incubated with the same somatostatin receptor-labeled fluorescence substance. After incubation, fluorescence signal and intensity in all cell cultures were analyzed at three different time points using a fluorescence microscope with 488 nm epi-illumination.

Results Sixteen WHO I, six WHO II, two WHO III meningioma primary cell cultures, and four dura cell cultures were analyzed. Fluorescence was detected in all meningioma cell cultures (22 cell culture stained strongly, 2 cell cultures moderately) directly after incubation up until 4 h later. There were no differences in the quality and quantity of fluorescence signal between the various meningioma grades. The fluorescence signal persisted unchanged during the analyzed period. In the negative control, dura cell cultures remained unstained.

Conclusions This study demonstrates the use of FAM-TOC in the selective fluorescent identification of meningioma cells in vitro. Further evaluation of the chemical kinetics of the applied somatostatin receptor ligand and fluorescence dye is warranted. As a next step, an experimental animal model is needed to evaluate these promising results in vivo.

Keywords Meningioma · Fluorescence · In vitro · Cell culture · Octreotide · Somatostatin receptor ligand

Abbreviations

5-ALA	Five-aminolevulinic acid
CO_2	Carbon dioxide
DAPI	4′,6-diamidin-2-phenylindol
DMEM	Dulbecco's modified Eagle medium
FAM-TOC	6-Carboxyfluorescein-Tyrosin3-Octreotide
FCS	Fetal calf serum
HE	Hematoxylin and eosin
Na-Fl	Sodium fluorescein
PBS	Phosphate-buffered saline
PFA	Paraformaldehyde
ROI	Region of interest
SPECT	Single-photon emission computed tomography
SSTR	Somatostatin receptor
WHO	World Health Organization

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This article is part of the Topical Collection on *Tumor - Meningioma*

✉ Stefan Linsler
stefan.linsler@uks.eu

[1] Klinik für Neurochirurgie, Universitätsklinikum des Saarlandes, 66421 Homburg, Saar, Germany

Introduction

Meningiomas are tumors composed of neoplastic meningothelial cells and account for about 30% of all intracranial tumors [33]. In its sporadic form, it is typically benign and slow growing, appearing mostly in the later decades of life. Histological features allow for the division of meningiomas into benign meningiomas (WHO grade I), atypical meningiomas (WHO grade II¸ and anaplastic meningiomas (WHO grade III), which represent 90.0 to 94.3, 4.7 to 7.2, and 1.0 to 2.8% of all meningiomas respectively [21, 22]. However, more than 8% of all meningiomas are characterized by aggressive clinical behavior with increased risk of tumor recurrence [3, 14–16, 18, 21, 22]. Therefore, the extent of resection, in line with the Simpson grading system, has been considered the most important prognostic factor alongside genetic and molecular biological features [6, 8, 16, 18, 19, 29]. It is hypothesized that recurrent tumor most often develops from unrecognized residual tumor tissue at the margins of surgical resection [20, 24, 32]. Several typical sites of residual meningioma tissue—and thus origins of tumor recurrence—have been noted. The typically observed "dural tail," consisting of a thickening of the dura mater adjacent to the meningioma, may lead to tumor recurrence [13, 25]. Small satellite lesions at a distance from the main tumor, tumor-infiltrated bone flap, or brain tissue are other typical sites that might be missed by the neurosurgeon [4, 5]. Therefore, numerous technical adjuncts have been used to improve the radicality of resection, especially in skull base meningiomas invading the cavernous sinus and surrounding cranial nerves, or parasagittal meningiomas invading the sagittal sinus. However, there is still a need or demand to visualize residual tumor tissue during meningioma surgery in order to minimize the rate of recurrence.

In the last decades, fluorescence-guided surgery has indeed helped in the safe radical resection of high-grade glioma surgery [30, 31]. Some authors have reported on the beneficial use of 5-ALA in metastasis [12]. However, to the authors' knowledge, there are no comparable results for meningiomas to date. Although, some authors have reported their first results in 5-ALA-guided meningioma surgery [17, 23, 26]. Other authors have also presented first results on Na-Fl fluorescence-guided meningioma surgery with a yellow-560 filter [1, 7]. However, there are still some pitfalls and challenges.

In conclusion, all these previous clinical studies demonstrate the need for a selective fluorescence dye in meningioma surgery, aiming at improving safe radical resection in order to prevent recurrences. The major drawback in available fluorescence labeling methods for meningiomas is the lack of excellent discrimination between dura and meningioma cells on the dural tail. The identification of the dural tail and remnant meningioma cells in this region could significantly improve the extent of resection in the future, resulting in even lower recurrence rates after surgery.

Therefore, the aim of this experimental study is to find an alternative fluorescence imaging method, which selectively stains meningioma cells. There have been previous reports conducted in nuclear medicine where tc-99 m pepreotide or 111 octreotide SPECT imaging were used to selectively identify recurrent meningioma tissues [10]. Furthermore, it is well-known that meningioma cells express somatostatin receptor (SSTR) 1–5 [9]. All five SSTRs are expressed ranging from 61.6 to 100% with a predominance of SSTR2 [28]. There is no significant difference in SSTR expression regarding age, sex, tumor location, and recurrence or WHO grading [28].

Therefore, the authors selected a fluorescence dye composed of a new somatostatin receptor ligand to analyze for a potential clinical application for the first time in meningioma cell cultures.

Methods

The study was approved by the local ethics committee (No. 93/16). Written informed consent was obtained from each patient participating in the study.

Primary tumor cell culture

Meningioma tissues were obtained from 24 patients undergoing surgery for resection of a meningioma at the Neurosurgical Department, Saarland University, Homburg, Germany. The tumor cells were cultivated in vitro according to our standard protocol as previously reported [11, 14, 15]: Tumor samples were minced with a scalpel and small scissors, and the resulting cell suspension was subsequently cultured in Dulbecco's modified Eagle medium (DMEM, Life Technologies, US) supplemented with 10% fetal calf serum (FCS, Firma Boehringer, Germany); 1% nonessential amino acids; and 1% penicillin/streptomycin in a moist atmosphere of 5% CO_2 at 37 °C. The medium was changed twice a week. This primary meningioma cell culture was used at early passages. Cells were subcultured when a confluence of 70% was reached.

Additionally, dura tissues obtained during surgical procedures in patients undergoing surgery for gliomas were cultivated in vitro and served as the negative control group in this experimental setup. The four fibroblastic cell cultures of dural tissue were primarily taken from the brain convexity of two females and two male patients.

The dural pieces were cultured in a cell culture flask with DME medium (Life Technologies, US) and FCS (Boehringer, Germany) in a moist atmosphere of 5% CO_2 at 37 °C as previously described in comparable experimental studies [27]. The medium was changed twice a week. This primary meningioma cell culture was used at early passages. Cells were subcultured when a confluence of 70% was reached.

Finally, the authors created a mixed cell culture comprising of the previously cultured dural fibroblasts and meningioma cells acquired after first passage. The mixed cells were cultured in a flask with DME medium (Life Technologies, USA) and FCS (Boehringer, Germany) in a moist atmosphere of 5% CO_2 at 37 °C as described above for less than a week before fluorescence staining.

The growing time for meningioma cells ranged from 7 to 34 days with an average time of 17.95 days. For dural fibroblasts, average growing time was 19.6 days with a range of 11 to 32 days. It should be noted, however, that the normal growing time range of all primary cultures was between 7 and 25 days.

Tumor histology

Meningioma grade was assessed by a combined histologic and morphometric approach on formalin-fixed, paraffin-embedded HE and Ki-67/Feulgen-stained tissue sections. All tumors were classified in accordance with the WHO classification of tumors of the nervous system of 2007 [21, 22]. Additionally, the dura tissues from the four negative controls were histopathologically confirmed as well.

Fluorescence labeling

After respective trypsinization of the tumor or dural cells with 2 ml trypsin, cells were cultivated in 12-well plates with DMEM for at least 24 h in a moist atmosphere of 5% CO_2 at 37 °C. On the next day, the cells were incubated for 5 min at 37 °C in an atmosphere of 5% $CO_2$with 1 ml DMEM and 10 μg FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide) (Fa. piCHEM, Forschungs- u. Entwicklungs gmbH, Austria) suspended in 1 ml aqua dest. The chemical formula is illustrated in Fig. 1. After incubation, the cells were washed with PBS and fixed on the well plates with 4% PFA/PBS for 10 min in a dark room. Finally, cells were stained with 10 μl DAPI-Antifade for cell nucleolus identification.

Fluorescence analysis

After fixation and DAPI staining, the fluorescence of the cell cultures was analyzed with fluorescence microscopy as previously described [2]. An inverted microscope (BX43, Olympus, Hamburg, Germany) with epifluorescence (U-TV05XC-3, Olympus, Hamburg, Germany) and phase contrast was used. A × 100 magnified objective was used in every case as standard protocol. Fluorescence was detected using epi-illumination with 488 nm. Exposure time was set at 25 s using an excitation fluence of $1 \leq J/cm^2$.

Using a camera (XC30, Olympus, Hamburg, Germany) attached to the microscope, the fluorescence signal was detected in a standardized fashion in all cell cultures at three different time points: directly after incubation, 1 and 4 h after incubation. The signal was processed and analyzed with cellSens Dimension software (Olympus, Hamburg, Germany). Fluorescence in mean of intensity per region of interest (ROI) was quantified digitally over at least three equal areas of interest for each cell culture at each time point. Representative areas of interest were chosen for the entire cells in the monolayer culture. Quantification of the fluorescence was established by standardized measurements of light intensity signal with the software. Hereby, intensity of fluorescence was defined as strong (= intensity > 15.0), mild (= intensity 15.0–7.0), vague (= intensity < 7.0–0.01) and no signal.

Statistics

The illustrations and analysis of data were performed using SPSS (SPSS, version 22, IBM Corporation, NY, US). Collected data were compared using Mann-Whitney *U* test and chi-squared test, to compare differences. The significance level was set at $p < 0.05$. Values are presented as means ± standard deviation.

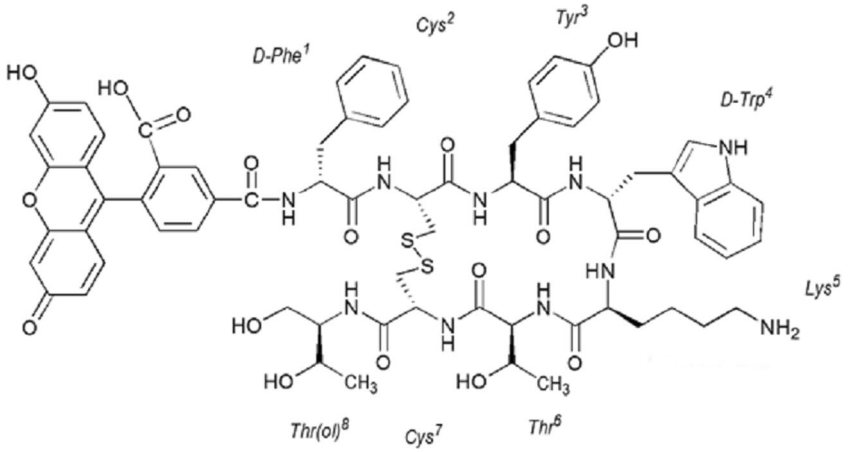

Fig. 1 Chemical formula structure of the FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide)

Table 1 Characteristics and fluorescence signal intensity directly after incubation in the cell cultures of 24 meningiomas (T) and 4 dura fibroblasts (D)

	Localization of the original tumor tissue	Gender	Histology	Fluorescence after incubation Strong	Mild	Vague	No
T 6982	Tuberculum sellae	M	Me WHO I	x			
T 6983	Olfactory groove	M	Me WHO I	x			
T 6992	Sphenoid wing	F	Me WHO I	x			
T 6993	Convexity	M	Me WHO III	x			
T 6998	Spinal	F	Me WHO I	x			
T 6999	Convexity	F	Me WHO I	x			
T 7000	Parasagittal	M	Me WHO II	X			
T 7013	Sphenoid wing	F	Me WHO I	X			
T 7016	Convexity	F	Me WHO I	X			
T 7017	Convexity	F	Me WHO I	X			
T 7020	Parasagittal	M	Me WHO II	X			
T 7021	Sphenoid wing	M	Me WHO I	X			
T 7024	Convexity	F	Me WHO I	X			
T 7033	Convexity	F	Me WHO I		x		
T 7037	Convexity	F	Me WHO I	X			
T 7038	Olfactory groove	M	Me WHO I	X			
T 7042	Parasagittal	M	Me WHO III	X			
T 7048	Convexity	F	Me WHO II	X			
T 7057	Convexity	M	Me WHO II	X			
T 7097	Convexity	F	Me WHO II		x		
T 7098	Posterior fossa	F	Me WHO II	X			
T 7102	Sphenoid wing	M	Me WHO I	X			
T 7104	Olfactory groove	M	Me WHO I	X			
T 7105	Convexity	F	Me WHO I	X			
D01	Convexity	M	Dura				x
D02	Convexity	F	Dura				x
D03	Convexity	M	Dura				x
D04	Convexity	F	Dura				x
T7105 + D4	Convexity	F	Me WHO I and dura	Only Me cells X			

Results

Tumor characteristics

Samples analyzed in this study were obtained from 13 females (54%) and 11 males (46%). Age at resection ranged from 27 to 81 years with an average of 53.3 years. The investigated primary human meningioma cell cultures represented 16 WHO I, 6 WHO II, and 2 WHO III meningiomas. The majority of meningiomas was located at the convexity ($n = 11$). Three meningiomas were located at the olfactory groove, four at the sphenoid, and one at the tuberculum sellae. There were three parasagittal, one posterior fossa, and one spinal meningioma.

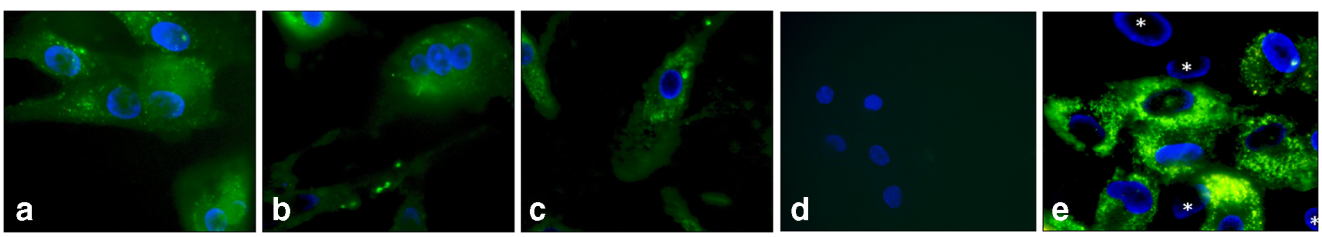

Fig. 2 Exemplary fluorescence imaging directly after incubation with FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide) under epifluorescence with 488 nm. There was no significance of fluorescence intensity in WHO I (**a**), WHO II (**b**), and WHO III meningiomas. Dural fibroblast cells did not show any uptake of the octreotide in fluorescence imaging (**d**; and marked with an asterisk in **e**)

Table 2 Chronological sequence of the fluorescence signal directly after incubation, after 1 h and after 4 h in cell culture ($n = 28$) for the tumors (T) and dura fibroblasts (D)

	Fluorescence directly after incubation				Fluorescence 1 h after incubation				Fluorescence 4 h after incubation			
	Strong	Mild	Vague	No	Strong	Mild	Vague	No	Strong	Mild	Vague	No
T 6982	x				x				x			
T 6983	x				x				x			
T 6992	x				x				x			
T 6993	x				x				x			
T 6998	x				x					x		
T 6999	x				x				x			
T 7000	x				x				x			
T 7013	x				x				x			
T 7016	x				x				x			
T 7017	x				x				x			
T 7020	x				x				x			
T 7021	x				x				x			
T 7024	x				x				x			
T 7033		X				X				x		
T 7037	x				x				x			
T 7038	x				x				x			
T 7042	x				x				x			
T 7048	x				x				x			
T 7057	x				x				x			
T 7097		X				X				x		
T 7098	x				x				x			
T 7102	x				x				x			
T 7104	x				x				x			
T 7105	x				x				x			
D01				x				x				x
D02				x				x				x
D03				x				x				x
D04				x				x				x

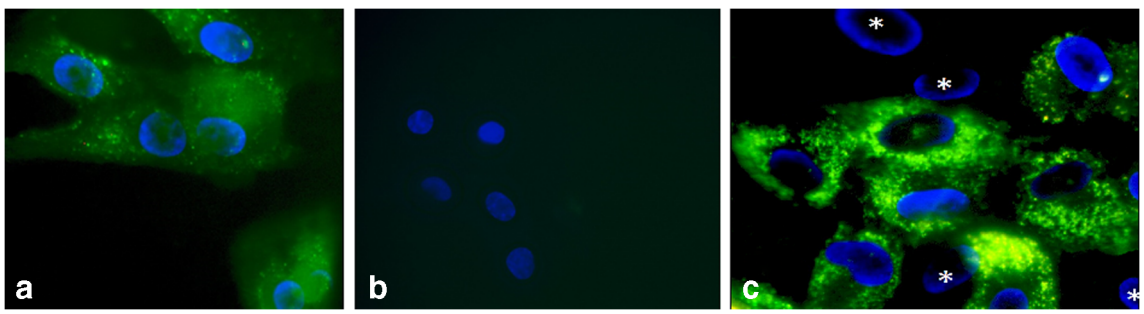

Fig. 3 Fluorescence imaging 4 h after incubation with FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide) under epifluorescence with 488 nm for WHO I meningioma (**a**), dura cells (**b**) and a mixed culture with meningioma WHO I, and fibroblasts (**c**). Meningioma cells showed a good fluorescence signal in our setting in every case, whereas there was no fluorescence signal in the dura cell culture. Dura cells are marked with an asterisk in (**c**)

Fluorescence intensity

Fluorescence signal was detected in all meningioma cell cultures directly after incubation with FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide). Two cell cultures revealed mild fluorescence signal, while the other 22 cell cultures revealed a strong fluorescence signal (Table 1). There was no significant difference in the quality or intensity of fluorescence between the different meningioma grades. Tumor localization, gender, or age of the patient showed no significant correlation to the fluorescence signal. Figure 2 illustrates exemplary cases of a meningioma WHO I, II, and III, dural fibroblasts, as well as combined meningioma-dural fibroblasts cell cultures after incubation with FAM-TOC.

The intensity of the fluorescence signal was accessed in all cell cultures at three different time points to identify for possible changes in the kinetics of the fluorescence signal. Thereby, incubation of the cell cultures in FAM-TOC showed direct tissue fluorescence in meningioma cells and a time-independent signal in all meningioma grades over the analyzed 4-h period. Although there was a decrease in the fluorescence intensity in one WHO grade 1 meningioma after 4 h, the authors could not detect any significant reduction of the fluorescence signal in the in vitro setup. Details are shown in Table 2.

As a negative control, the dura cell culture showed no fluorescence signal. Also, in the mixed cell culture with dural and meningioma cells, the dural fibroblasts remained without any fluorescence signal (Fig. 3).

Discussion

The somatostatin receptor dye FAM-TOC (5,6-Carboxyfluoresceine-Tyr3-Octreotide) used in this study showed selective fluorescence signal in meningioma cell cultures. This is in line with results from a previous report using 111-Indium Octreotide SPECT-imaging for selective detection of recurrent meningiomas [10]. The fluorescence signal was detectable in every case of our in vitro experimental study immediately as well as several hours after incubation. This is caused by the uptake of FAM-TOC (as somatostatin receptor ligand) in SSTR2, which is present at the cell membrane and cytoplasm of meningioma cells [9, 10, 28].

There was no accelerated decrease in the fluorescence signal and no significant differences between the different tissue probes. The dura cells did not show any fluorescence staining with FAM-TOC in cell culture alone or in combination with meningioma cells as shown in Fig. 3. Therefore, the described fluorescence imaging method may be the best available selective dye for meningioma tissue. Furthermore, the in vitro results support the hypothesis that an identification of the dural tail and remnant meningioma cells in this region could be possible in vivo and as well as intraoperatively. Further analysis of the dural tail and the infiltration zone was not possible in the experimental setup of this study. Therefore, the authors suggest further examination of their hypothesis in an in vivo laboratory setting. This would be the best methodological setup in analyzing the fluorescence and selectivity of the presented fluorescence dye in the infiltrated dura at the margins of meningiomas.

On the other hand, the lack of significant differences in fluorescent staining in the cell cultures between grades I and III meningiomas, suggest that FAM-TOC cannot serve as an immediate intraoperative marker to help differentiate high-grade meningiomas.

Furthermore, the best suitable application form of the labeled receptor ligand is still unclear in vivo. This might be possible either via intravenous or topical application on site during surgery, as this would be comparable to the aforementioned application in cell cultures. To the author's knowledge, FAM-TOC is yet to be examined in an in vivo model.

Study limitations

The authors are yet to carve out the detailed kinetics of the fluorescence signal in their experimental study. Stable fluorescence signal could only be observed right after incubation up until 4 h post-application. Further detailed in vitro studies are warranted to identify the fluorescence kinetics with the serotonin receptor ligand FAM-TOC after incubation in meningioma cells. Additionally, the effect of cell bleaching could not be accessed. Furthermore, in this current study, dura cells served as the sole negative control. Future studies could also implement glia cells or neurons and other fibroblasts as a negative control.

Nevertheless, the authors were able to demonstrate for the first time a selective fluorescence imaging method for meningioma cells in vitro, which may be used intraoperatively in meningioma surgery to significantly improve the extent of radical and safe resection of tumor tissue on the dural tail.

Conclusions

In summary, the authors consider their results of selective fluorescence imaging of meningioma cells in vitro as a potential new avenue of intraoperative fluorescence imaging in meningioma surgery in the future. For further evaluation of this hypothesis, the kinetics of the used serotonin receptor ligand and fluorescence dye needs to be analyzed in further studies. As a next step, an experimental animal model is needed to evaluate these promising results in vivo and to identify the best application form.

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Compliance with ethical standards

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

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

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Akcakaya MO, Goker B, Kasimcan MO, Hamamcioglu MK, Kiris T (2017) Use of sodium fluorescein in meningioma surgery performed under the YELLOW-560 nm surgical microscope filter: feasibility and preliminary results. World Neurosurg 107:966–973
2. Bedwell J, MacRobert AJ, Phillips D, Bown SG (1992) Fluorescence distribution and photodynamic effect of ALA-induced PP IX in the DMH rat colonic tumour model. Br J Cancer 65:818–824
3. Beks JW, de Windt HL (1988) The recurrence of supratentorial meningiomas after surgery. Acta Neurochir 95:3–5
4. Borovich B, Doron Y (1986) Recurrence of intracranial meningiomas: the role played by regional multicentricity. J Neurosurg 64:58–63
5. Borovich B, Doron Y, Braun J, Guilburd JN, Zaaroor M, Goldsher D, Lemberger A, Gruszkiewicz J, Feinsod M (1986) Recurrence of intracranial meningiomas: the role played by regional multicentricity. Part 2: clinical and radiological aspects. J Neurosurg 65:168–171
6. da Silva CE, Peixoto de Freitas PE (2016) Recurrence of skull base meningiomas: the role of aggressive removal in surgical treatment. J Neurol Surg B Skull Base 77:219–225
7. da Silva CE, da Silva JL, da Silva VD (2010) Use of sodium fluorescein in skull base tumors. Surg Neurol Int 1:70
8. Ding D, Starke RM, Hantzmon J, Yen CP, Williams BJ, Sheehan JP (2013) The role of radiosurgery in the management of WHO Grade II and III intracranial meningiomas. Neurosurg Focus 35:E16
9. Graillon T, Romano D, Defilles C, Saveanu A, Mohamed A, Figarella-Branger D, Roche PH, Fuentes S, Chinot O, Dufour H, Barlier A (2017) Octreotide therapy in meningiomas: in vitro study, clinical correlation, and literature review. J Neurosurg 127:660–669
10. Hellwig D, Samnick S, Reif J, Romeike BF, Reith W, Moringlane JR, Kirsch CM (2002) Comparison of tc-99m depreotide and in-111 octreotide in recurrent meningioma. Clin Nucl Med 27:781–784
11. Henn W, Cremerius U, Heide G, Lippitz B, Schroder JM, Gilsbach JM, Bull U, Zang KD (1995) Monosomy 1p is correlated with enhanced in vivo glucose metabolism in meningiomas. Cancer Genet Cytogenet 79:144–148
12. Kamp MA, Fischer I, Buhner J, Turowski B, Cornelius JF, Steiger HJ, Rapp M, Slotty PJ, Sabel M (2016) 5-ALA fluorescence of cerebral metastases and its impact for the local-in-brain progression. Oncotarget 7:66776–66789
13. Kawahara Y, Niiro M, Yokoyama S, Kuratsu J (2001) Dural congestion accompanying meningioma invasion into vessels: the dural tail sign. Neuroradiology 43:462–465
14. Ketter R, Kim YJ, Storck S, Rahnenfuhrer J, Romeike BF, Steudel WI, Zang KD, Henn W (2007) Hyperdiploidy defines a distinct cytogenetic entity of meningiomas. J Neuro-Oncol 83:213–221
15. Ketter R, Urbschat S, Henn W, Feiden W, Beerenwinkel N, Lengauer T, Steudel WI, Zang KD, Rahnenfuhrer J (2007) Application of oncogenetic trees mixtures as a biostatistical model of the clonal cytogenetic evolution of meningiomas. Int J Cancer 121:1473–1480
16. Ketter R, Rahnenfuhrer J, Henn W, Kim YJ, Feiden W, Steudel WI, Zang KD, Urbschat S (2008) Correspondence of tumor localization with tumor recurrence and cytogenetic progression in meningiomas. Neurosurgery 62:61–69 discussion 69-70
17. Knipps J, Beseoglu K, Kamp M, Fischer I, Felsberg J, Neumann LM, Steiger HJ, Cornelius JF (2017) Fluorescence behavior and dural infiltration of meningioma analyzed by 5-aminolevulinic acid-based fluorescence: operating microscope versus mini-spectrometer. World Neurosurg 108:118–127
18. Linsler S, Kraemer D, Driess C, Oertel J, Kammers K, Rahnenfuhrer J, Ketter R, Urbschat S (2014) Molecular biological determinations of meningioma progression and recurrence. PLoS One 9:e94987
19. Linsler S, Keller C, Urbschat S, Ketter R, Oertel J (2016) Prognosis of meningiomas in the early 1970s and today. Clin Neurol Neurosurg 149:98–103
20. Linsler S, Fischer G, Skliarenko V, Stadie A, Oertel J (2017) Endoscopic assisted supraorbital keyhole approach or endoscopic endonasal approach in case of tuberculum sellae meningioma: which surgical route should be favoured? World Neurosurg 104:601–611
21. 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
22. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820
23. Millesi M, Kiesel B, Mischkulnig M, Martinez-Moreno M, Wohrer A, Wolfsberger S, Knosp E, Widhalm G (2016) Analysis of the surgical benefits of 5-ALA-induced fluorescence in intracranial meningiomas: experience in 204 meningiomas. J Neurosurg 125:1408–1419
24. Morofuji Y, Matsuo T, Hayashi Y, Suyama K, Nagata I (2008) Usefulness of intraoperative photodynamic diagnosis using 5-aminolevulinic acid for meningiomas with cranial invasion: technical case report. Neurosurgery 62:102–103 discussion 103-104
25. Rokni-Yazdi H, Azmoudeh Ardalan F, Asadzandi Z, Sotoudeh H, Shakiba M, Adibi A, Ayatollahi H, Rahmani M (2009) Pathologic significance of the "dural tail sign". Eur J Radiol 70:10–16
26. Scheichel F, Ungersboeck K, Kitzwoegerer M, Marhold F (2017) Fluorescence-guided resection of extracranial soft tissue tumour infiltration in atypical meningioma. Acta Neurochir 159:1027–1031
27. Schick B, Wolf G, Romeike BF, Mestres P, Praetorius M, Plinkert PK (2003) Dural cell culture. A new approach to study duraplasty. Cells Tissues Organs 173:129–137

28. Silva CB, Ongaratti BR, Trott G, Haag T, Ferreira NP, Leaes CG, Pereira-Lima JF, Oliveira Mda C (2015) Expression of somatostatin receptors (SSTR1-SSTR5) in meningiomas and its clinicopathological significance. Int J Clin Exp Pathol 8:13185–13192
29. Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22–39
30. 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
31. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, Group AL-GS (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
32. Valery CA, Faillot M, Lamproglou I, Golmard JL, Jenny C, Peyre M, Mokhtari K, Mazeron JJ, Cornu P, Kalamarides M (2016) Grade II meningiomas and Gamma Knife radiosurgery: analysis of success and failure to improve treatment paradigm. J Neurosurg 125: 89–96
33. Wohrer A, Waldhor T, Heinzl H, Hackl M, Feichtinger J, Gruber-Mosenbacher U, Kiefer A, Maier H, Motz R, Reiner-Concin A, Richling B, Idriceanu C, Scarpatetti M, Sedivy R, Bankl HC, Stiglbauer W, Preusser M, Rossler K, Hainfellner JA (2009) The Austrian Brain Tumour Registry: a cooperative way to establish a population-based brain tumour registry. J Neuro-Oncol 95:401–411

Comments

Very interesting if this flourescence could be of clinical use in the future. These results are very early but if proven specific enough with respect to per example invasion of dura there is a big potential.

Jane Skjoth-Rasmussen
Copenhagen, Denmark