Acta Neurochirurgica (2022) 164:229–238
https://doi.org/10.1007/s00701-021-05025-5

TECHNICAL NOTE - TUMOR - MENINGIOMA

Proposal of a new grading system for meningioma resection: the Copenhagen Protocol

Jeppe Haslund-Vinding[1] · Jane Skjoth-Rasmussen[1] · Lars Poulsgaard[1] · Kaare Fugleholm[1] · Christian Mirian[1] · Andrea Daniela Maier[1,2] · Thomas Santarius[3] · Frantz Rom Poulsen[1,2,3,4,5,6,7,8,9,10,11] · Torstein Meling[9] · Jiri Junior Bartek[1,4,11] · Petter Förander[4,11] · Vibeke Andrée Larsen[6] · Bjarne Winther Kristensen[4,7] · David Scheie[4] · Ian Law[8] · Morten Ziebell[1] · Tiit Mathiesen[1,4,10]

Received: 15 July 2021 / Accepted: 12 October 2021 / Published online: 29 October 2021

Abstract

Introduction The extent of meningioma resection is the most fundamental risk factor for recurrence, and exact knowledge of extent of resection is necessary for prognostication and for planning of adjuvant treatment. Currently used classifications are the EANO-grading and the Simpson grading. The former comprises radiological imaging with contrast-enhanced MRI and differentiation between "gross total removal" and "subtotal removal," while the latter comprises a five-tiered differentiation of the surgeon's impression of the extent of resection. The extent of resection of tumors is usually defined via analyses of resection margins but has until now not been implemented for meningiomas. PET/MRI imaging with ^{68}Ga-DOTATOC allows more sensitive and specific imaging than MRI following surgery of meningiomas.

Objective To develop an objective grading system based on microscopic analyses of resection margins and sensitive radiological analyses to improve management of follow-up, adjuvant therapy, and prognostication of meningiomas. Based on the rationale of resection-margin analyses as gold standard and superior imaging performance of ^{68}Ga DOTATOC PET, we propose "Copenhagen Grading" for meningiomas.

Results Copenhagen Grading was described for six pilot patients with examples of positive and negative findings on histopathology and DOTATOC PET scanning. The grading could be traceably implemented and parameters of grading appeared complementary. Copenhagen Grading is prospectively implemented as a clinical standard at Rigshospitalet, Copenhagen.

Conclusion Copenhagen Grading provided a comprehensive, logical, and reproducible definition of the extent of resection. It offers promise to be the most sensitive and specific imaging modality available for meningiomas. Clinical and cost-efficacy remain to be established during prospective implementation.

Keywords Meningioma · Neurosurgery · Neurooncology · Neuropathology · Neuroradiology

Introduction

Meningioma has become the most common brain tumor [31], and management options that range from dismissal of incidental findings over follow-up with wait and scan [17] to aggressive surgery are repeatedly discussed [25]. A major determinant of the best strategy is long-term tumor control [19, 20, 26]. Studies with long-term follow-up reveal a disturbingly high recurrence rate after surgery even if apparent gross total removal was achieved [2, 8, 15, 16, 24, 30, 33, 39]. Recurrence of a previously operated tumor is an undisputable evidence that some tumor cells were left behind and have grown. Time to recurrence varies with biological qualities of a tumor [29], but the actual risk of recurrence is binary. The tumor can recur if neoplastic cells are left behind and not treated, while a completely removed tumor without remaining cells cannot recur. Meningiomas comprise a well-demarcated tumor, yet meningioma cells invade adjacent mesenchymal tissues and a macroscopically evident tumor border does not necessarily allow identification and removal of all neoplastic cells. Intraoperative or radiological

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

✉ Jeppe Haslund-Vinding
jeppe.lohfert.haslund-vinding.01@regionh.dk

Extended author information available on the last page of the article

visualization of individual tumor cells is not feasible; hence, surgery and definition of extent of resection (EOR) must depend on indirect measurement and proxy parameters of EOR. For systemic cancers, surgeons typically rely on pathology examinations of resection margins which provides a reproducible assessment of EOR which is reliable enough to allow stratification of adjuvant treatment and follow-up [10, 11, 13]. This classification has not been practical for meningiomas, since growth patterns may disagree with feasibility of harvesting tissue for analyses of resection margins and, moreover, because histopathology may be insufficient to distinguish between normal and neoplastic meningeal cells [9].

For meningiomas, EOR has instead relied on two different approaches and variations thereof. The classic description of EOR is a structured report of the surgeon's assessment of whether tumor has been biopsied, subtotally removed, completely removed, or completely removed with additional management of proposed dural and bone invasion as described by Simpson in 1957 [39]. The alternative approach is postoperative MRI imaging as described in EANO guidelines [14]. The surgeon's intraoperative assessment lacks objectively verifiable criteria and does not allow an estimate of microscopic residual cells after completed surgery [37]. A radiological assessment is not sensitive enough to rule out residual tumor masses [40]. Spatial resolution of MRI imaging can leave residual tumors with up to 1,000,000 cells undetectable. Moreover, MRI imaging is not specific. Surgery commonly leads to tissue reactions and scarring with contrast enhancement that may be impossible to differentiate from tumor on an MRI image.

An updated agreement regarding how to report the extent of meningioma resection is warranted, as also concluded by a recent RANO review [34].

Yet, immunohistochemistry has developed to improve diagnosis of meningioma and imaging with PET for somatostatin receptors, almost exclusively expressed by tumor cells in patients with meningioma, provide superior sensitivity and specificity compared to contrast enhanced MRI [3–5, 27].

There is a need for a traceable and reproducible system to describe extent of resection for meningiomas [37]. We propose use of a combination of the most sensitive and specific imaging modality paired with optimal immunohistochemistry.

This technical note aims to describe a novel grading system that combines analyses of resection margins and PET imaging of somatostatin receptors. The note comprises a proposal for the system and a user's guide. Herein, we present our grading system and show the application our first six patients as a proposal to wide implementation of Copenhagen Grading for maximally traceable reporting of extent of resection of meningiomas.

Methods

Copenhagen Grading was designed to describe presence or absence of residual meningioma tissue after surgery by combining imaging and histology for tumors suspected to be meningiomas from pre-surgical scanning and confirmed by intraoperative analysis of frozen tissue. The classification combines results of immunohistochemistry from surgical biopsies and DOTATOC-PET scanning at follow-up after 3 months. Copenhagen Grading is organically implemented, and we have proposed a preliminary follow-up algorithm which is to be evaluated and adapted during continuous follow-up of included patients. Clinical data is prospectively recorded for evaluation and adaption during implementation.

Surgical biopsies

After as complete a resection as feasible, biopsies are taken from 4 different quadrants of the resection margin, marked and sent to pathology at the conclusion of surgery. Alternatively, a complete strip of dura surrounding the tumor can be sent separately if feasible (marked as "complete resection margin"). A conscious effort is made to include any area where the surgeon is least confident to have removed all tumor tissue. For intraventricular and posterior third ventricular meningiomas, biopsies are obtained from resection margins of the choroid plexus depending on the symmetry of the attachment. "Area of doubt" resembles areas outside the resection margin where the surgeon might suspect residual tumor cells, i.e., dura or bony structures. These sites are biopsied and marked as "area of doubt (AOD)" (Figs. 1, 2, 3 and 4).

The grade is 0 if the margins or any "areas of doubt" are free and 1 if the margins or any "areas of doubt" contain meningioma cells by routine histology plus immunohistochemistry for EMA and SSTR2 if needed for differential diagnostics[9].

Brain invasion is automatically considered "Copenhagen grade 1."

It is optional to add molecular analyses of the tumor-specific signature if immuno-histopathology or histopathology remains equivocal.

Imaging

At 3 months after surgery, routine radiological follow-up is undertaken with MRI or CT and ^{68}Ga-DOTATOC-PET CT or MRI22, depending on available spatial resolution of scanners. The grade is 0 if there is no detectable tumor and 1 if the images reveal a specific ^{68}Ga-signal.

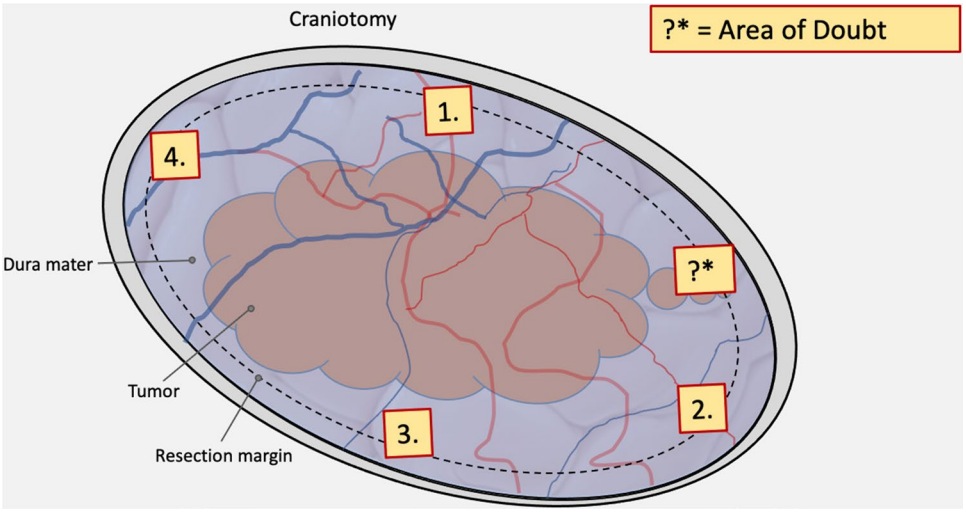

Fig. 1 Illustration of perioperative field. The aim is to obtain a circular resection margin of dura where it is feasible. Biopsies are taken from 4 different quadrants of the resection margin. "Area of doubt" biopsies are taken from the borders of the resection margin or bony structures

The Copenhagen Grade

The Copenhagen Grade is thus a combination of histopathology (0 or 1) and radiological imaging (0 or 1). It is expressed as 0/0, 1/0, 0/1, or 1/1 depending on the empirical observations. Histopathology is reported as "1" if at least one of resection margin—or AOD biopsies—is positive for tumor. Any tumor with demonstration of brain invasion from histopathology is graded as "1" from histopathology. Brain invasion is defined in agreement with WHO grading characterized by irregular groups of tumor cells infiltrating the adjacent cerebral parenchyma, without an intervening layer of leptomeninges [18, 21].

The extent of follow-up is tailored depending on the Copenhagen Grade and tumor phenotype.

Results

We present our first six patients with complete assessment of extent of resection according to Copenhagen Grading (Table 1). The preliminary experience indicated that biopsies could be obtained without technical difficulties. Biopsies from resection margins or an "area of doubt" that were sent as separate samples were analyzed during routine histopathology to either contain or not contain meningioma cells. Post-operative scanning with MRI and DOTATOC-PET was successfully obtained during follow-up 11–14 weeks after surgery.

All patients had been described to have undergone gross total resection. Four tumors were perioperatively assessed to have been removed according to Simpson grade 2, and one each as grade 1 and grade 3. The histopathology showed residual tumor in three patients. MR imaging showed residual tumor in two patients and DOTATOC-PET in three. One patient was positive on histopathology but negative on MRI and DOTATOC-PET; one was positive on DOTATOC-PET but negative on histopathology and MRI (Table 1).

Typical Copenhagen Grades 0/0, 1/0, 0/1, and 1/1 are illustrated in a case example (Fig. 5).

Estimated as Simpson grade II

Histopathology: WHO grade I. Dura biopsies without remaining tumor cells. "Area of doubt" biopsy showed lamellar bone structure and meningioma cells

Imaging: DOTATOC-PET and MRI without signs of remaining tumor. PET-DOTATOC and MRI co-registration showing expected activity uptake due to tissue healing in relation to the craniotomy and dura-substitute and no signs of remaining tumor

Copenhagen Grading: 1/0

Discussion

It has been possible to implement Copenhagen Grading for meningiomas. Our first cases illustrate the grading and suggest that histopathology and DOTATOC-PET imaging add complementary information to the evaluation of extent of resection. We interpret the data to indicate preliminary support for the concept of combining histology and the presently most sensitive and specific imaging biomarker to allow a dichotomized description of residual meningioma after surgery.

During routine implementation into the workflow during surgery, histopathology, and imaging, local routines must be developed and validated. Typically, surgeons must incorporate biopsies into surgical routine after removal of the main bulk of tumor and biopsies must be marked

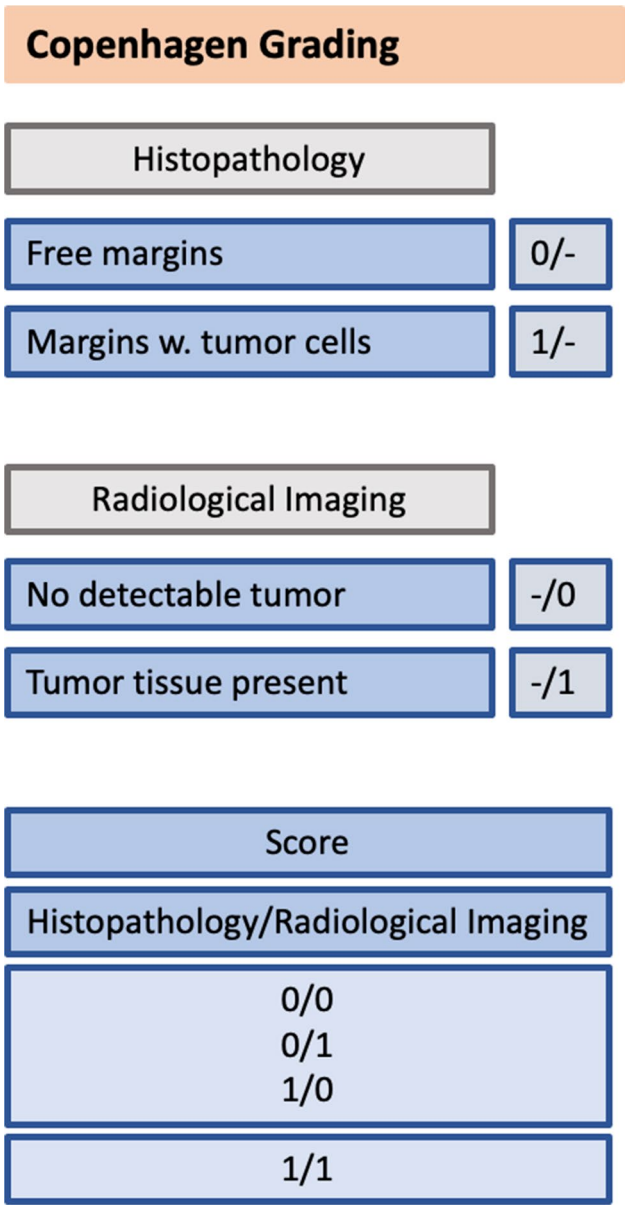

Fig. 2 Copenhagen Grading for meningiomas: score system depending on the empirical observations

and sent separately for histopathology. These two steps are feasible within a surgical checklist and separately marked biopsies are processed routinely by pathologists who develop the routine and evaluate Copenhagen grades as part of a routine histology report.

Imaging is dependent on availability of a PET facility and easily offered to all patients who are eligible; participation in follow-up imaging is not different from routine follow-up with MRI or CT. Our assessment is that Copenhagen Grading could be implemented as a feasible and a potential objective grading system. The combination of histopathology and imaging appeared to improve sensitivity to detect residual tumor.

It may be technically problematic to obtain representative and relevant intraoperative biopsies from resection margins, particularly from tumors with difficult cranial base locations or potential invasion of mesenchymal tissues. Nonetheless, a tissue biopsy that can be diagnosed with sensitive biomarkers such as EMA and SSTR2, which provide 96% specificity, is far better than reliance only on postoperative MRI scanning or the surgeon's subjective impression. Biopsies can be harvested during surgery and be processed for analysis without urgency. A risk of failure to obtain representative tissues must be accepted with any tissue based diagnostic method. We postulate, in agreement with our surgical experience, that even difficult cranial base locations allow that also far sides of a tumor attachment can be reached with instruments, yet any surgical attempt to obtain a representative biopsy can fail in more than 5% of cases even in diagnostic image-guided surgery [12, 22]. However, we noted that biopsies were not omitted because of technical difficulties.

We thus consider the use of histology on resection margins as feasible, promising and relevant.

Recently molecular biomarkers for aggressive phenotypes (TERT, CDKN2A) have been validated in large meta-analyses [28, 42] and found feasible for clinical implementation in meningioma grading. Furthermore, genetic and epigenetic landscapes allow novel classifications based on meningioma biology [6, 7, 23, 32, 41–43]. Next-generation sequencing (NGS) of a targeted meningioma gene panel could be a specific discriminator between different neoplastic and non-neoplastic meningeal cells, which we expect to correlate with the clinical course. We consider that improved biological data from molecular characteristics would be particularly powerful to predict the fate of a patient when combined with a highly traceable description of the resection such as we propose.

^{68}Ga-DOTATOC PET is known to offer better diagnostic information of residual or recurrent meningioma than MRI scanning [4, 5]. Presently, the major drawback for wide implementation is that ^{68}Ga-DOTATOC PET scanning requires equipment and expertise, which is mostly available in specialized centers. Still, PET scanning is widely available in national centers and scanning is undertaken electively approximately 3 months after surgery. Elective, ambulatory scanning is feasible and must then be weighed against cost. Our preliminary impression is that unequivocal data on tumor residues would change MRI follow-up and use of adjuvant therapies to an extent that may very well decrease cost of follow-up while empowering patients with less uncertainty of a potential cure of disease.

We cannot yet assess the clinical impact of grading or its cost-efficiency, but it is very likely that wide implementation of Copenhagen Meningioma Grading can increase

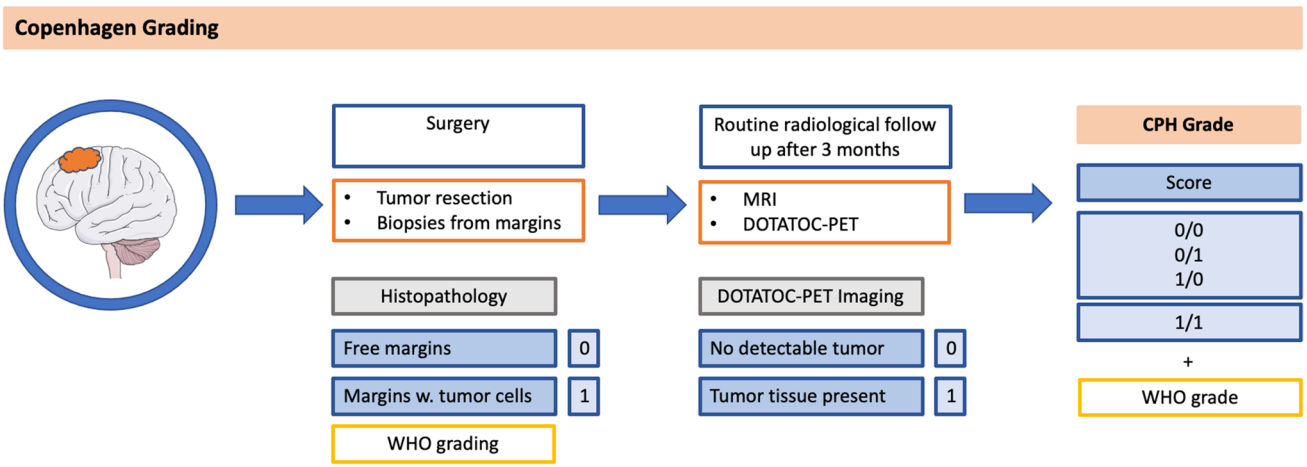

Fig. 3 The Copenhagen Grading setup including histopathology from per-operative biopsies and imaging at 3 months follow-up

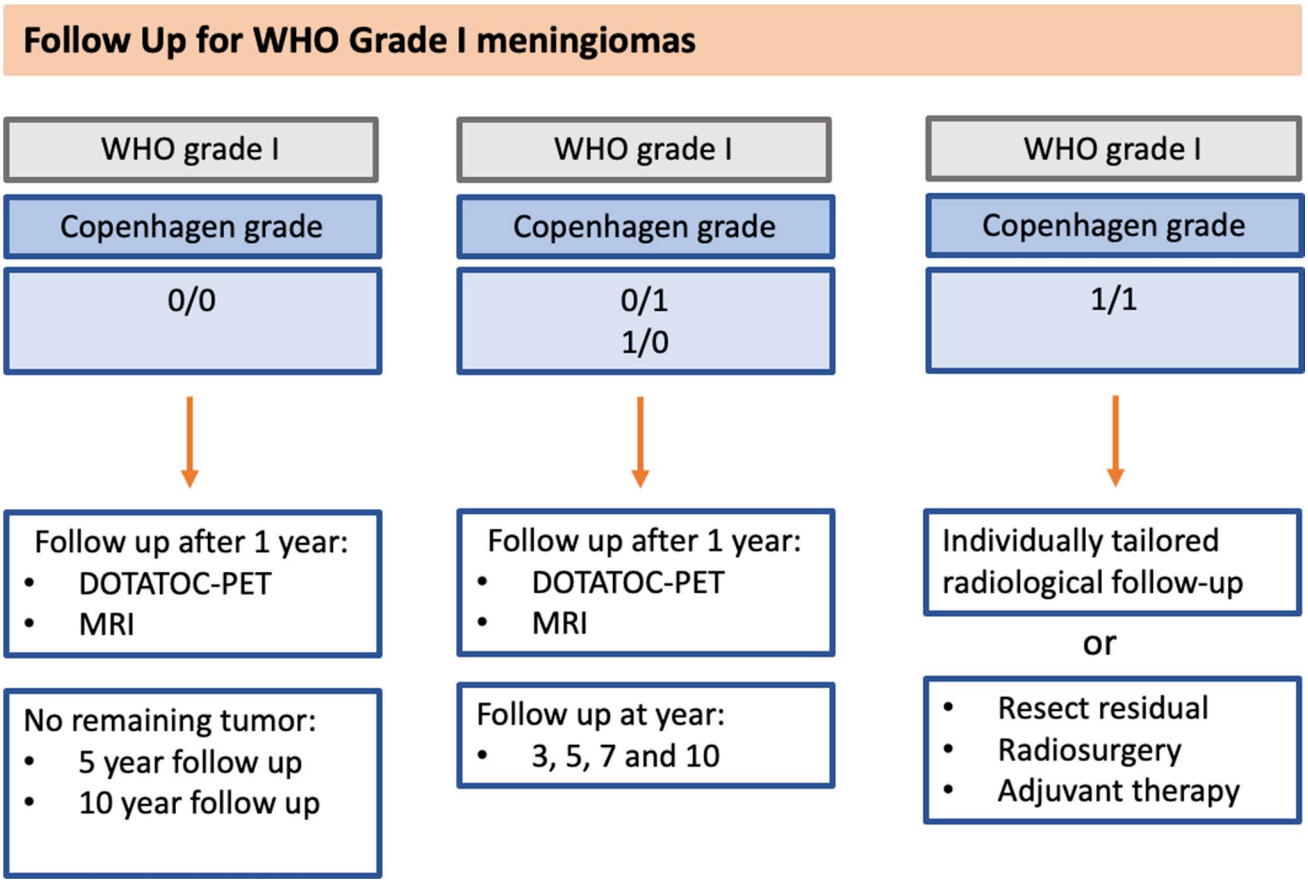

Fig. 4 Preliminary follow-up algorithm. The extent of follow-up is tailored depending on the Copenhagen Grading and tumor phenotype.

efficiency in follow-up and save cost. We have indicated how better traceable information on EOR can produce a stratified follow-up with fewer regular MRI scans. Moreover, better information on EOR is likely to supply patients with better discrimination between potential cure or harboring a chronic condition.

The dichotomized information of presence of residual neoplastic cells is fundamental, although not always admitted.

Table 1 Preliminary results on 6 enrolled patients from December 2020 until March 2021.

Caseno.	Location	WHO grade	Simpson grade	Dura/AOD biopsy	Histological evaluation of biopsy	MR finding	DOTATOC-PET finding	CPH grading
1	Convexity sin.	I	2	Dura biopsy obtained	No residual cells in dura	No residual tumor	No residual tumor	**0/0**
2	Convexity sin.	I	2	Dura biopsy + AOD obtained	Bone biopsy w. residual cells (AOD)	No residual tumor	No residual tumor	**1/0**
3	Convexity sin.	I	2	Dura biopsy obtained	No residual cells in dura	No residual tumor	No residual tumor	**0/0**
4	Cavernous sinus + suprasellar	I	3	AOD biopsy obtained	Bone biopsy w. residual cells (AOD)	Residual tumor	Residual tumor	**1/1**
5	Convexity sin.	I	1	Dura biopsy obtained	AOD w. residual cells	Residual tumor	Residual tumor	**1/1**
6	Convexity sin.	I	2	Dura biopsy obtained	No residual cells in dura	No residual tumor	Residual tumor	**0/1**

Area of doubt = AOD. The biopsies are categorized as: Dura biopsy + AOD obtained = both dura biopsy and AOD biopsy; Dura biopsy obtained = only dura biopsy obtained; AOD biopsy obtained = AOD biopsy only

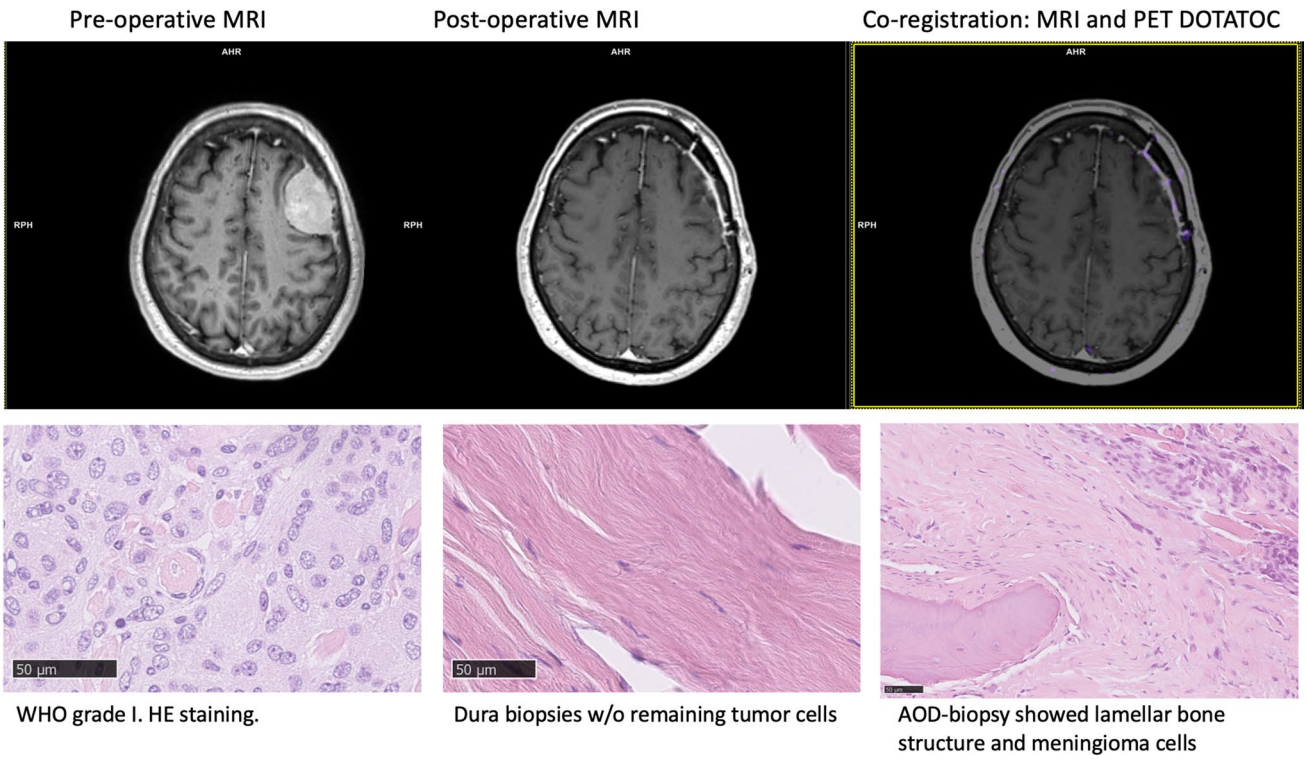

Fig. 5 Case 2: A 63-year-old woman with a left-sided convexity meningioma. Underwent operation with tumor removal, resection margin with 4 sites + "area of doubt" biopsy from adjacent bone. Resected dura was replaced with artificial dura substitute

Recurrences are possible only if neoplastic cells are present and it is usually considered possible to remove a benign meningioma completely. Usually, a "risk of recurrence" is used as an amalgamated function of residual tumor volume—if any—and biological qualities such as growth rate [37]. We argue that biological qualities should be analyzed separately from extent of resection. The risk of recurrence is a function of residual cells, while the detection of a recurrence depends on how fast tumors grow. We have recently analyzed a cohort of meningiomas with true long-term follow-up and demonstrated

that the biomarker Ki-67 proliferation index (Ki-67 PI) primarily correlated with *time to recurrence*; suggesting that any tumor may recur if neoplastic cells remain—if follow-up is long enough [29]. We suggest that optimum information on extent of resection allows a nuanced assessment of the biological qualities of any residual tumor including tailoring of follow-up and adjuvant or additional treatments. The biological qualities that affect growth rate and invasiveness must be assessed from known biomarkers such as WHO grades [21], Ki-67 PI [1, 35], TERT-promoter mutations, and homozygous deletion of CDKN2A/B [28, 38]. Such information should be used to select additional treatments and design individualized follow-up [36]. Better standardized subgroups that have been characterized from both aspects allow better trials. We have primarily targeted WHO grade 1 meningiomas but consider our grading useful for all meningiomas. The need to optimally target additional or adjuvant therapy is probably even greater for WHO grade II.

Copenhagen grading integrates different diagnostic modalities with the expectation that they may disagree; their strengths and weaknesses of sensitivity and specificity may differ and agreement between the different modalities is not primarily desirable. The grading is asymmetrical, since any objective finding that points at residual tumor shifts the patients into a classification where need for additional management must consider that the patient has residual disease and we have designed the grading to allow the best available way to detect residual tumor with certainty.

This is a technical note that does not show long-term outcomes or benefits. The primary benefit is the theoretical advantage of superior traceability, sensitivity, and specificity. Sensitivity and specificity cannot be evaluated without long-term follow-up; the lack of validation is a major weakness. Unfortunately, traditional prospective trials to validate use of Copenhagen Grading of meningiomas are not feasible. The slow growth of meningiomas limits relevance of short-term prospective trials. We suggest that Copenhagen Grading is organically implemented. Organic implementation entails continuous re-evaluation of treatment and findings so that suboptimal strategies are changed according to experience and judgment while functional strategies are maintained. Information is collected prospectively and analyzed critically. The main parameters to validate during follow-up are whether Copenhagen Grading proves to be traceable, reproducible, and support standardization for better targeted meningioma subgroup management.

Conclusion

This technical note describes Copenhagen Grading for extent of resection of meningiomas, which is based on the rationale of resection-margin analyses as gold standard and superior imaging performance of ^{68}Ga-DOTATOC PET. The preliminary observations suggest that Copenhagen Grading is technical, feasible, and traceable. It may comprise the much-needed grading system that allows standardized clinical research and thereby improves management of follow-up, adjuvant therapy, and prognostication of meningiomas. Presentation of the grading is a prerequisite for organic development of applications and amendments.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contribution JHV and TM drafted the manuscripts. JHV made the illustrations and collected data with IL, ADM, BWK and DS. TM, JHV, MZ, JSR, LP, KF, IL, BWK, and DS participated in the original design of the Copenhagen Grading for Meningioma. The remaining authors all gave thorough input in their field of expertise and helped design the final draft. All authors read and approved the final manuscript

Declarations

Ethics approval Implementation of Copenhagen Grading is a Quality Assurance Project approved by the Department of Neurosurgery, Rigshospitalet. Specific ethics approval in not relevant per Danish legislation.

Consent to participate Not applicable.

Consent for publication All authors have given their consent.

Competing interests The authors declare no competing interests.

References

1. Abry E, Thomassen IØ, Salvesen ØO, Torp SH (2010) The significance of Ki-67/MIB-1 labeling index in human meningiomas: a literature study. Pathol Res Pract 206(12):810–815
2. Adegbite AB, Khan MI, Paine KW, Tan LK (1983) The recurrence of intracranial meningiomas after surgical treatment. J Neurosurg 58(1):51–56
3. Afshar-Oromieh A, Giesel FL, Linhart HG, Haberkorn U, Haufe S, Combs SE, Podlesek D, Eisenhut M, Kratochwil C (2012) Detection of cranial meningiomas: comparison of ^{68}Ga-DOTATOC PET/CT and contrast-enhanced MRI. Eur J Nucl Med Mol Imaging 39(9):1409–1415
4. Bashir A, Vestergaard MB, Binderup T, Broholm H, Marner L, Ziebell M, Fugleholm K, Mathiesen T, Kjær A, Law I (2020) Pharmacokinetic analysis of [(68)Ga]Ga-DOTA-TOC PET in meningiomas for assessment of in vivo somatostatin receptor subtype 2. Eur J Nucl Med Mol Imaging 47(11):2577–2588
5. Bashir A, Ziebell M, Fugleholm K, Law I (2015) A potential role of 68Ga-DOTATOC PET in modifying eligibility to surgery in patients with recurrent meningioma. J Nucl Med Radiat Ther. https://doi.org/10.4172/2155-9619.1000256
6. Bi WL, Greenwald NF, Abedalthagafi M et al (2017) Genomic landscape of high-grade meningiomas. NPJ genomic Med. https://doi.org/10.1038/s41525-017-0014-7

7. Birzu C, Peyre M, Sahm F (2020) Molecular alterations in meningioma: prognostic and therapeutic perspectives. Curr Opin Oncol 32(6):613–622
8. Borovich B, Doron Y (1986) Recurrence of intracranial meningiomas: the role played by regional multicentricity. J Neurosurg 64(1):58–63
9. Boulagnon-Rombi C, Fleury C, Fichel C, Lefour S, Marchal Bressenot A, Gauchotte G (2017) Immunohistochemical approach to the differential diagnosis of meningiomas and their mimics. J Neuropathol Exp Neurol 76(4):289–298
10. Brouwer de Koning SG, Vrancken Peeters M-JTFD, Jóźwiak K, Bhairosing PA, Ruers TJM (2018) Tumor resection margin definitions in breast-conserving surgery: systematic review and meta-analysis of the current literature. Clin Breast Cancer 18(4):e595–e600
11. Brouwer de Koning SG, Weijtmans P, Karakullukcu MB, Shan C, Baltussen EJM, Smit LA, van Veen RLP, Hendriks BHW, Sterenborg HJCM, Ruers TJM (2020) Toward assessment of resection margins using hyperspectral diffuse reflection imaging (400-1,700 nm) during tongue cancer surgery. Lasers Surg Med 52(6):496–502
12. Giamouriadis A, Perera D, Safdar A, Vergani F, Bhangoo R, Gullan R, Ashkan K (2019) Safety and accuracy of frameless electromagnetic-navigated (AXIEM(TM))-guided brain lesion biopsies: a large single-unit study. Acta Neurochir (Wien) 161(12):2587–2593
13. Goffredo P, Zhou P, Ginader T, Hrabe J, Gribovskaja-Rupp I, Kapadia M, You YN, Hassan I (2020) Positive circumferential resection margins following locally advanced colon cancer surgery: Risk factors and survival impact. J Surg Oncol 121(3):538–546
14. Goldbrunner R, Minniti G, Preusser M et al (2016) EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol 17(9):e383–e391
15. Hasseleid BF, Meling TR, Rønning P, Scheie D, Helseth E (2012) Surgery for convexity meningioma: Simpson Grade I resection as the goal: clinical article. J Neurosurg 117(6):999–1006
16. Jääskeläinen J (1986) Seemingly complete removal of histologically benign intracranial meningioma: late recurrence rate and factors predicting recurrence in 657 patients. A multivariate analysis. Surg Neurol 26(5):461–469
17. Jadid KD, Feychting M, Höijer J, Hylin S, Kihlström L, Mathiesen T (2015) Long-term follow-up of incidentally discovered meningiomas. Acta Neurochir (Wien) 157(2):225–230 discussion 230
18. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK (2002) The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 61(3):215–225
19. Lemée J-M, Corniola MV, Da Broi M, Joswig H, Scheie D, Schaller K, Helseth E, Meling TR (2019) Extent of resection in meningioma: predictive factors and clinical implications. Sci Rep 9(1):5944
20. Lemée J-M, Corniola MV, Meling TR (2020) Benefits of re-do surgery for recurrent intracranial meningiomas. Sci Rep 10(1):303
21. 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(6):803–820
22. Lu Y, Yeung C, Radmanesh A, Wiemann R, Black PM, Golby AJ (2015) Comparative effectiveness of frame-based, frameless, and intraoperative magnetic resonance imaging-guided brain biopsy techniques. World Neurosurg 83(3):261–268
23. Maier AD, Stenman A, Svahn F, Mirian C, Bartek JJ, Juhler M, Zedenius J, Broholm H, Mathiesen T (2021) TERT promoter mutations in primary and secondary WHO grade III meningioma. Brain Pathol 31(1):61–69
24. Mathiesen T, Lindquist C, Kihlström L, Karlsson B (1996) Recurrence of cranial base meningiomas. Neurosurgery 39(1):2–9
25. Mathiesen T, Pettersson-Segerlind J, Kihlström L, Ulfarsson E (2014) Meningiomas engaging major venous sinuses. World Neurosurg 81(1):116–124
26. Meling TR, Da Broi M, Scheie D, Helseth E (2019) Meningiomas: skull base versus non-skull base. Neurosurg Rev 42(1):163–173
27. Milker-Zabel S, Zabel-du Bois A, Henze M, Huber P, Schulz-Ertner D, Hoess A, Haberkorn U, Debus J (2006) Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI, and [68Ga]-DOTATOC-PET. Int J Radiat Oncol Biol Phys 65(1):222–227
28. Mirian C, Duun-Henriksen AK, Juratli T et al (2020) Poor prognosis associated with TERT gene alterations in meningioma is independent of the WHO classification: an individual patient data meta-analysis. J Neurol Neurosurg Psychiatry 91(4):378–387
29. Mirian C, Skyrman S, Bartek JJ, Jensen LR, Kihlström L, Förander P, Orrego A, Mathiesen T (2020) The Ki-67 proliferation index as a marker of time to recurrence in intracranial meningioma. Neurosurgery. https://doi.org/10.1093/neuros/nyaa226
30. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL (1985) Meningioma: analysis of recurrence and progression following neurosurgical resection. J Neurosurg 62(1):18–24
31. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, Barnholtz-Sloan JS (2019) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 21(Suppl 5):v1–v100
32. Patel AJ, Wan Y-W, Al-Ouran R et al (2019) Molecular profiling predicts meningioma recurrence and reveals loss of DREAM complex repression in aggressive tumors. Proc Natl Acad Sci U S A 116(43):21715–21726
33. Pettersson-Segerlind J, Orrego A, Lönn S, Mathiesen T (2011) Long-term 25-year follow-up of surgically treated parasagittal meningiomas. World Neurosurg 76(6):564–571
34. Rogers L, Barani I, Chamberlain M, Kaley TJ, McDermott M, Raizer J, Schiff D, Weber DC, Wen PY, Vogelbaum MA (2015) Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. J Neurosurg 122(1):4–23
35. Roggendorf W, Schuster T, Peiffer J (1987) Proliferative potential of meningiomas determined with the monoclonal antibody Ki-67. Acta Neuropathol 73(4):361–364
36. Sahm F, Schrimpf D, Stichel D et al (2017) DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 18(5):682–694
37. Schwartz TH, McDermott MW (2020) The Simpson grade: abandon the scale but preserve the message. J Neurosurg:1–8
38. Sievers P, Hielscher T, Schrimpf D et al (2020) CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. Acta Neuropathol 140(3):409–413
39. Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20(1):22–39
40. Slot KM, Verbaan D, Bosscher L, Sanchez E, Vandertop WP, Peerdeman SM (2018) Agreement between extent of meningioma resection based on surgical simpson grade and based on postoperative magnetic resonance imaging findings. World Neurosurg 111:e856–e862
41. Suppiah S, Nassiri F, Bi WL et al (2019) Molecular and translational advances in meningiomas. Neuro Oncol 21(Suppl 1):i4–i17
42. Williams EA, Santagata S, Wakimoto H et al (2020) Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. Acta Neuropathol Commun 8(1):171

43. Youngblood MW, Duran D, Montejo JD et al (2019) Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas. J Neurosurg:1–10

Comments

All meningiomas, such as fingerprints, nose prints, or a pinna, are different. [1,2] They are different in terms of clinical presenting features, radiological imaging characters, and histological subtleties, and more importantly in the pattern of their behavior and outcome. The "malignant" fault of a meningioma is its proximity to the brain and spinal cord and its occasional proclivity to ensnare neural structures. Meningioma should be christened as benign microscopically, malignant behaviourally, or rather positionally.

Between the idea (of benignancy)
And the reality (of behaviour),
Between the scene (under the microscope)
And the seer (the pathologist)
Falls the shadow (of ambiguity).
(Modified from The Hallow Men by T.S. Eliot)
The authors present a novel grading system "Copenhagen grading" to assess the extent of meningioma resection and to improve the management of follow up, adjuvant therapy and prognostication.

All meningiomas can be classified into Good or Bad, only in retrospect. Evaluation after several years of treatment can determine the true colors of the tumors. You can remove the tumor, the whole tumor, and nothing but tumor without removing the tumor diathesis or the ability to form the tumor.

Presenting symptoms, meningioma location, extensions, relationship with adjoining structures, vascularity, and consistency vary, making the management unique in every case. Likewise, the cellularity and the growth pattern of all meningiomas are different. Some indicators such as extradural or extracranial extension and involvement of dural sinuses (including cavernous sinus) are indicative of a higher growth potential and an enhanced propensity to recur. Histological grading may help in prognosticating the long-term outcome.

The recurrences depend more on the growth pattern of the tumor. The rate of recurrence of a meningioma is independent of the extent of tumor resection. The radicality of resection will also depend on the aggression and extensions of the meningioma. More extensive the presence of the tumor, more difficult is the resection and the likelihood of recurrence is higher. More circumscribed meningiomas are easier to remove and the long-term outcome is better. The best imaging techniques and the most evolved operative microscopes do not touch the basic character of a neuraxial tumor. There lies a message for the neurosurgeon: "Less is more."

Assessing or grading the tumor is good, but it can essentially be a futile exercise. From a surgeon's perspective it appears that surgery is the only practical fact. The answer to treatment of meningiomas is safe resection to obtain symptom-free time for the patient, an act that can be repeated when mandatory.

Atul Goel
Mumbai,India
References:
1. Goel A, Kothari M. Editorial: Cavernous sinus meningiomas. J Neurosurg. 2010;113:1085
2. Goel A, Kothari M. Meningiomas: Are they curable? J Craniovertebr Junction Spine. 2016 Jul-Sep;7(3):133-4.

When coming up with a new grading system, this is usually based on large series, long-term consistent application and more often a consortional effort to demonstrate applicability beyond single institution borders. Therefore, this cannot be more than a proposal derived from a very small patient group which in some institutions is less than a week's load. Nonetheless, it is an interesting approach to add in a more refined way the evaluation of procedural quality to the big picture of meningioma grading. Very elaborate molecular based grading systems for meningioma have been published or accepted for high-ranking publication this year, providing a very elaborate in-depth analysis of cellular heterogeneity and tumor biology which is bound to have a highly important impact on the clinical course. Nonetheless, even with equal molecular characteristics, the fate of a patients is as much determined by the quality of the resection. In that aspect, an attempt to improve the assessment of the surgical result is relevant and the proposed evaluation by the Copenhagen group is one option.

Manfred Westphal
Hamburg, Germany

Authors and Affiliations

Jeppe Haslund-Vinding[1] · Jane Skjoth-Rasmussen[1] · Lars Poulsgaard[1] · Kaare Fugleholm[1] · Christian Mirian[1] · Andrea Daniela Maier[1,2] · Thomas Santarius[3] · Frantz Rom Poulsen[1,2,3,4,5,6,7,8,9,10,11] · Torstein Meling[9] · Jiri Junior Bartek[1,4,11] · Petter Förander[4,11] · Vibeke Andrée Larsen[6] · Bjarne Winther Kristensen[4,7] · David Scheie[4] · Ian Law[8] · Morten Ziebell[1] · Tiit Mathiesen[1,4,10]

[1] Department of Neurosurgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[2] Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[3] Department of Neurosurgery, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[4] Department of Clinical Neuroscience, Section for Neurosurgery, Karolinska Institutet, Stockholm, Sweden

[5] Department of Neurosurgery, Odense University Hospital, University of Southern Denmark, Odense, Denmark

[6] Department of Radiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[7] Department of Clinical Medicine and Biotech Research and Innovation Center (BRIC), University of Copenhagen, Copenhagen, Denmark

[8] Department of Clinical Physiology, Nuclear Medicine and PET, Copenhagen University Hospital, Copenhagen, Denmark

[9] Department of Neurosurgery, Geneva University Hospital, Geneva, Switzerland

[10] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[11] Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden