Open Medicine

Meningioma recurrence

--Manuscript Draft--

Manuscript Number:	OPENMED-D-16-00052
Full Title:	Meningioma recurrence
Article Type:	Mini-Review
Keywords:	meningioma; pathology; predisposing factors; recurrence
Corresponding Author:	Tibor Hortobagyi, MD PhD FRCPath EFN University of Debrecen Medical and Health Science Center Debrecen, HUNGARY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Debrecen Medical and Health Science Center
Corresponding Author's Secondary Institution:	
First Author:	Tibor Hortobagyi, MD PhD FRCPath EFN
First Author Secondary Information:	
Order of Authors:	Tibor Hortobagyi, MD PhD FRCPath EFN
	Janos Bencze, MD
	Greta Varkoly, MD
	Mahan C Kouhsari, MD
	Álmos Klekner, MD PhD
Order of Authors Secondary Information:	
Abstract:	Meningioma accounts for more than 30% of all intracranial tumours. It affects mainly the elderly above the age of 60 with a female:male ratio of 3:2. The prognosis is variable, usually favourable with no progression in tumour grade and no recurrence in WHO grade 1 tumours. However, a minority of tumours represent atypical (grade 2) or anaplastic (grade 3) meningiomas and this heterogeneity is also reflected in histopathological appearances. Irrespective of the grade, the size of the tumour and the localisation may have severe, sometimes lethal consequences. Following neurosurgical interventions to remove the tumour, recurrence and progression in WHO grade may occur. Our knowledge on predisposing histomorphological and molecular factors of recurrence is rather limited. These can be classified as I) demographic II) environmental, III) genetic and epigenetic IV) imaging, V) neuropathological, VI) neurosurgical. In view of the complex background of tumour recurrence, the recognition of often subtle signs of increased risk of recurrence requires close collaboration of experts from several medical specialties. This multidisciplinary approach results in better therapy and less complications related to tumour recurrence.
Suggested Reviewers:	Mara Popovic, MD, PhD Professor, University of Ljubljana mara.popovic@mf.uni-lj.si Expert in clinical neuropathology.
	Penelope Korkopolou, Professor MD PhD, University of Athens, Medical School pkorkol@med.uoa.gr Expert in clinical neuropathology.
	Elena Martinez-Saez, MD EFN Consultant, Vall đHebron University Hospital eamartin@vhebron.net Expert in clinical neuropathology.

	Zsolt Kopniczky, MD PhD Consultant, University of Szeged kopniczky@hotmail.com Expert on neurosurgery and oncology of brain tumours.
	Zsolt Zador, MD MRCS(Eng) Consultant, Greater Manchester Neuroscience Centre zadzso@gmail.com Expert in neurosurgery of brain tumours.
Opposed Reviewers:	

Meningioma recurrence

Tibor Hortobágyi*[1], János Bencze*[1], Gréta Varkoly[1], Mahan C Kouhsari[1], Álmos Klekner[2]

[1]Division of Neuropathology, Institute of Pathology, [2]Department of Neurosurgery, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

*equal contribution

Correspondence to:

Tibor Hortobágyi *MD PhD FRCPath EFN*

Division of Neuropathology, Institute of Pathology,

University of Debrecen,

Debrecen, Nagyerdei krt. 98.

H-4032, Hungary

Email: hortobagyi@med.unideb.hu

Abstract

Meningioma accounts for more than 30% of all intracranial tumours. It affects mainly the elderly above the age of 60 with a female:male ratio of 3:2. The prognosis is variable, usually favourable with no progression in tumour grade and no recurrence in WHO grade 1 tumours. However, a minority of tumours represent atypical (grade 2) or anaplastic (grade 3) meningiomas and this heterogeneity is also reflected in histopathological appearances. Irrespective of the grade, the size of the tumour and the localisation may have severe, sometimes lethal consequences. Following neurosurgical interventions to remove the tumour, recurrence and progression in WHO grade may occur. Our knowledge on predisposing histomorphological and molecular factors of recurrence is rather limited. These can be classified as I) demographic II) environmental, III) genetic and epigenetic IV) imaging, V) neuropathological, VI) neurosurgical. In view of the complex background of tumour recurrence, the recognition of often subtle signs of increased risk of recurrence requires close collaboration of experts from several medical specialties. This multidisciplinary approach results in better therapy and less complications related to tumour recurrence.

Introduction

Meningioma is one of the most frequent intracranial tumour. The prevalence peaks between the age of 60 and 70 years with a female:male ratio of 3:2. Nevertheless, the tumour may also occur in children. The most frequent localisations are parasagittal, lateral convexity, the wings of sphenoid bone, anterior fossa close to the olfactory nerve, the sellar region, posterior fossa in the vicinity of foramen magnum, respectively[1]. Most meningiomas are histologically benign. The WHO classification distinguishes three histological grades (1-2-3) and 15 subtypes[2]. Although meningiomas are usually histologically benign, space occupying lesions within the close skull can never be considered absolutely risk free, as due to the increase of the intracranial pressure they potentially may lead to life-threatening complications. Because recurrence and progression are well-known and not infrequent characteristics of meningiomas, a thorough analysis and better understanding of contributory factors are of crucial importance. In the current review of literature we assessed the predictive factors of tumour recurrence with focus on clinical consequences, histological alterations and risk factors related to the tumour treatment itself. Independent risk factors, such as sex and age, have also been analysed. Special emphasis has been devoted to predictive signs detectable by imaging techniques. The predictive values of immunohistochemical and other molecular markers in relation histological grade is increasingly recognised and therefore reviewed. Finally, the extent of surgical resection reflected by the Simpson grade appears very closely associated with the risk of recurrence. In summary, in this review we assess predictive factors derived from several neuro-specialties, because their combined assessment can help to reach the best clinical decision on patient care (Figure 1).

Predisposing factors of meningioma recurrence

I. Demographic

The role of age and sex has been studied in relation to risk of recurrence. However, there has been no significant correlation between this two factors[3–6]

II. Environmental

An important environmental and/or iatrogenic factor is ionising radiation of the head and neck region. The increased incidence of meningiomas among survivals of the Hiroshima nuclear disaster of the Second World War also supports this notion. However, most cases of radiation-induced meningiomas are iatrogenic and related to the diagnostic irradiation in dental practice. Therapeutic irradiation (radiotherapy) appears highly relevant and there is growing body of evidence to support this[7,8]. Interestingly, traumatic head injury also increases the risk of meningioma 1 or 2 decades after the trauma in a dose dependent manner (and apparently unrelated to the severity of injury)[9]. The female predominance of meningioma rises the possibility of hormonal effects in the pathogenesis although large scale epidemiological studies have not provided unequivocal evidence to prove hormonal factors in pathogenesis and pathomechanism[10]. Nevertheless, it is well-known that during pregnancy meningioma may undergo rapid growth, which could have lethal outcome[11]. In breast cancer sufferers there is also modest increase in incidence[12]. Long term exogenous hormone replacement therapy has also been implicated tumorigenesis[13]. Hu et al. in a comprehensive analysis examined the role of various environmental factors, in the Chinese population[14]. The results reveal that smoking significantly increases the incidence of meningioma in women. Similarly lead, tin, cadmium as an occupational hazard also increases meningioma incidence in affected workers. In contrast, food rich in fruits and vegetables decreases the chance of having a meningioma[14]. Although alcohol consumption has been implicated as a risk factor for meningioma, there are no convincing evidence to support this hypothesis[15]. With the advent of novel telecommunication techniques, in particular mobile phones, the question has emerged whether there is an association between meningioma development and use of cell phones. Interphone company conducted a study which concluded there was no such association[16]. Nevertheless we have to take into account that there are not many research reports on this field and the follow-up period is relatively short because mobile phones have become widely used in the past 20 years or so.

III. Genetic and epigenetic

Meningioma is also component of numerous familiar tumour syndromes. It is most frequent in neurofibromatosis type 2 (NF2) and can also occur in other congenital and familial diseases: multiple endocrine neoplasia type 1 (MEN1), Gorlin-, Cowden-, Gardner-, Turcot-, von Hippel–Lindau-(VHL) and Li–Fraumeni syndrome[17]. The *NF2* gene is located on the long

arm of chromosome 22, coding tumour suppressor protein merlin. In sporadic cases (i.e. in meningiomas unrelated to tumour syndromes) there is mutation in 60% of cases. The frequency and type of mutation in various meningioma grades is roughly identical[18]. A novel avenue to understand meningioma pathogenesis is the research into epigenetic mechanisms. One of the first discovered epigenetic change in tumours is aberrant DNA methylation. Although *NF2* is relatively frequently mutated in meningioma, epigenetic alteration of *NF2* is rare. In contrast, *TIMP3*, *TP73* és *RASSF1A* promoters and *HOXA7*, HOXA9, *HOXA10* homebox genes are often hypermethylated in meningiomas. Another epigenetic change, histone modification, has no proven involvement in the pathogenesis. The third major epigenetic factor, the micro RNAs (miRNAs), are important in regulating post-translational silencing. miR-190a is increased, whereas miR-29c-3p and miR-219-5p are decreased in a subset of meningiomas and these tumours have higher risk of recurrence[19].

IV. Imaging

In tumour diagnostics and follow-up imaging is crucial. The characteristic dural tail detectable on CT and MR images, the peritumoral edema, calcification are all important features[1]. Significant correlation has been found between tumour size (>50mm), shape (mushroom), localisation (base of skull), presence of brain invasion, and the severity of peritumoral oedema[3,20–23]. The latter is important in recurrence because oedema increases the chance of brain invasion by the tumour which is a key factor in recurrence[24]. The large size, basal localisation and malignant histological features have association with increased severity of peritumoral edema[25].

V. Neuropathological

Histological grade

The clinical behaviour and risk of recurrence has very close association with the histological grade of the tumour. The histological grade and the extent of resection appears to be the two most important predictive factors of recurrence. According to the WHO classification, meningiomas are grouped in three grades (grade I, II, III). According to the typical morphological appearances and the mitotic index (assessed by the number of mitosis per 10 high power microscopic fields (HPF) there are 15 histological subtypes[2]. WHO grade I has 9,

whereas both WHO II and WHO grade III has 3 subtypes (Table 1). Clear cell meningioma is grade II if intracranial and grade I. when occurs in the vertebral canal.

In WHO grade II „atypical" meningioma minimum three of the following histomorphological features are detectable: increased cellularity, small cells with increased nucleus/cytoplasm ratio, prominent nucleoli, 'patternless' or sheet-like growth, focal small, geographic necrosis, 4 or more mitosis/10 HPF. In anaplastic (WHO grade III.) meningioma there are obvious malignant cytological features, such as undifferentiated growth, which makes them similar to carcinoma, melanoma or sarcoma (regarding cytological atypia). In anaplastic meningioma there are 20 or more mitosis/10 HPF.

Several studies have proven the close association between histological grade and risk of recurrence. In higher grade tumours (i.e.: grade II, III) the increased cellularity, higher mitotic rate and presence of necrotic lesions predict the increased chance of recurrence[3,21]. Significant relation has been established both in grade II (atypical) grade III (anaplastic) meningiomas. However, in anaplastic meningiomas these features are associated with less favourable outcome[26]. Consistent with this recurrence-free survival and median time to recurrence were also significantly longer in atypical as compared to anaplastic meningiomas. Nevertheless, recurrence is not only a features of higher grade (II and III) meningiomas, because it occurs on benign (grade I) meningiomas, although less frequently. A study focusing on grade I tumours demonstrated that the chance of recurrence is higher in benign meningiomas which have small atypical areas within the neoplasm[27]. Overall the far most important prognostic factor regarding tumour recurrence is the histological grade. In WHO grade I tumours the chance of recurrence is 7-25%, in grade II 29-59%, whereas in grade III. 50-94%[2].

Immunohistochemical markers

In immunohistochemical studies the two most frequently examined proteins are Ki-67 and p53. The role in tumour recurrence has been extensively studied.

p53 is a transcription factor, with an important role in regulation of cell cycle, preservation of genomic integrity, induction of apoptosis and inhibition of angiogenesis[28]. p53 is activated by a wide range of cell damaging insults, such as oxidative stress, hypoglycaemia, hypoxia, DNA damage, oncogene expression, ribosomal dysfunction, telomere damage[29]. p53 one of

the most important tumour suppressor protein and more than 50% of tumours harbour p53 mutation[15,16]. Despite the large number of studies, the role of p53 in meningioma development and recurrence is not clear. Some authors describe significant correlation between p53 immunoreactivity and recurrence[30,31], whereas other studies could not confirm this[6].

Ki-67 protein is expressed in mitotic cells. In the routine pathological diagnostics the protein is detected by the Mib-1 antibody clone. Ki-67 is detectable in all phases of active cell cycle, however it is missing in G_0. Furthermore, it plays role in ribosomal-RNA synthesis[32]. The amount of the protein has close correlation with the proliferative activity of the cell; in the interphase it is localized in the nucleoli, whereas in the mitotic phase it is on the surface of chromosomes. Therefore, it is an excellent marker to detect the proliferative pool of a given cell population[33]. Numerous studies have demonstrated significant correlation between increased Ki-67 (Mib-1) labelling index and recurrence[31,34,35].

The Ki-67 labelling index is increasing with WHO grade in meningiomas. Interestingly, in recurring WHO grade I tumours a higher Ki-67 labelling index is present[31]. Also, there is significant correlation between extent of peritumoral oedema and expression of the marker[36].

The immunohistochemistry and other molecular studies rendered electron microscopic analysis less relevant and important in meningiomas; however, in rare and unusual cases it may be contributory to the diagnosis[37].

Molecular and genetic studies establish novel fields of research of meningioma pathogenesis. Immunohistochemistry is considered as a standard and well established tool to test and analyse novel proteins implicated in tumorigenesis. Therefore, it is still important research tool. The tissue microarray (TMA) technique enables cheap and rapid assessment of candidate proteins in large numbers of tumour samples[38]. Recent article raise the possibility that poly(ADP-ribose) polymerase-1 (PARP1), which is an enzyme involved DNA repair, may have prognostic implications in meningiomas[39].

VI. Neurosurgical

In meningiomas with clinical symptoms the surgical resection is the primary choice of treatment in the majority of the cases. The aim of the surgical procedure is the complete resection of tumour (if possible), in order to achieve best quality of life and reduce the risk of recurrence. The extent of resection is graded according to Simpson in a 5-tear scale[24]. There is close correlation between Simpson grade and risk of recurrence[3]. In higher Simpson grade (III-V) the disease free survival is shorter, quality of life is reduced with an increased chance of early recurrence of the tumour[5,22,39,40] (Table 2). Rarely, 'seeding metastasis' may occur along the surgical tract in deep seated meningiomas[41].

In cranial base meningiomas the surgical removal often bears higher risk of post-operative complications. In such situations stereotactic radiosurgery can be successful for tumor control. The main indications for both treatment methods (i.e. surgery and radiosurgery) are the radiological or neurological progression. However, in a great proportion of cranial base meningiomas – especially in the elderly – follow-up proves no progression - in this case in symptomless patients a neurosurgical procedure or radiosurgery is not evidently necessary. On the other hand, increasing tumor size can increase the risk at the repeat surgical removal or irradiation. Thus, one main challenge for clinicians is to determine factors that correlates with tumor progression in grade I meningiomas. For this reason, some studies have been already made. One of them is the investigation of the ornithine decarboxylase (ODC) activity and mRNA expression in meningiomas[42]. This report describes a significant correlation between ODC mRNA level in meningiomas with later recurrence and meningiomas without recurrence (despite the same Ki-67 proliferative index in both populations). These findings suggests a role of ODC gene expression in meningiomas recurrence.

Conclusion

Although meningiomas are frequent tumours, the mechanism underlying pathogenesis, recurrence and progression is still poorly understood. With the recent advances in diagnostics, treatments and research methods, there is a good hope for reduced recurrence and more efficient treatment of it. This requires a multidisciplinary approach and will have major impact on more effective, personalised therapies and overall better clinical outcome for meningioma patients.

Acknowledgements

Financial support has been received from the National Brain Research Program, Hungary (KTIA 13 NAP-A-II/7 and KTIA 13 NAP-A-V/3) and AGR_PIAC_13-12013-0008.

Conflict of interest statement

Authors state no conflict of interest.

References

1. Uduma U.F., Emejulu J.C. Intracranial meningiomas in the present era of modern neuroimaging: diagnostic and management options, with radiological illustrations. Orient J. Med., 2013, 25, 67-74

2. Perry A., Louis D.N., Scheithauer B.W., Budka H., von Deimling A.: Meningiomas. In: Louis DN, Ohgaki H., Wiestler O.D., cavenee W.K. (Eds.). WHO classification of tumours of the central nervous system. pp. 164-172. IARC. Lyon. 2007.

3. Ildan F., Erman T., Göçer A.I., Tuna M., Bağdatoğlu H., Çetinalp E., et al. Predicting the probability of meningioma recurrence in the preoperative and early postoperative period: a multivariate analysis in the midterm follow-up. Skull Base, 2007, 17, 157-171

4. Adegbite A.B., Khan M.I., Paine K.W., Tan L.K. The recurrence of intracranial meningiomas after surgical treatment. J Neurosurg., 1983, 58, 51-56

5. Mahmood A., Qureshi N.H., Malik G.M. Intracranial meningiomas: analysis of recurrence after surgical treatment. Acta Neurochir (Wien), 1994, 126, 53-58

6. Trott G., Pereira-Lima J.F.S., Leães C.G.S., Ferreira N.P., Barbosa-Coutinho L.M., Oliveira M.C. Abundant immunohistochemical expression of dopamine D2 receptor and p53 protein in meningiomas: follow-up, relation to gender, age, tumor grade, and recurrence. Brazilian J. Med. Biol. Res., 2015, 48, 415-419

7. Ron E., Modan B., Boice J.D., Alfandari E., Stovall M., Chetrit A., et al. Tumors of the brain and nervous system after radiotherapy in childhood. N. Engl. J. Med., 1988, 319, 1033-1039

8. Umansky F., Shoshan Y., Rosenthal G., Fraifeld S., Spektor S. Radiation-induced meningioma. Neurosurg. Focus, 2008, 24, e7

9. Phillips L.E., Koepsell T.D., van Belle G., Kukull W.A., Gehrels J-A., Longstreth W.T. History of head trauma and risk of intracranial meningioma: population-based case-control study. Neurology, 2002, 58, 1849-1852

10. Wiemels J., Wrensch M., Claus E.B. Epidemiology and etiology of meningioma. J Neurooncol., 2010, 99, 307-314

11. Lusis E.A., Scheithauer B.W., Yachnis A.T., Fischer B.R., Chicoine M.R., Paulus W., et al. Meningiomas in pregnancy: a clinicopathologic study of 17 cases. Neurosurgery, 2012, 71, 951-961

12. Custer B.S., Koepsell T.D., Mueller B.A. The association between breast carcinoma and meningioma in women. Cancer, 2002, 94, 1626-1635

13. Qi Z-Y., Shao C., Huang Y-L., Hui G-Z., Zhou Y-X., Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. PLoS One, 2013, 8, 0083261

14. Hu J., Little J., Xu T., Zhao X., Guo L., Jia X., et al. Risk factors for meningioma in adults: a case-control study in northeast China. Int. J. Cancer, 1999, 83, 299-304

15. Galeone C., Malerba S., Rota M., Bagnardi V., Negri E., Scotti L., et al. A meta-analysis of alcohol consumption and the risk of brain tumours. Ann. Oncol., 2013, 24, 514-523

16. The INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int. J. Epidemiol., 2010, 39, 675-694

17. Murnyák B., Szepesi R., Hortobágyi T. [Molecular genetics of familial tumour syndromes of the central nervous system]. Orv. Hetil., 2015, 156, 171-177

18. Murnyák B., Csonka T., Hortobágyi T. Molecular Pathology of Meningiomas. Ideggyogy. Sz., 2015,68, 292-300

19. Murnyák B., Bognár L., Klekner Á., Hortobágyi T. Epigenetics of Meningiomas. Biomed. Res. Int., 2015, 2015, 532451

20. McCarthy B.J., Davis F.G., Freels S., Surawicz T.S., Damek D.M., Grutsch J., et al. Factors associated with survival in patients with meningioma. J. Neurosurg., 1998, 88, 831-839

21. Böker D.K., Meurer H., Gullotta F. Recurring intracranial meningiomas. Evaluation of some factors predisposing for tumor recurrence. J. Neurosurg. Sci., 1985, 29, 11-17

22. Nakasu S., Nakasu Y., Nakajima M., Matsuda M., Handa J. Preoperative identification of meningiomas that are highly likely to recur. J. Neurosurg., 1999, 90, 455-462

23. Maillo A., Orfao A., Espinosa A.B., Sayagués J.M., Merino M., Sousa P., et al. Early recurrences in histologically benign/grade I meningiomas are associated with large tumors and coexistence of monosomy 14 and del(1p36) in the ancestral tumor cell clone. Neuro. Oncol., 2007, 9, 438-446

24. Mantle R.E., Lach B., Delgado M.R., Baeesa S., Bélanger G. Predicting the probability of meningioma recurrence based on the quantity of peritumoral brain edema on computerized tomography scanning. J. Neurosurg., 1999, 91, 375-383

25. Bitzer M., Wöckel L., Morgalla M., Keller C., Friese S., Heiss E., et al. Peritumoural brain oedema in intracranial meningiomas: influence of tumour size, location and histology. Acta Neurochir. (Wien), 1997, 139, 1136-1142

26. Palma L., Celli P., Franco C., Cervoni L., Cantore G. Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. J. Neurosurg., 1997, 86, 793-800

27. Marciscano A.E., Stemmer-Rachamimov A.O., Niemierko A., Larvie M., Curry W.T., Barker F.G., et al. Benign meningiomas (WHO Grade I) with atypical histological features: correlation of histopathological features with clinical outcomes. J. Neurosurg., 2016, 124, 106-114

28. Koshland D.E. Molecule of the year. Science, 1993, 262, 1953.

29. Bieging K.T., Attardi L.D. Deconstructing p53 transcriptional networks in tumor suppression. Trends Cell Biol., 2012, 22, 97-106

30. Cho H., Ha S.Y., Park S.H., Park K., Chae Y.S. Role of p53 gene mutation in tumor

aggressiveness of intracranial meningiomas. J. Korean Med. Sci., 1999, 14, 199-205

31. Ozen O., Demirhan B., Altinörs N. Correlation between histological grade and MIB-1 and p53 immunoreactivity in meningiomas. Clin. Neuropathol., 2005, 24, 219-224

32. Bullwinkel J., Baron-Lühr B., Lüdemann A., Wohlenberg C., Gerdes J., Scholzen T.. Ki-67 protein is associated with ribosomal RNA transcription in quiescent and proliferating cells. J. Cell Physiol., 2006, 206, 624-635

33. Scholzen T., Gerdes J. The Ki-67 protein: from the known and the unknown. J. Cell Physiol., 2000, 182, 311-322

34. Terzi A., Saglam E.A., Barak A., Soylemezoglu F. The significance of immunohistochemical expression of Ki-67, p53, p21, and p16 in meningiomas tissue arrays. Pathol. Res. Pract., 2008, 204, 305-314

35. Perry A., Stafford S.L., Scheithauer B.W., Suman V.J., Lohse C.M. The prognostic significance of MIB-1, p53, and DNA flow cytometry in completely resected primary meningiomas. Cancer, 1998, 82, 2262-2269

36. Ide M., Jimbo M., Yamamoto M., Umebara Y., Hagiwara S., Kubo O. MIB-1 staining index and peritumoral brain edema of meningiomas. Cancer, 1996, 78, 133-143

37. Bodi I., Hortobágyi T., Buk S. A 72-year-old woman with right frontal extra-axial mass. Brain Pathol., 2008, 18, 279-282

38. Jawhar N.M.T. Tissue Microarray: A rapidly evolving diagnostic and research tool. Ann. Saudi Med., 2009, 29, 123-127

39. Csonka T., Murnyák B., Szepesi R., Kurucz A., Klekner Á., Hortobágyi T. Poly(ADP-ribose) polymerase-1 (PARP1) and p53 labelling index correlates with tumour grade in meningiomas. Folia Neuropathol., 2014, 52, 111-120

40. http://radiopaedia.org/articles/simpson-grade

41. Mahore A., Chagla A., Goel A. Seeding metastases of a benign intraventricular meningioma along the surgical track. J. Clin. Neurosci., 2010, 17, 253-255

42. Klekner A., Röhn ., Schillinger G., Schröder R., Klug N., Ernestus R.I. ODC mRNA as a prognostic factor for recurrence in meningiomas. J. Neuro-oncol., 2001, 53, 67-75

Legends

Figure 1. Possible factors in meningioma recurrence

Table 1. WHO classification of meningiomas (Modified from Perry *et al.*[2])

Table 2. Simpson grading system for removal of meningiomas (Modified from *www.radiopaedia.org*[40])

Figure 1

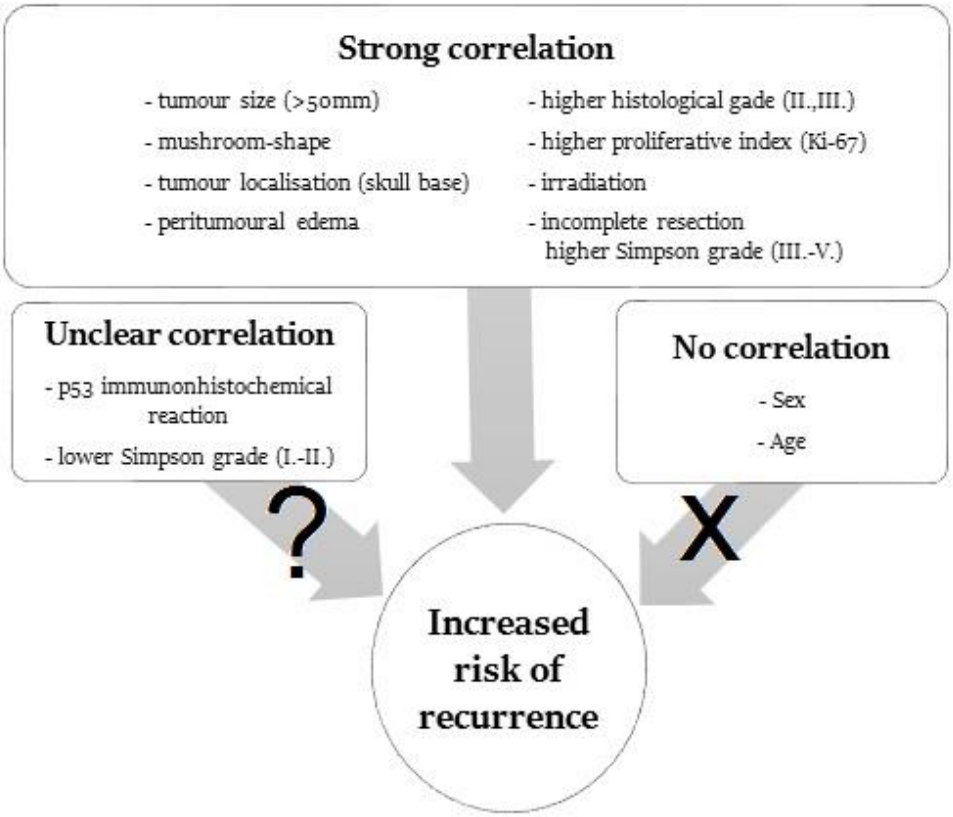
Strong correlation
- tumour size (>50mm)
- mushroom-shape
- tumour localisation (skull base)
- peritumoural edema
- higher histological gade (II.,III.)
- higher proliferative index (Ki-67)
- irradiation
- incomplete resection higher Simpson grade (III.-V.)
Unclear correlation
- p53 immunonhistochemical reaction
- lower Simpson grade (I.-II.)
No correlation
- Sex
- Age
?
X
Increased risk of recurrence

Table 1

WHO grade I.-	*meningothelial*	*fibroblastic*	*transitional*	*psammomatous*	*angiomatous*
	microcystic	*secretory*	*lymphoplasmacyte-rich*	*metaplastic*	*clear cell (spinal)*
WHO grade II.	*chordoid*	*clear cell (intracranial)*	*atypical*		
WHO grade III.	*papillary*	*rhabdoid*	*anaplastic*		

Table 2

	EXTENT OF MACROSCOPIC RESECTION	REMOVAL OF DURAL TAIL	RISK OF RECURRENCE (10 YEAR INTERVAL)
GRADE I	*Macroscopically complete* (tumour, involved bones and venous sinuses)	*Macroscopically complete*	*9%*
GRADE II	*Macroscopically complete* (tumour)	*Coagulation*	*19%*
GRADE III	*Macroscopically complete* (tumour)	*No resection*	*29%*
GRADE IV	*Partial removal*	*No resection*	*44%*
GRADE V	*Simple decompression with or without biopsy*	*No resection*	*100%*

LICENSE TO PUBLISH

Please read the terms of this agreement, print, sign, scan and send via Editorial Manager.

Open Medicine ("Journal")

De Gruyter Open Ltd. ("Journal Owner", also referred to as "You" in the Creative Commons license mentioned in section 1 below)

Article entitled ("Work" or "article"): MENINGIOMA RECURRENCE

Author/s: (also referred to as "Licensor/s") TIBOR HORTOBÁGYI, JÁNOS BENCZE, GRETA VARKOLY, MAHAN C KOUHSARI, ÁLMOS KLEKNER

Corresponding author: (if more than one author) TIBOR HORTOBÁGYI

1. License

The non-commercial use of the article will be governed by the Creative Commons Attribution-NonCommercial-NoDerivs license as currently displayed on http://creativecommons.org/licenses/by-nc-nd/3.0/., except that sections 2 through 8 below will apply in this respect and prevail over all conflicting provisions of such license model. Without prejudice to the foregoing, the author hereby grants the Journal Owner the exclusive license for commercial use of the article (for U.S. government employees: to the extent transferable) according to section 2 below, and sections 4 through 9 below, throughout the world, in any form, in any language, for the full term of copyright, effective upon acceptance for publication.

2. Author's Warranties

The author warrants that the article is original, written by stated author/s, is currently not under consideration, has not been published before, contains no unlawful statements, does not infringe the rights of others, is subject to copyright that is vested exclusively in the author and free of any third party rights, and that any necessary written permissions to quote from other sources have been obtained by the author/s.

3. User Rights

Under the Creative Commons Attribution-NonCommercial-NoDerivs license, the author(s) and users are free to share (copy, distribute and transmit the contribution) under the following conditions: 1. they must attribute the contribution in the manner specified by the author or licensor, 2. they may not use this contribution for commercial purposes, 3. they may not alter, transform, or build upon this work.

4. Rights of Authors

Authors retain the following rights:

- copyright, and other proprietary rights relating to the article, such as patent rights,
- the right to use the substance of the article in future own works, including lectures and books,
- the right to reproduce the article for own purposes, provided the copies are not offered for sale,
- the right to self-archive the article.

5. Co-Authorship

If the article was prepared jointly with other authors, the signatory of this form warrants that he/she has been authorized by all co-authors to sign this agreement on their behalf, and agrees to inform his/her co-authors of the terms of this agreement.

6. Termination

This agreement can be terminated by the author or the Journal Owner upon two months' notice where the other party has materially breached this agreement and failed to remedy such breach within a month of being given the terminating party's notice requesting such breach to be remedied. No breach or violation of this agreement will cause this agreement or any license granted in it to terminate automatically or affect the definition of Journal Owner. After the lapse of forty (40) years of the date of this agreement, this agreement can be terminated without cause by the author or the Journal Owner upon two years' notice. The author and the Journal Owner may agree to terminate this agreement at any time. This agreement or any license granted in it cannot be terminated otherwise than in accordance with this section 6.

7. Royalties

This agreement entitles the author to no royalties or other fees. To such extent as legally permissible, the author waives his or her right to collect royalties relative to the article in respect of any use of the article by the Journal Owner or its sublicensee.

8. Miscellaneous

The Journal Owner will publish the article (or have it published) in the Journal, if the article's editorial process is successfully completed and the Journal Owner or its sublicensee has become obligated to have the article published. Where such obligation depends on the payment of a fee, it shall not be deemed to exist until such time as that fee is paid. The Journal Owner may conform the article to a style of punctuation, spelling, capitalization and usage that it deems appropriate. The author acknowledges that the article may be published so that it will be publicly accessible and such access will be free of charge for the readers. The Journal Owner will be allowed to sublicense the rights that are licensed to it under this agreement. This agreement will be governed by the laws of England and Wales.

9. Scope of the Commercial License

The exclusive right and license granted under this agreement to the Journal Owner for commercial use is as follows:

- to prepare, reproduce, manufacture, publish, distribute, exhibit, advertise, promote, license and sub-license printed and electronic copies of the article, through the Internet and other means of data transmission now known or later to be developed; the foregoing will include abstracts, bibliographic information, illustrations, pictures, indexes and subject headings and other proprietary materials contained in the article,
- to exercise, license, and sub-license others to exercise subsidiary and other rights in the article, including the right to photocopy, scan or reproduce copies thereof, to reproduce excerpts from the article in other works, and to reproduce copies of the article as part of compilations with other works, including collections of materials made for use in classes for instructional purposes, customized works, electronic databases, document delivery, and other information services, and publish, distribute, exhibit and license the same.

Where this agreement refers to a license granted to Journal Owner in this agreement as exclusive, the author commits not only to refrain from granting such license to a third party but also to refrain from exercising the right that is the subject of such license otherwise than by performing this agreement.
The Journal Owner will be entitled to enforce in respect of third parties, to such extent as permitted by law, the rights licensed to it under this agreement.
If the article was written in the course of employment by the US or UK Government, and/or arises from NIH funding, please consult the Journal Owner for further instructions.

Author's Signature: .....

Name printed: TIBOR HORTOBÁGYI

Date: 12/APRIL/2016

DE GRUYTER
OPEN