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Recurrence-associated chromosomal anomalies in meningiomas: Single-institution study and a systematic review with meta-analysis

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ABSTRACT

Complete removal of a meningioma (MG) does not guarantee relapse-free survival. Alterations on several chromosomes responsible for MG recurrence were suggested, although their role was not validated by a systematic review. Following the analysis of own 161 cases, all previously published data has been collected for evidence synthesis. Based on own series, WHO grade >I (odds ratio (OR) = 92.0; 95%CI: 19.1–443.5) and a combination of loss of heterozygosity (LOH) on 1p and 14q (OR = 10.2; 95%CI: 19–55.7) were the independent recurrence-specific prognosticators. The deleterious role of LOH on 1p/14q was demonstrated in a subset of parasagittal and falcine MGs. A total of 742 cases and 10 studies were pooled for the Individual Patient Data and Aggregate Data models of meta-analysis, respectively. The prognostic role of WHO classification (OR = 90.4) and anomaly of chromosome 14 (OR = 3.5) was confirmed. LOH on 14 showed lesser impact on recurrence than suggested by the WHO grading (area under the curve 0.65 for LOH vs. 0.74 for WHO). Fixed effect model of meta-analysis provided high summarized OR values for 1p (OR = 5.4; 95%CI: 3.6–8.1) and 14q (OR = 7.6; 95%CI: 4.3–13.6), and low for chromosome 22 (OR = 1.6; 95%CI: 1.1–2.4). Final appraisal of recurrence-associated chromosomal alterations indicated that arms 1p and 14q deserve attention while predicting MG recurrence.

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1. Introduction

Meningiomas (MGs) are the most frequent intracranial tumour, accounting for up to 30% of the neoplasms in that location. Although most of them are slow-growing, solitary and benign tumours, their aggressive biological behaviour has been reported [1–3]. These tumours are regarded by experienced surgeons as easy to manage, however their complete removal is occasionally precluded due to the vicinity of vital structures. Even after total resection, about 3–10% of MGs relapse [4] and a less favourable prognosis is attributed to younger age, malignant histology and unnoticed brain invasion [1,5–8]. The World Health Organization (WHO) classification has facilitated estimating the prognosis [2,3,5,6,9]. In addition to the WHO classification, histopathological findings such as Ki-67/MIB-1 labelling index and proliferating cell nuclear antigen can independently predict the behaviour of a MG [3,10].

The molecular basis of MG's malignant behaviour has been recently scrutinized. A broad array of genetic alterations has been suggested, including complete or partial chromosome loss or gain, gene mutation and methylation [1–4,6,7,10–19]. Concerning the karyotype level, allelic loss of heterozygosity (LOH) on chromosomes 1, 6, 10, 14, and 22 has been postulated to increase the risk of malignant behaviour of sporadic MGs [2,4,11–13,15,18,20,21]. Beyond the deleterious role of a single anomaly, various configurations of LOH on several chromosomes were attributed to more aggressive phenotype of MG [4,12]. Most studies associated molecular aberrations with tumorigenesis, increased replication rate, histological progression or a higher WHO grade, occasionally focused on tumour recurrence [4,11,16]. According to Lee, who collected the largest cohort, the arm losses of 6q and 14q were the most reliable indicators of the MG relapse [4]. The previously published case series rarely exceeded 100 specimens, the investigators evaluated non-replicated chromosomal alterations and/or utilized completely different clinical endpoints. As of yet, genetic exams in MGs have not been applied in routine clinical practice. Moreover, dispersed molecular findings were never summarized in a systematic review. For these reasons, the molecular biology of MGs seems unjustly underappreciated while the development of a recurrence-specific genomic landscape seems feasible [16].

The aim of our study was to gather all the previous reports of MG-specific chromosomal alterations in order to extract reliable prognostic molecular biomarkers.

2. Material and methods

2.1. Study design

This study evaluated the impact of chromosomal alterations in sporadic MGs on recurrence. Following the identification of chromosomal arm losses in the entire own series of MGs, the individual features of tumour recurrence pooled including all accessible data from the existing literature and using PRISMA methodology. (For details – see 'Systematic Review methodology' in the electronic supplementary materials.)

2.2. Own series

The diagnosis of sporadic non NF1/NF2-related intracranial MG was based on the contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI) of the head, followed by histopathological examination. Following the approval of the local Bioethics Committee a total of 136 MGs of various intracranial locations were collected prospectively since 2002. All consenting patients were managed operatively at two neurosurgery departments (institution name deleted for peer-review purposes), gross total resection was intended in all of them. Basic demographics included patient age, sex and MG location. The Simpson grading for the extent of the tumour removal was utilized, though sparsely reported. The resection rate was not analyzed because it did not adhere to the RANO criteria for volumetric tumour remnant assessment [22]. The majority of patients were followed-up (121 of 136; 89.0%), however the follow-up time was not standardized. As the time to remote postoperative brain imaging was not established in the protocol, both the follow-up and time to recurrence were not valid for the statistical analysis. All tumour specimens were classified as grade I, II or III according to the World Health Organization (WHO) criteria, relevant to the year of assessment [9,23]. (For details – see 'Loss of heterozygosity analysis' in the electronic supplementary materials.)

During the surgery for the MG recurrence, the tissues were biopsied only for pathology and the genetic evaluation was skipped. A subgroup of recurrent MGs of parasagittal and falcine locations was selected throughout the entire group to demonstrate the recurrence-associated chromosomal anomalies, such as the 1p/14q alteration.

2.3. Systematic review and meta-analysis

For details – see 'Systematic Review methodology' in the electronic supplementary materials.

3. Results

3.1. Own series

Our study group consisted of 161 patients, (104 females, 64.6% and 57 males, 35.4%) diagnosed with MG. Their mean age was 56.1 (SD $\pm$ 14.5; min–max 22–92). The study group consisted of a total of 161 patients harbouring meningiomas. 104 of our patients were female (64.6%), and 57 were male (35.4%). 138 of the resected tumours were WHO grade 1 (85.7%), 22 were grade 2 (13.7%) and only one was grade 3 (0.6%). Of the entire cohort, a total of 35 meningiomas (21.7%) recurred during follow-up. (As noted in Methods, the follow-up time was not measured nor standardized.) As suspected, tumour recurrence strongly depended on the WHO grade ($p < 0.01$), specifically; 10.1% grade I (14 of 138), 90.9% grade II (20 of 22) and 100% (1 of 1) of grade III tumours relapsed. Among the determined set of loci, the recurrence rate was significantly greater when chromosome arms 1p (cytoband 1p33-32.3;), 14q (14q32.33) or 22q (22q11.23) were affected. On the contrary, LOH on chromosome arms 9p

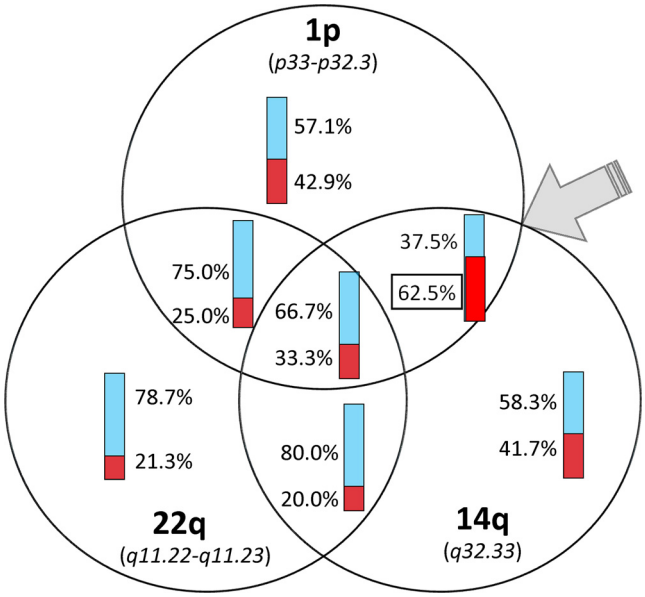

Fig. 1 – Venn diagram demonstrating the coexistence of chromosomal alterations. The influence on tumour recurrence was demonstrated on the colour bars – red and blue reflect the fraction of recurrent and non-recurrent meningiomas, respectively (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.).

and 18p determined WHO grade II/III. Interestingly, aberration in two loci (1p33-32.3 and 22q 22q11.23) was the prognostic factor of either tumour recurrence or a higher WHO grade.

Mutual relationships between the significant aberrations of particular chromosomes were verified. More than one LOH was encountered in 73.8% (93 of 126) of patients without and 91.4% (32 of 35) of those with MG recurrence ($p = 0.53$). On the other hand, patients with subsequent MG surgery had a significantly greater total number of LOHs (3.9; SD ± 2.9) than patients without recurrence (2.7; SD ± 2.8) ($p = 0.02$). Considering particular chromosome arms, mutual alterations of 1p and 14q posed a greater risk of relapse (62.5%) compared to the others (37.5%) ($p < 0.01$). Although frequently occurring in MGs, the LOH on 22q or its combination with 1p or 14q were not correlated with future tumour recurrence in our series (Fig. 1).

Since the coexistence of loss on 1p and 14q was a relapse-specific chromosomal anomaly, these cases needed elaboration. Out of all 8 patients exhibiting LOHs on 1p/14q, 3 had MG located in the falcine/parasagittal region. We went forward and re-evaluated all relapsed tumours of the above location (parasagittal/falcine); 3 patients with LOH on 1p/14q exhibited distinct features from the rest of the cases. Thereby, new MGs were encountered distally from their original location as well as demonstrated local malignancy or an atypical spread along the superior sagittal sinus.

All significant variables of single univariate comparisons were subjected to stepwise logistic regression. Out of the multitude of analyzed factors, only 1p/14q LOH status ($p < 0.01$; OR = 10.2, 95%CI: 1.9–55.7) and WHO grade II/III ($p < 0.01$; OR = 92.0, 95%CI: 19.1–443.5) were statistically significant and were independent prognostic factors of the tumour recurrence. Subsequent analysis aimed to estimate the principal component of multivariate model, therefore the ROC curves between these two factors were compared. AUC of 1p/14q and that of the WHO grade was 0.56 (95%CI: 0.48–0.64) and 0.79 (95%CI: 0.72–0.85) respectively. The insignificant difference between the two AUCs (Z-score = 3.3, $p = 0.23$) confirmed the similar role of either factor in the prediction of tumour recurrence (Fig. 3).

3.2. *Systematic review and meta-analysis*

The initial search yielded 423 records, of which 144 were valid for eligibility evaluation (Table 1).

Cases/reports were excluded due to either reporting recurrences only or not mentioning them at all, reporting generalized data only or insufficient data about genetics. Merely 6 full texts (particularly those published before 2000) were not available. 10 studies reported the percentages only and built the aggregate data model. Whereas 21 studies (including our large series of MGs) provided original subjects for the Individual Patient Data (IPD) meta-analysis of. 742 individuals. The interesting features of the pooled cohort were: slight female predominance and prevalent age between the 5th and 7th decade of life. All features of the cohort were consistent with the population data [24]. MGs most frequently occupied the convexity, skull base or falcine/parasagittal region. The detailed characteristic of the cohort is presented in Table 2.

The total recurrence rate for the entire cohort amounted to 21.4% (159 of 742). The range between authors (among case series $n \geq 25$) in terms of reported recurrences was 4.7–46.8% (SD ± 12.8%). Patient age ($p = 0.31$), location of MG ($p = 0.06$) and its complete removal (Simpson grades 1 vs. 2/3) did not influence future recurrence. Interestingly, male sex was more prone to experience tumour recurrence (25.6% for males; 15.0% for females; $p < 0.01$). As expected, the WHO grade MG, was positively correlated with the recurrence rate. That denoted 11.2% (51 of 454), 41.2% (56 of 136), and 58.8% (30 of 51) for WHO 1–3 grades respectively (Fig. 4).

On the subchromosomal level, the previously published reports occasionally replicated the previously established disease-specific bands, including 1p36, 9p, 9p21.3, 10q, 14q, 14q32.33, 22q. Therefore, we created the derivative variables clustering any alteration in a given chromosome arm and added new variables to the analysis. In univariate statistics, LOH on 13 different loci correlated with the recurrence status, of which 3 (4p, 14q11.2 and combined 1p/14q) were different than those referring to the WHO grading. (Table 2 – electronic supplementary materials.)

All variables significant in the above univariate analyses were included in the stepwise logistic regression that aimed to identify independent recurrence-associated factors. Thereby, parallel to the WHO grades II/III ($p < 0.01$, OR 90.38; 95%CI: 18.68–437.27), any alteration within chromosome 14 ($p = 0.04$, OR 3.52; 95%CI: 1.02–12.13) increased the risk of MG relapse. 89.68% of cases were correctly classified to the regression model. The comparison of ROC curves between the WHO grading and any LOH on chromosome 14 indicated WHO grade II or III as a prominent prognostic factor of tumour recurrence (AUC of WHO = 0.74, 95%CI: 0.69–0.78; AUC of LOH on 14 = 0.65, 95%CI: 0.59–0.70; Z-score = 1.9 and $p = 0.06$ for comparison

Patient	Type of meningioma	LOH on 1	9	10	14	18	22	Combined LOH on 1p/14q	Number of relapses
✓ 1	Meningothelial	X			X			X	2
2	Mixtum	X	X				X		4
3	Mixtum						X		1
4	Mixtum	X			X		X	X	2
5	Mixtum	X					X		2
✓ 6	Mixtum	X		X	X		X	X	4
7	Meningothelial					X	X		1
8	Fibroblasticum						X		1
9	Mixtum					X			2

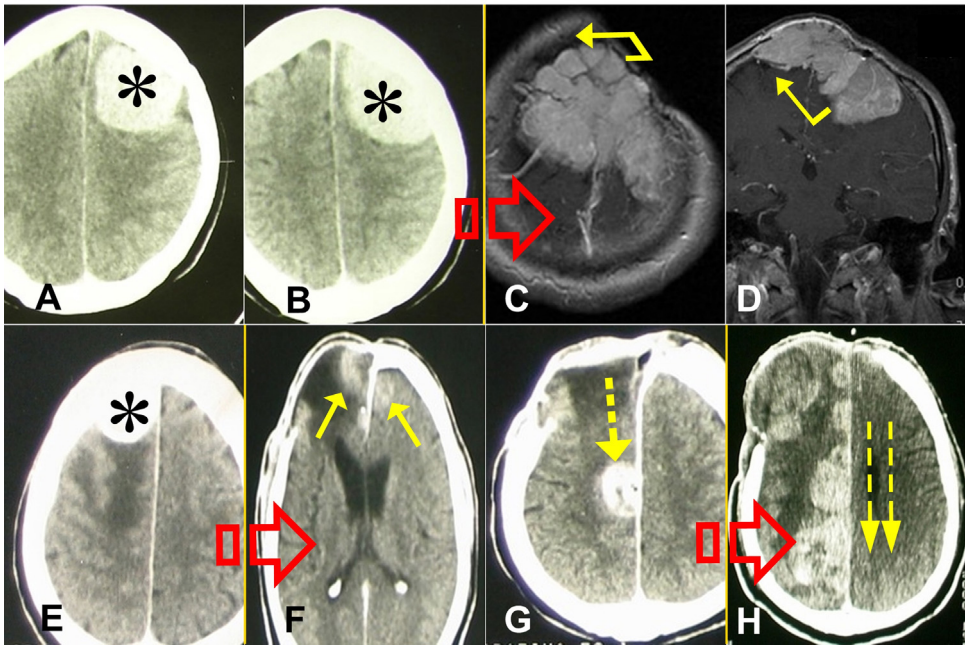

Fig. 2 – Parasagittal/falcine meningiomas. The aggressive behaviour of benign meningiomas (MGs) attributed to concurrent anomalies on 1p and 14q. Chromosomal alterations were shown in the table, particularly the combined LOH on 1p/14q. Tumour progression was demonstrated in patients number 1 (A–D) and 6 (E–H). The red arrow denotes head scans after the MG recurrence. The primary tumour location was marked with an asterisk (*) on axial planes of preoperative computer tomography. Patient 1: C, D – axial and coronal planes, respectively, of 8-year postoperative magnetic resonance imaging presenting recurrent MG crossing the midline, arachnoid matter and bony margins (yellow arrows). Patient 6: F, G – 1-year follow-up scans revealed recurrent MG on both sides of superior sagittal sinus (solid line yellow arrow) and in distant falcine location (dashed line yellow arrow). H – extremely aggressive character behaviour of the recurred MG (still WHO grade I) presented in <2 years from the primary diagnosis. The seemingly complete tumour removal did not prevent regrowth distant from the original location. This pattern of progression seems unusual for benign MGs; the metastasis along the falx and/or superior sagittal sinus was strongly suspected (either venous or cerebrospinal fluid routes are probable). *Abbreviation*: LOH – loss of heterozygosity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

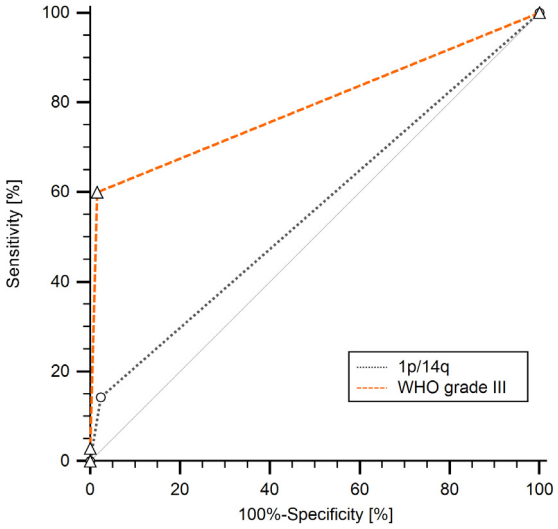

Fig. 3 – Receiver operating characteristic (ROC) curves of WHO grading and concurrent LOHs on chromosome arms 1p and 14q. Area under ROC curve of WHO grading was greater than those of double LOH status, though the difference between the areas was not statistically significant. *Abbreviations*: WHO – World Health Organization, LOH – loss of heterozygosity.

between the AUCs) (Fig. 5). The WHO grading had higher prediction value for the tumour recurrence (sensitivity of 62.77 (95%CI: 54.1–70.9) and specificity of 79.96 (95%CI: 76.2–83.4)) than LOH on 14 status (sensitivity of 50.00 (95%CI: 26.0–74.0) and specificity of 72.84 (95%CI: 61.8–82.1)). Particularly, 65.8% (25 of 38) of tumours presenting with both WHO grades II/III and any LOH on 14 recurred, compared to only 8.9% (20 of 224) of without these features.

According the results of the IPD meta-analysis, the WHO tumour grading should be considered together with alterations within chromosome 14 while predicting the MG recurrence. To note, all relapse-specific genetic aberrations valid in univariate comparisons (LOH on 4p, 14q11.2 and combined 1p/14q) were excluded from the stepwise regression model and remained invalid.

Out of all studies included in the quantitative synthesis, 10 of them were suitable for the Aggregated Data model of meta-analysis. Total ORs (fixed effects model) were calculated for above loci. The highest OR was obtained for LOH on arm 14q and therefore it is the most prominent recurrence-related abnormality (OR = 7.59; 95%CI: 4.25–13.58). The confidence interval for LOH on 1p was narrow (OR = 5.59; 95%CI: 3.59–8.05) which reflected OR estimation of higher accuracy than for 14q anomaly. On the other hand, greater heterogeneity was observed among studies investigating LOH on 1p (Cochrane-Q = 11.65, $p = 0.02$) than 14q (Cochrane-Q = 5.15, $p = 0.08$).

4. Discussion

Molecular biology has become as a powerful tool that has contributed to diagnosing tumours, the understanding the tumorigenesis and created a promising target for future therapies. Despite its potential, the application of genetics in MGs has neither been widely accepted nor incorporated into the clinical practice [3,16]. An unexpected and rapid recurrence of a locally aggressive tumour may occur even after the complete removal of a benign MG (Fig. 2 Fig. 2). High WHO grades are an undisputed yet imprecise prognostic factor in MG recurrence [5,8]. Parallel to the WHO classification, surgical completeness, and high KI-67 index determine progression-free survival [8,10]. However, due to some yet unexplored factors the regrowth remains unpredictable in a small subset of MGs [11,21]. Precise determination of tumour behaviour would streamline the patient-tailored therapy by allowing early screening for surgery vs. expectant management as well as to modify the extent of resection. A specific genotype of recurring MGs has been sought for years. Steudel et al. [18] correlated cytogenetic changes with clinical findings and proved the deleterious role of chromosome 22 anomaly on MG recurrence. Other papers confirmed the role of instability within this chromosome, though did not replicate its impact on relapse occurrence or progression-free survival [11,13,14,20]. Mutation or loss of gene *NF2* located on 22q is responsible for tumorigenesis, as found in up to one half of MGs [6,17,21]. Ketter et al. examined almost 200 patients for cytogenetic aberrations on chromosome 22 and 1 using Giemsa banding and demonstrated the need for recurrence-associated cytogenetic classification of MGs [13]. Patients with monosomy or any loss of the short arm of one chromosome 1 had worse prognosis than others [13]. Authors created a regimen of patient surveillance following surgery based on both the WHO grade and structure of chromosomes 1 and 22 [13]. Studies of the deleterious role of chromosome 1 in predicting tumour behaviour revealed that deleted regions of arm 1p (1p34.2-ter) with multiple cancer-associated genes are frequently found in recurred MGs [21]. Three other studies also demonstrated strong influence of LOH on 1p on recurrence [2,8,12]. Loss on 14q (together with 6q) was more common in recurrent tumours [4]. Two independent studies [12,15] postulated coexisting anomalies of 1p and 14q to increase the probability of relapse. Pfisterer et al. performed multivariate analysis of clinical factors related with surgery, magnetic resonance spectroscopy, histopathology and three chromosomal aberrations [15]. Aggressive phenotype of sporadic MG was involved with abnormalities within 1p and 14q. Hamilton proved that 1p/14q co-deletion is strongly associated with tumour recurrence, specifically relapse OR of 52.5 and 15.7 for LOH on 1p36 and 14q11.2 respectively [12]. The analysis of our series definitely supports the findings of the above two authors. Identical chromosome arms, namely 1p and 14q were identified in either uni- or multivariate analysis to increase the incidence of relapse. The combination of LOH on 1p and 14q was an independent prognostic factor, parallel to WHO grade II or III. As several loci were evaluated in own series, we verified the role of total number of genetic abnormalities in a single patient. Higher number of aberrations correlated with higher recurrence rate. This result is clearly supported by literature [4], but remains invalid when analyzed together with the WHO grading and combined LOH on 1p/14q. Another key finding of our series is that the relapse-related regions were different from the alterations specific for higher WHO grade. Domingues et al. isolated only the

Table 1 – The prevalence of the loss of heterozygosity (LOH) in selected loci.

	Locus of LOH	Recurrent	Non-recurrent	*P* value	WHO I	WHO II / III	*P* value
		% of column			% of column		
	XXX karyotype	0	100	*.52*	3.6	0	*.78*
1	1p*	42.9	26.2	*.09*	28.3	39.1	*.42*
	1p36.23	20.0	13.5	*.49*	13.0	26.1	*.19*
	1p36.13	25.7	15.9	*.27*	17.4	21.7	*.83*
	1p36.12	11.8	10.3	*.94*	10.2	13.0	*.97*
	1p33	8.6	7.9	*.82*	7.3	13.0	*.60*
	1p33-32.3	**34.3** (12 of 35 recurred)	12.7 (16 of 126 non-recurred)	***<.01***	14.5	**34.8**	***.04***
	1p32.3	28.6	15.9	*.14*	17.4	26.1	*.48*
	1p.21.1	2.9	7.1	*.59*	7.3	0	*.39*
9	9p*	8.6	2.4	*.23*	1.5	**17.4**	***<.01***
	9p22.1 (d9s319)	2.9	2.4	*.65*	0	**8.7**	***<.01***
	9p21.3	2.9	0	*.49*	0	4.4	*.30*
10	10p12.1	0	1.6	*.91*	1.5	0	*.66*
	10q*	8.6	9.5	*.87*	9.4	8.7	*.78*
	10q24.2	5.7	2.4	*.65*	2.9	3.6	*.78*
	10q26.12	2.9	5.6	*.83*	5.1	4.4	*.71*
	10q26.13	5.7	2.4	*.65*	2.9	4.4	*.78*
14	14q*	**28.6** (10 of 35 recurred)	11.1 (14 of 126 non-recurred)	***.02***	13.0	26.1	*.19*
	14q32.33 (d14s1010)	17.1	7.1	*.14*	7.3	17.4	*.23*
18	18p11.31	20.0	7.9	*.08*	8.0	**26.1**	***.02***
20	20q13.2	17.1	19.8	*.91*	18.8	21.7	*.97*
22	22q*	**80.0** (22 of 35 recurred)	57.1 (72 of 126 non-recurred)	***.02***	60.1	73.9	*.30*
	22q11.23 (d22s449)	**40.0** (14 of 35 recurred)	19.1 (24 of 126 non-recurred)	***.02***	18.8	**52.2**	***<.01***
	22q11.22	2.9	2.4	*.65*	2.9	0	*.92*
	22q12.23-q12.1	11.4	3.2	*.12*	5.1	4.4	*.71*
	22q12.1 (d22s298)	0	2.4	*.83*	2.2	0	*.91*
	22q12.1-q12.2	40.0	34.1	*.66*	35.5	34.8	*.87*
	22q12.2 (merlin/*NF2*)	0	2.4	*.83*	2.2	0	*.91*

The percentages refer to columns of either recurrent, non-recurrent, WHO I or II/III subset. Significant comparisons are in bold. Orange colour denotes significant differences in LOH between the recurring and non-recurring meningiomas. Blue colour denotes that difference between WHO I and WHO II/III grades. *Abbreviations*: LOH – loss of heterozygosity, WHO – World Health Organization grading system, * – denotes any loss of heterozygosity encountered in the given chromosome arm.

alteration of chromosomes 7, 14, and 18 as of predictive value for poor outcome [11]. However, the authors emphasized that the above individual chromosomes lost their prognostic value once a complex karyotype (≥2 altered chromosomes) was included in the analysis. Our results do not share that opinion as a combination of alterations on 1p and 14q retained the genetic model of recurrence. Domingues noted that del(1p36) and monosomy 14 coexisted in several relapsing tumours in her series, which can explain these discrepancies [11].

Our prospective study has substantial drawbacks. Despite the scrupulous specimen collection for several years and 27 examined loci, our series was limited to only TWO neurosurgical centres, time-to-recurrence was not tracked, either CT or MRI was used and timing of imaging for recurrence was not established. Of concern, not every sample was informative for all examined loci, thus the results were obtained for valid data. Various loci were examined, pathologists utilized inconsistent 3rd or 4th editions of the WHO classification, and unselected

Location	Recurrence rate [%]	*any LOH on* 1	14
Parasagittal / falx	25.0↑	-	44.4
Lateral ventricle	0	50.0	-
Tentorium	6.7	52.4	46.2
Cranial base	**10.2**↓	**32.4**↓	**25.9**↓
Convexity	19.4↑	-	41.2

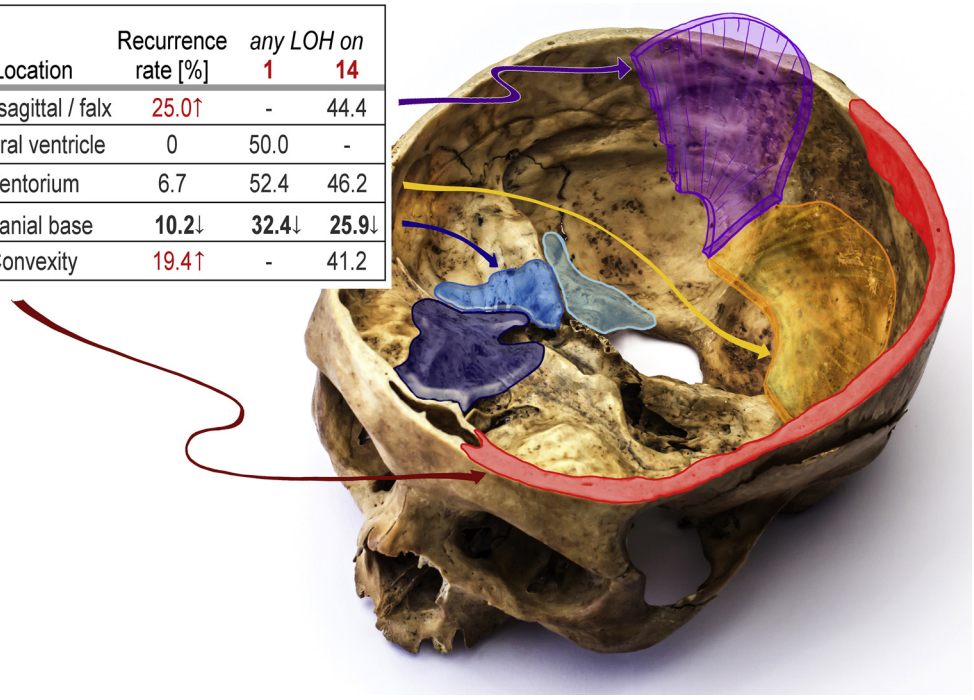

Fig. 4 – Recurrence rates and percentages of meaningful chromosomal alterations for specific tumour locations. Cranial base meningiomas recurred less frequently and had less abnormalities within chromosomes 1 and 14. *Abbreviations*: WHO – World Health Organization, LOH – loss of heterozygosity.

Table 2 – Patient characteristics – single cohort pooled for the individual patient data meta-analysis.

Feature	Mean (±SD; min–max)	Data completeness (%)	Comparison to population of meningiomas ($n \sim 17$k) [1]
Age [years]	55.3 (±14.6; 10–101)	68.9	57.4 (1–96) ($p < 0.01$)
	Fraction [% of complete observations]		
Sex		69.7	69.7% females ($p < 0.01$)
Females	59.2		
Males	40.8		
WHO		86.4	95.6% benign ($p < 0.01$)
1	70.8		
2	21.2		
3	8.0		
Location		46.9	NS
Convexity	47.4		
Skull base	28.2		
Parasagittal/falx	18.4		
Tentorium	4.3		
Ventricle	1.7		
GTR	78.3	22.4*	NS
Simpson grade (resection completeness)		3.8*	NS
1	35.7		
2	35.7		
3	28.6		

Abbreviations: SD – standard deviation, GTR – gross total resection, * – insufficient data completeness, NS – not stated, k – kilo (10^3).

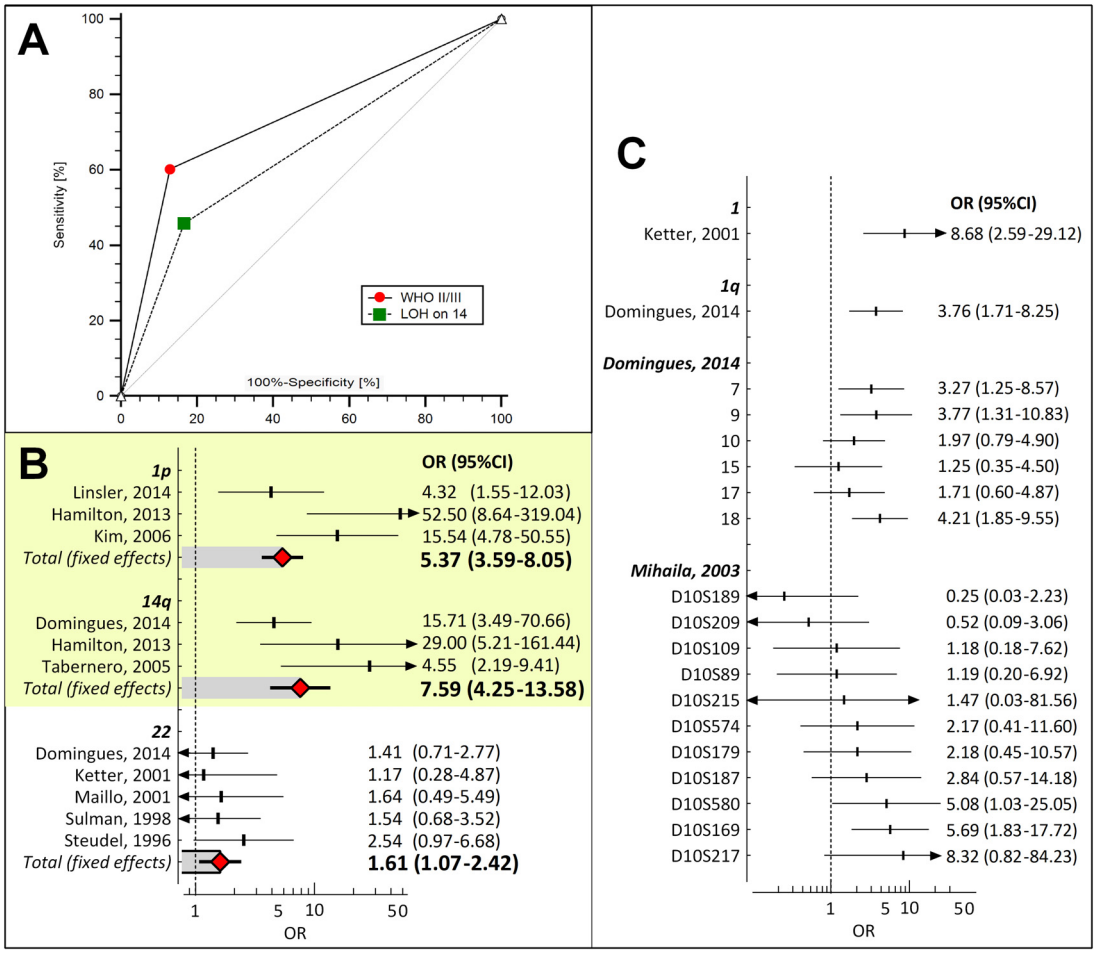

Fig. 5 – Receiver operating characteristic (ROC) curves of WHO grades II/III and LOH on chromosome arms 14. B–C. Forest plots of Aggregate Data model of meta-analysis of chromosomal aberrations. Relevant odds ratios (OR) were provided with their 95% confidence intervals (95%CI). B. Aggregate OR (fixed effects model) for loss of heterozygosity (LOH) on 1p, 14q and 22. Note that total OR for LOH on 14q represent the highest value.

locations entailed different resection rates. In LOH studies, it is difficult to distinguish between losses of one allele or gains of the other when there could be contaminations due to non-tumoral cells from the stroma. Furthermore, clinical and demographic data (including Simpson grade, detailed location, age, sex and occasionally even the WHO grade) were sparsely reported. Although the authors of previous papers provided either raw or summarized patient data, all were included. We aimed to not miss relevant data in synthesizing and therefore utilized both methodologies (IPD and Aggregate Data).

Following Domingues et al. [11], we presented the second largest series evaluating a broad array of regions for their putative prognostic value.

Encouraged by the obtained prognostic value of 1p/14q alterations, we discovered a certain characteristic. The parasagittal and falcine locations were selected for two reasons: because we noticed that in the pooled cohort the recurrence rate was the highest in those locations and also because 3 of 8 cases with the 1p/14q alteration were parasagittal/falcine MGs. We intended to demonstrate an unusual recurrence pattern in two of our cases (Fig. 2) of parasagittal MGs with the 1p/14q alteration. Detailed analysis of patients with recurring MGs of parasagittal and falx locations revealed that combined chromosomal alteration on 1p and 14q entail rapid progression. Aggressive behaviour is demonstrated by the regrowth of MG separated from its primary origin. The progression pattern of recurrent MGs mimicked drop metastases within cerebrospinal fluid as in other neuroepithelial brain tumours, but were limited to a single location. One study described an aggressive phenotype of MG and attributed its occurrence to loss of 1p and 14q, but is limited to a small series [25].

The authors of relevant reviews on MGs simply lumped together the previous findings and listed recurrence-specific loci: 1p, 9p, 10q, 14q, 14p and 22 and regarded them as recurrence-specific abnormalities [3,7,10,17,26]. Lee et al. first utilized the Gene Expression Omnibus database to stipulate a specific genetic profile of recurrent MGs in a combination of own series and pooled cohort [4]. Since chromosomal aberrations have not been pooled yet, it is vital to examine all accessible factors at karyotype level in a full systematic review fashion. The Cochrane Collaboration recommends pooling

case series in rare disease research, such as our meta-analysis [27]. By means of both analytical approaches, the WHO classification (particularly grade II and III) and any alteration on chromosome 14p and 1p characterized the recurrence trend in MGs. Confronting the clinical data with cytogenetic findings yield MG-specific pattern of recurrence. Until proven otherwise, these variables (WHO, LOH on 1p, 14q and 14) CAN BE regarded as independent factors of tumour aggressive behaviour. Multivariate analysis rejected specific loci and otherwise included summarized variables such as any loss on arms 1p or 14q. Moreover, pooled cohorts carry a risk of publication bias, including the authors' individual preferences in selecting published series, buried negative results, different candidate genes assessed using different laboratory methods (FISH, microsatellite, and CGH), the reviewers' rejections of noteworthy manuscripts or simply the language barrier [28].

Beyond the chromosomal level, alternative genetic pathways should be included in the interpretation of progression in some MGs [2,4,11]. To date, we have merely touched the tip of the iceberg in recognizing a pattern of tumour progression and the development of an individualized molecular therapy for MGs remains elusive.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pjnns.2016.08.003.

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