

# 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

Angel Maillo, Alberto Orfao, Ana B. Espinosa, José María Sayagués, Marta Merino, Pablo Sousa, Monica Lara, and María Dolores Tabernero

Neurosurgery Service (A.M., M.M., P.S., M.L.) and Investigation Unit/IECSCYL (A.B.E., M.D.T.), University Hospital of Salamanca, 37007 Salamanca, Spain; and Department of Medicine, Cancer Research Center and Cytometry Service, University of Salamanca, 37007 Salamanca, Spain (A.O., J.M.S.)

Tumor recurrence is the major clinical complication in meningiomas, and its prediction in histologically benign/grade I tumors remains a challenge. In this study, we analyzed the prognostic value of specific chromosomal abnormalities and the genetic heterogeneity of the tumor, together with other clinicobiological disease features, for predicting early relapses in histologically benign/grade I meningiomas. A total of 149 consecutive histologically benign/grade I meningiomas in patients who underwent complete tumor resection were prospectively analyzed. Using interphase fluorescence in situ hybridization, we studied the prognostic impact of the abnormalities detected for 11 different chromosomes, together with other relevant clinicobiological and histopathological characteristics of the disease, on recurrence-free survival (RFS) at 2.5, 5, and 10 years. From the prognostic point of view, losses of chromosomes 9, 10, 14, and 18 and del(1p36) were associated with a shorter RFS at 2.5, 5, and 10 years. Similarly, histologically benign/grade I meningiomas showing coexistence of monosomy 14 and del(1p36) in the ancestral tumor cell clone displayed a

higher frequency of early relapses. In fact, coexistence of -14 and del(1p36) in the ancestral tumor cell clone, together with tumor size, represented the best combination of independent prognostic factors for the identification of those patients with a high risk of an early relapse. Our results indicate that patients with large histologically benign/grade I meningiomas carrying monosomy 14 and del(1p36) in their ancestral tumor cell clone have a high probability of relapsing early after diagnostic surgery. These findings suggest the need for closer follow-up in this small group of patients. *Neuro-Oncology* 9, 438–446, 2007 (Posted to *Neuro-Oncology* [serial online], Doc. D06-00125, August 17, 2007. URL <http://neuro-oncology.dukejournals.org>; DOI: 10.1215/15228517-2007-026)

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**T**umor recurrence is the major clinical complication of meningiomas, occurring in between 10%–15% and 25%–37% of patients undergoing curative surgery after a 5- to 10-year follow-up period, respectively. Although relapses may occur 10 or more years after complete tumor resection, in a high proportion of

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Address correspondence to Angel Maillo, Servicio de Neurocirugía, Hospital Universitario de Salamanca, Paseo de San Vicente, 58, 37007 Salamanca, Spain (a\_maillo@yahoo.es).

cases they develop in the first years following curative surgery. Among other disease features, such as patient age, tumor location, extent of tumor resection, and proliferation-associated markers,<sup>1-5</sup> tumor histology has long proven to be a powerful independent prognostic factor for recurrence-free survival (RFS). Accordingly, while only a minor proportion of all histologically benign/grade I meningiomas relapse, most atypical and anaplastic tumors do recur in the first years after complete surgical removal of the lesion.<sup>6-20</sup> However, in absolute numbers, the majority of the relapses correspond to histologically benign meningiomas, even among those cases showing recurrence early after diagnosis. In line with this, more recent studies have shown that specific genetic abnormalities such as del(1p36) and monosomy 14 alone or combined in the ancestral tumor cell clone as assessed by fluorescence in situ hybridization (FISH) in association with clinicopathological disease features such as tumor size and/or patient age<sup>15,21-31</sup> can be of further help in predicting outcome, independent of tumor histology. Despite this, prediction of those relapses occurring among histologically benign tumors in the first years following diagnostic surgery still remains a major challenge.

In the present study, we prospectively analyzed the prognostic value of specific chromosomal abnormalities and the genetic heterogeneity of the tumor, together with other clinicobiological disease features, for predicting early relapses in histologically benign/grade I meningiomas. Our results, based on a series of 149 patients who underwent complete tumor resection, show that most relapses occurring during the first 2.5 years after surgery correspond to large tumors in which del(1p36) and monosomy 14 coexist in the ancestral tumor cell clone, providing a new scoring system for the stratification of histologically benign tumors at diagnosis, according to risk of early relapse.

## Materials and Methods

### Patients

A total of 149 patients with histologically benign/grade I meningiomas (43 males, 106 females; mean age, 59 ± 14 years; range, 13–84 years) from a series of 171 consecutive patients diagnosed with meningioma at the Neurosurgery Service of the University Hospital of Salamanca were prospectively included in this study. In all cases, histological diagnosis and classification were performed by an experienced neuropathologist according to WHO criteria<sup>32</sup> and confirmed by a second independent experienced neuropathologist. A total of 22 cases were not entered into the study: eight were excluded due to incomplete resection of the tumor, and 14 corresponded to grade II and grade III tumors. In all other cases, a complete surgical resection of the tumor was performed according to the Simpson's criteria<sup>33</sup> (grade 1, 4%; grade 2, 35%; grade 3, 61%).

According to tumor localization, most ( $n = 134$ ; 90%) meningiomas corresponded to intracranial tumors, and only 15 (10%) were spinal meningiomas. According to

their intracranial localization, the former tumors were distributed as follows: convexity, 27%; parasagittal and tentorial, 33%; ventricular, 2%; and cranial base, 38%. The great majority of the tumors corresponded to meningotheliomatous meningiomas (78%), 12% were psammomatous tumors, 9% were transitional, and 1% were fibroblastic meningiomas. Following diagnostic surgery, none of the patients received any additional antitumor-directed therapy. Tumor size was reported as the longest diameter of the tumor mass on MR or CT images.

Median follow-up at the moment of closing this study was 73 months (range, 6–241 months). Follow-up studies were performed according to a standardized clinicobiological protocol, including MRI techniques performed 3 months after surgery and every 12 months thereafter; whenever clinical signs and/or symptoms were noted and a relapse was suspected, additional MRI studies were performed. In recurrent meningiomas, histological diagnosis was confirmed after tumor resection, and all recurrent cases showed histological behavior identical to that of the corresponding meningiomas studied at diagnosis.

### Interphase FISH Studies

In all cases, freshly frozen tumor samples obtained at diagnostic surgery were used for interphase FISH (iFISH) analysis of numerical abnormalities of chromosomes 1p, 1q, 7, 9, 10, 11, 14, 15, 17, 18, 22, X, and Y according to techniques that have been previously described in detail.<sup>15,34,35</sup> Based on the iFISH patterns, the presence of one or more tumor cell clones was defined as previously described.<sup>36</sup> To define intratumoral clonal evolution in those tumors with multiple subclones, we assumed that karyotypic abnormalities shared by all subclones represented the earliest changes, whereas the latter cytogenetic changes would be present in only some of the tumor cell clones. In all those cases in which two or more cell clones were present by iFISH, an ancestral tumoral cell clone could be identified as that carrying only those karyotype abnormalities common to all tumor cells.

Seventy cases (47%) showed the presence of a single tumor cell clone, with 55 of these cases (79%) consisting of either diploid tumor cells with no abnormalities for any of the chromosomes studied ( $n = 46$ ; 66%) or neoplastic cells carrying monosomy 22 ( $n = 9$ ; 13%) as the sole cytogenetic alteration; in the other 15 patients (21%), different chromosomal abnormalities were detected. In turn, 79 cases (53%) showed two or more tumor cell clones by iFISH. In these cases, the ancestral tumor cell clone frequently showed losses of one or more chromosomes ( $n = 72$ ; 92%); these corresponding to -22 alone (32 cases; 41%) or associated with other chromosome losses ( $n = 21$ ; 27%), loss of chromosome 1p36 ( $n = 21$ ; 27%), monosomy 14 ( $n = 11$ ; 14%), and nullosomy Y in males ( $n = 5$ ; 6%). Numerical abnormalities of chromosomes 7 (3%), 9 (4%), 10 (7%), 11 (1%), 15 (3%), 17 (5%), 18 (3%), and X (7%) were detected in a minority of cases.

**Statistical Methods**

For all continuous variables included in the study, mean values and their standard deviation and range were calculated using SPSS (version 11.0; SPSS Inc., Chicago, IL, USA); for categorical variables, frequencies were used. To establish the statistical significance of the differences observed between groups, the Student *t*-test and Mann-Whitney *U*-test were used for continuous variables; for qualitative variables, the chi-square test was applied (cross-tab; SPSS). RFS curves were plotted according to the method of Kaplan and Meier, and the one-sided log-rank test was used to establish the statistical significance of the differences observed between curves (survival; SPSS). Multivariate analysis of prognostic factors for RFS was performed using the Cox stepwise regression model (regression; SPSS). In this part of the study, only those variables showing a significant association with RFS in the univariate analysis were included. Values of *p* lower than 0.05 were considered statistically significant.

**Results**

Overall, at the moment of closing this study, 20 of the 149 cases studied had relapsed, with nine of the relapses occurring during the first 30 months after diagnostic surgery (median time to recurrence, 30 months; Table 1); among the other 11 relapses, four occurred between months 39 and 60 after diagnostic surgery, five between months 61 and 120, and the other two recurrences were diagnosed at months 122 and 241 of follow-up. From the prognostic point of view, losses of chromosomes 9 (*p* = 0.01), 18 (*p* = 0.005), 10 (*p* < 0.0001), and 14 (*p* = 0.001) and del(1p36) (*p* = 0.008) were associated with a shorter RFS at 2.5 years, the latter three also showing a significant impact on RFS at both 5 and 10 years (Table 2). Similarly, histologically benign/grade I meningiomas showing coexistence of monosomy 14 and del(1p36) in the ancestral tumor cell clone displayed a higher frequency of relapses during the first 30 months

after diagnostic surgery (*p* < 0.0001) as well as at 5 and 10 years (*p* = 0.0003 and *p* < 0.0001, respectively; Table 2, Fig. 1E). Other clinical features of the disease showing an adverse impact on the occurrence of tumor relapses included (1) male gender (*p* = 0.01), ventricular tumors (*p* = 0.05), and tumor size > 50 mm in diameter (*p* < 0.0001) at 2.5 years; (2) younger patient age (*p* = 0.02) and tumor size > 50 mm (*p* = 0.004) at 5 years; and (3) younger patient age (*p* = 0.002), male gender (*p* = 0.05), and tumor size > 50 mm (*p* = 0.003) at 10 years (Table 2, Fig. 1A–D).

Multivariate analysis of prognostic factors for RFS at 30 months showed that tumor size (*p* = 0.008) together with coexistence of both del(1p36) and monosomy 14 in the ancestral tumor cell clone (*p* = 0.001) was the best combination of independent parameters for predicting RFS early after diagnosis in histologically benign/grade I meningiomas. Interestingly, at both 5 and 10 years of follow-up, in addition to tumor size and the karyotype of the ancestral tumor cell clone, patient age (*p* = 0.008 and *p* = 0.001, respectively) and abnormalities of chromosome 10 (*p* = 0.004 and *p* = 0.01, respectively) also proved to have independent prognostic value for RFS in benign/grade I meningiomas (Tables 2 and 3). Based on these results, a prognostic score was built. Patients carrying tumors larger than 50 mm as well as those carrying both del(1p36) and monosomy 14 as the earliest detectable chromosome lesions were assigned a score of 1 each. Based on this score, three different groups of patients at distinct risk of early recurrence were identified: a good prognostic category that included most cases (*n* = 92), with a score of 0 and a recurrence risk at 30, 60, and 120 months of 0%, 5%, and 8%, respectively; an intermediate group (*n* = 46) with a score of 1 and a relapse risk of 7%, 11%, and 11% at 2.5, 5, and 10 years, respectively; and a poor prognostic category, with only 11 cases, showing a score of 2 and risk of relapse at 2.5, 5, and 10 years of 45%, 45%, and 45%, respectively (*p* < 0.0001; Fig. 1F). Although none of the other variables analyzed significantly improved prediction of RFS at 2.5 years in the multivariate study, other cytoge-

**Table 1.** Clinical, histopathological, and cytogenetic characteristics of those meningioma patients showing relapse within the first 30 months after complete tumor resection at diagnostic surgery

Case No.	Age	Gender	Tumor Location	Histological Subtype	iFISH Findings at Diagnosis	Time from Diagnosis to Relapse (Months)
1	13	Female	Cranial base	Meningotheliomatous	-1p, -9, -10, -22/TT	12
2	60	Male	Parasagittal	Meningotheliomatous	-1p, -10, -14q	29
3	46	Male	Parasagittal	Meningotheliomatous	-1p, -14q, -22	24
4	43	Female	Ventricular	Meningotheliomatous	+7	23
5	65	Male	Tentorial	Meningotheliomatous	-Y	12
6	63	Male	Convexity	Meningotheliomatous	-1p, -10, -14q, -22, -Y	23
7	43	Male	Convexity	Meningotheliomatous	-1p, -14q, -10/+15	11
8	60	Female	Convexity	Meningotheliomatous	-1p, -14q, -22, +9	22
9	50	Male	Parasagittal	Meningotheliomatous	-22, -14q	27

Abbreviations: iFISH, interphase fluorescence in situ hybridization; TT, tetraploidy.

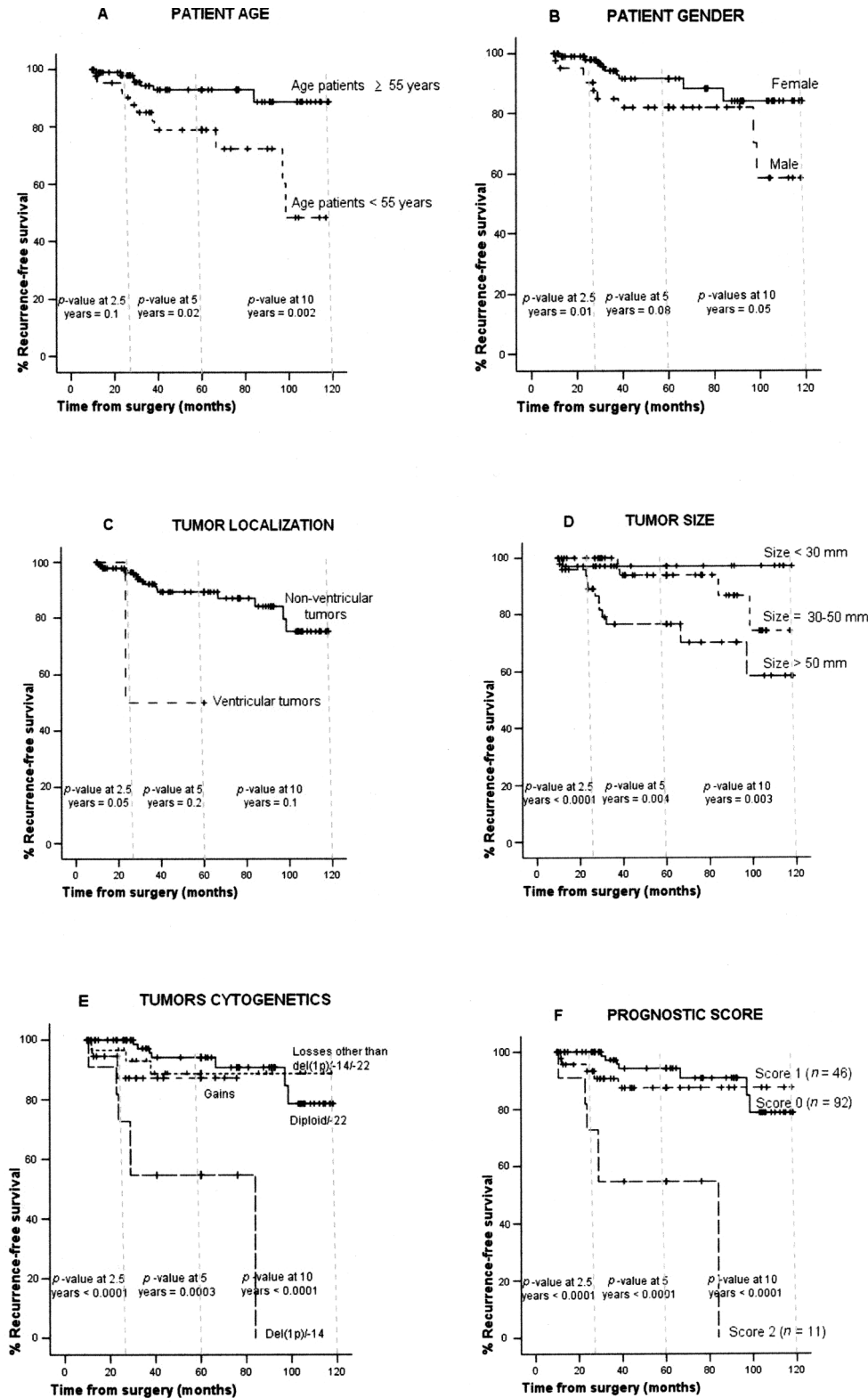


Fig. 1. Recurrence-free survival (RFS) at 30, 60, and 120 months of histologically benign/grade I meningioma tumors ( $n = 149$ ), according to patient age (A), gender (B), tumor location (C), tumor size (D), and the cytogenetic abnormalities detected in the ancestral tumor cell clone defined as the tumor cell clone carrying only those chromosomal abnormalities common to all tumor cells in the sample (E: diploid/ $-22$ ; losses other than  $-22$  or  $-1p/-14$ ; gains;  $-1p/-14$ ). F shows RFS curves at 30, 60, and 120 months according to the proposed prognostic score for predicting early relapses in histologically benign/grade I meningiomas. In this prognostic score, two variables were considered with a prognostic score of either 0 or 1: tumor size (score 0 for tumors  $< 50$  mm, score 1 for tumors  $> 50$  mm) and the presence (score 1) or absence (score 0) of both monosomy 14 and  $del(1p36)$  in the ancestral tumor cell clone.

**Table 2.** Prognostic impact of the cytogenetic characteristics of histologically benign/grade I meningiomas on early recurrence-free survival (n = 149)

Variable	Group	No. Patients (%)	% Recurrences from Total Cases	Prognostic Factors for Recurrence-Free Survival								
				75% Recurrence-Free Survival			Univariate Analysis (p Value)			Multivariate Analysis (p Value)		
				30 m	60 m	120 m	30 m	60 m	120 m	30 m	60 m	120 m
Chromosome 1p36	Diploid	92 (62)	3	NR	NR	NR	0.008	0.009	0.01	0.06	0.05	0.05
	Losses	32 (23)	18	NR	NR	84 m						
	Gains	22 (15)	0	NR	NR	97 m						
Chromosome 1q	Diploid	108 (73)	6	NR	NR	NR	0.9	0.8	0.8			
	Losses	1 (1)	0	NR	NR	NR						
	Gains	39 (26)	5	NR	NR	NR						
Chromosome 7	Diploid	97 (73)	6	NR	NR	98 m	0.7	0.4	0.6			
	Losses	0 (0)	0	NR	NR	NR						
	Gains	36 (27)	8	NR	NR	NR						
Chromosome 9	Diploid	107 (72)	6	NR	NR	NR	0.01	0.8	0.07	0.7	0.3	0.4
	Losses	2 (1)	50	12 m	12 m	12 m						
	Gains	40 (27)	5	NR	NR	97 m						
Chromosome 10	Diploid	104 (70)	6	NR	NR	NR	<0.0001	0.0001	0.0002	0.05	0.004	0.01
	Losses	5 (3)	60	23 m	23 m	23 m						
	Gains	39 (27)	0	NR	NR	97 m						
Chromosome 11	Diploid	42 (76)	7	NR	NR	NR	0.3	0.6	0.2			
	Losses	0 (0)	0	NR	NR	NR						
	Gains	13 (24)	15	NR	NR	97 m						
Chromosome 14	Diploid	97 (65)	3	NR	NR	NR	0.001	0.03	0.04	0.06	0.5	0.4
	Losses	19 (13)	26	29 m	29 m	29 m						
	Gains	32 (22)	3	NR	NR	97 m						
Chromosome 15	Diploid	106 (71)	6	NR	NR	NR	0.8	0.6	0.6			
	Losses	0 (0)	0	NR	NR	NR						
	Gains	43 (29)	7	NR	NR	97 m						
Chromosome 17	Diploid	106 (71)	7	NR	NR	NR	0.8	0.9	0.7			
	Losses	1 (1)	0	NR	NR	NR						
	Gains	42 (28)	5	NR	NR	97 m						
Chromosome 18	Diploid	66 (67)	6	NR	NR	84 m	0.005	0.06	0.08	0.05	0.9	0.8
	Losses	5 (5)	40	23 m	23 m	29 m						
	Gains	28 (28)	0	NR	NR	NR						
Chromosome 22	Diploid	59 (40)	5	NR	NR	98 m	0.6	0.7	0.8			
	Losses	82 (55)	6	NR	NR	NR						
	Gains	8 (5)	13	29 m	29 m	NR						
Chromosome X	Diploid	103 (70)	7	NR	NR	NR	0.7	0.7	0.9			
	Losses	17 (12)	6	NR	NR	97 m						
	Gains	27 (18)	4	NR	NR	NR						
Chromosome Y	Diploid	26 (58)	9	NR	NR	84 m	0.9	0.7	0.8			
	Losses	9 (20)	12	NR	NR	NR						
	Gains	10 (22)	11	NR	38 m	38 m						
No. of tumor cell clones	1 clone	67 (45)	4	NR	NR	NR	0.3	0.5	0.6			
	≥2 clones	82 (55)	8	NR	NR	97 m						

(continued)

**Table 2.** Prognostic impact of the cytogenetic characteristics of histologically benign/grade I meningiomas on early recurrence-free survival ( $n = 149$ ) (continued)

Variable	Group	No. Patients (%)	% Recurrences from Total Cases	Prognostic Factors for Recurrence-Free Survival								
				75% Recurrence-Free Survival			Univariate Analysis ( $p$ Value)			Multivariate Analysis ( $p$ Value)		
				30 m	60 m	120 m	30 m	60 m	120 m	30 m	60 m	120 m
Karyotype of the ancestral tumor cell clone	Diploid	50 (36)	0	NR	NR	NR	<0.0001	0.0003	<0.0001	0.001	0.04	0.02
	-22	42 (28)	0	NR	NR	NR						
	-1p/-14q	11 (7)	46	23 m	24 m	24 m						
	Chromosome losses other than -22 and -1p/-14q	28 (18)	7	NR	NR	NR						
	Chromosome gains	18 (11)	11	NR	NR	NR						

Abbreviations: NR, not reached; m, months.

netic abnormalities involving losses of chromosomes 10 and 18 together with tumor location showed a predictive value close to statistical significance ( $p \geq 0.05$  and  $\leq 0.1$ ).

## Discussion

Until now, reports about the prognosis of meningioma patients have mainly focused on the 5- to 10-year RFS. From a practical point of view, this does not favor the use of prognostic scoring systems established already at diagnosis to help in deciding on closer follow-up of those patients at a higher risk of relapse after relatively long remission periods (e.g., 5–10 years). Because of this, in practice, a closer follow-up of meningioma patients who underwent curative surgery is frequently restricted to histologically atypical and anaplastic tumors.<sup>14,35,37,38</sup> Despite this, it is well known that, in absolute numbers, most relapses occurring in meningioma patients correspond to histologically benign/grade I tumors,<sup>19,39–41</sup> as also found in our series, where 20 of 27 recurrent tumors corresponded to histologically benign/grade I meningiomas (data not shown). Previous studies have shown that the use of specific cytogenetic markers such as del(1p36) and monosomy 14, either in the whole tumor cell population including the ancestral tumor cell clone or in some tumor cells, in combination with tumor size and age, is of great help in the prognostic stratification of histologically benign/grade I meningiomas.<sup>15,21–31</sup> However, little information exists about the prognostic factors for predicting early relapses among histologically benign/grade I tumors. In the present study, we searched for the best combination of prognostic factors for predicting early relapses among histologically benign/grade I meningiomas. RFS at 2.5 years was chosen as an end point of interest since during this early period around

half of all relapses occurred, their frequency clearly decreasing thereafter. We have previously shown that age together with monosomy 14 was the best combination of variables for predicting RFS in histologically benign meningiomas after a median follow-up of more than 5 years.<sup>15</sup> Further studies from our group and others indicate that tumor size could also be of additional prognostic value in this regard. In the present study, monosomy 14 and tumor size showed a significant association with the occurrence of early relapses in histologically benign/grade I meningiomas, while age appeared to be informative only after longer follow-up periods. Other clinical and cytogenetic variables showing a prognostic impact on the 30-month RFS included patient gender, tumor location and size, del(1p36), and losses of chromosomes 9, 10, and 18. In fact, all these clinical and cytogenetic variables have been identified as potentially associated with RFS once histologically benign and malignant meningiomas are considered together.<sup>10,16,23,24,29,42–44</sup>

Until now, it has been well established that meningiomas are cytogenetically heterogeneous tumors both at the inter- and intratumoral cell level.<sup>45–49</sup> In recent years, multicolor iFISH approaches have been systematically applied to the study of large series of meningioma patients, as in the present study, and hypothetical models of intratumoral clonal evolution have been proposed based on the cytogenetically different tumor cell clones detected.<sup>50</sup> Despite this, no study has been reported so far in which the prognostic impact of the number of tumor cell clones, or the intratumoral pathways of clonal evolution, has been analyzed in histologically benign meningiomas. In the present study, we show that, while the number of cytogenetically identified clones in a tumor had no significant impact on predicting early RFS in histologically benign meningiomas, coexistence of monosomy 14 and del(1p36) in the ancestral tumor cell clone was a power-

**Table 3.** Prognostic impact of the clinicobiological characteristics of histologically benign/grade I meningiomas on early recurrence-free survival (*n* = 149)

Variable	Group	No. Patients (%)	% Recurrences from Total Cases	Prognostic Factors for Recurrence-Free Survival								
				75% Recurrence-Free Survival			Univariate Analysis ( <i>p</i> Value)			Multivariate Analysis ( <i>p</i> Value)		
				30 m	60 m	120 m	30 m	60 m	120 m	30 m	60 m	120 m
Age (years)	<55	47 (32)	11	NR	NR	66 m	0.1	0.02	0.002		0.008	0.001
	≥55	102 (68)	4	NR	NR	NR						
Sex	Male	43 (29)	14	NR	NR	31 m	0.01	0.08	0.05	0.4	0.2	0.6
	Female	106 (71)	3	NR	NR	NR						
Tumor location	Convexity	36 (24)	8	NR	NR	97 m	0.05	0.2	0.1	0.5	0.7	0.9
	Parasagittal or tentorial	44 (29)	9	NR	NR	NR						
	Ventricular	3 (2)	43	23 m	23 m	23 m						
	Cranial base	51 (34)	2	NR	NR	41 m						
	Spinal	15 (10)	0	NR	NR	NR						
Histologic subtype	Meningotheliomatous	107 (78)	9	NR	NR	NR	0.2	0.2	0.3			
	Psammomatous	17 (12)	0	NR	NR	NR						
	Transitional	13 (9)	0	NR	NR	NR						
	Fibroblastic	2 (1)	0									
Tumor size	<30 mm	36 (24)	6	NR	NR	NR	<0.0001	0.004	0.003	0.008	0.01	0.003
	30–50 mm	64 (43)	10	NR	NR	98 m						
	>50 mm	49 (33)	25	NR	NR	97 m						
Simpson's grade	1	6 (4)	17	NR	NR	NR	0.4	0.7	0.3			
	2	52 (35)	4	NR	NR	NR						
	3	91 (61)	7	NR	NR	97 m						
DNA ploidy status	DNA diploid	126 (84)	5	NR	NR	NR	0.4	0.9	0.6			
	DNA aneuploid	23 (16)	9	NR	NR	84 m						
% S phase + G2M tumor cells	≤1	43 (29)	2	NR	NR	NR	0.8	0.8	0.8			
	>1	106 (71)	5	NR	NR	97 m						

Abbreviations: NR, not reached; m, months.

ful adverse prognostic factor for early relapses in these patients. In fact, together with tumor size, it represented the best combination of independent prognostic factors for the identification of a relatively small group of patients with an early relapse risk of around 45%, in contrast to a larger group of individuals that showed an extremely low frequency (2%) of recurrences during the first 2.5 years after diagnostic surgery. Interestingly, coexistence of monosomy 14 and del(1p36) in the ancestral tumor cell clone is not restricted to histologically benign/grade I meningiomas but is also observed at significantly higher frequencies among histologically atypical and anaplastic meningiomas (25% vs. 8% in the present series), supporting the more aggressive behavior of meningiomas carrying these cytogenetic features.

Until now, several genes have been identified at chromosome 1p32 to 1p36 that could help to explain the more aggressive behavior of meningioma tumors carrying del(1p36), including the *COKN2C* (*p18<sup>INK4C</sup>*), *p73*, *RAD45L*, and alkaline phosphatase genes.<sup>51–53</sup> Despite this, the potential role of these genes as tumor suppressor genes in the pathogenesis of meningiomas remains unknown. In turn, regarding chromosome 14, no tumor suppressor genes have been clearly identified as potentially involved in determining the clinical behavior of meningiomas, either at the most frequently deleted regions (from 14q21 to 14q32) or at other parts of chromosome 14.<sup>54,55</sup> However, Lusis et al.<sup>56</sup> recently suggested that the *NDRG2* gene localized at 14q11.2 could be involved in tumor progression since it is under-

expressed in anaplastic meningiomas due to methylation. In addition, it should be noted that recent results<sup>36</sup> based on both cytogenetic and histological data indicate that development of recurrent meningiomas after complete tumor resection could be frequently due to regrowth of the primary tumor and rarely associated with emergence of an unrelated meningioma. In line with this, in the present study, all recurrent tumors displayed histological behavior identical to that of their corresponding diagnostic meningiomas.

Altogether, these results indicate that, independent of the genes involved, coexistence of del(1p36) and monosomy 14 confers a unique pattern of tissue involvement and/or clonogenic potential to those histologically benign/grade I meningiomas carrying both abnormalities in their ancestral tumor cell clone. Interestingly, this does not appear to be related to the proliferative index of meningioma tumor cells since the percentage of S phase or S + G2 phase cells did not demonstrate a significant prognostic impact at any of the RFS end points analyzed. However, due to the low number of relapses occurring in the first 2.5 years after surgery ( $n = 9$ ), our results require further confirmation in a longer series of histologically benign/grade I meningiomas.

In summary, in the present study, we show that histologically benign/grade I meningiomas displaying a large tumor size and carrying both monosomy 14 and del(1p36) in their ancestral tumor cell clone have a high probability of relapsing during the first 2.5 years after diagnostic surgery, and they should be followed more closely and/or treated differently from the other cases.

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