

Outcome of Untreated Meningiomas

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ABSTRACT: **Background:** Nowadays meningiomas are frequently detected incidentally. Their natural history has not yet been established because it is difficult to predict the growth pattern. Therefore, the management, after the radiological diagnosis, is still controversial.

Objectives: To evaluate the clinical outcome and growth rate of conservatively treated meningiomas at our tertiary center, identify prognostic factors of tumor growth, and suggest guidelines based on the available data and our experience.

Methods: We reviewed the clinical records of 56 patients with 63 untreated meningiomas. Most were diagnosed incidentally. Clinical features and imaging findings at diagnosis and during follow-up were compared between growing and non-growing tumors. Potential patient- and tumor-related predictive factors for growth were analyzed.

Results: The study group included 46 women (52 meningiomas) and 10 men (11 meningiomas) aged 39–83 years. Mean tumor size was 18 ± 11 mm (range 3–70 mm) at diagnosis and 22 ± 11 mm (range 8–70 mm) at last follow-up; mean follow-up time was 65 ± 34 months (range 15–152 months). During follow-up 24 tumors (38%) grew at a rate of 4 mm per year; none became symptomatic. Only two prognostic factors were statistically significantly associated with low growth rate: older age and tumor calcifications.

Conclusions: Given our finding of a low growth incidence of meningiomas in the elderly, we support conservative management in patients aged 70 years or older. Calcifications into the meningioma are also indicative of slow growth, suggesting a conservative strategy. Surgery is recommended in younger patients in whom tumor growth occurs more often and a longer follow-up is necessary.

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Symptomatic meningiomas are usually treated surgically. For asymptomatic meningiomas, observation is a valid option, particularly if the tumor is small, the patient is elderly, or the clinical condition is poor. Because data on the natural history and growth rate of incidental meningiomas are still insufficient [2-8], management is empiric. The purpose of this study was to review the natural history and growth rate of meningiomas treated conservatively in our department over a 14-year period, to identify possible risk factors for tumor growth, and to suggest management guidelines based on a literature review and our experience.

PATIENTS AND METHODS

The clinical records and imaging studies of patients with conservatively treated brain meningiomas who attended Rabin Medical Center between 1994 and 2008 were reviewed. All patients were referred to our outpatient clinic by family physicians after undergoing diagnostic imaging. The diagnosis was based on findings of a uniformly enhanced extra-axial dural-based mass by computed tomography or magnetic resonance imaging. The decision for conservative management was made on a case-by-case basis by the attending neurosurgeon and was contingent on the presence of at least one of the following criteria: a) elderly patient; b) high operative risk due to tumor location or patient's clinical condition, or both; c) patient refusal of surgery.

For the purposes of the study, the meningiomas were classified as growing or non-growing, and the groups were compared for the following variables: patient age and gender, tumor location and size, tumor calcification, and duration of follow-up. Tumor size was calculated according to largest diameter in the anteroposterior or mediolateral dimension. Tumor location was defined as convexital or skull base. Radiological control was performed 6–9 months after diagnosis and yearly thereafter. The endpoint of the study was the last radiological examination or surgery. At every ambulatory visit, the surgical option was reconsidered.

STATISTICAL ANALYSIS

Continuous parameters were recorded as mean \pm standard deviations. Pearson correlation coefficient (r) and the significance for it (P) were calculated between the variables. Chi-square test or Fisher's exact test was used, as appropriate.

The introduction of advanced neuroimaging techniques has led to the accurate investigation of minor symptoms such as headache or vertigo. As a result, not only are neurological pathologies detected earlier but incidental findings are diagnosed more frequently. In Israel, this is particularly true for meningioma, which has a relatively high rate of occurrence [1].

ate, to analyze statistically significant differences in categorical variables between groups, and Student's *t*-test was used to analyze differences between growing and non-growing tumors. A logistic regression model was fitted to the data to predict tumor growth. *P* values ≤ 0.05 were considered statistically significant.

RESULTS

PATIENT AND TUMOR DATA

The clinical data are given in Table 1. The study group consisted of 56 patients with 63 tumors: 46 women (83%) with 52 tumors (83%) and 10 men with 11 tumors. Five patients had two tumors and one patient had three. Mean patient age was 64 ± 10 years (range 39–83 years). The diagnosis was incidental in 54 patients. Forty-eight meningiomas (76%) were located in the convexital area and 15 in the skull base (24%). Mean tumor size at diagnosis was 18 ± 11 mm (range 3–70 mm). Eighteen tumors (29%) were partially calcified. The mean duration of follow-up was 65 ± 34 months (range 15–152 months). Except for two patients who ultimately underwent surgery, the follow-up time was at least 3 years. At the last radiological examination mean tumor size was 22 ± 14 mm (range 8–70 mm). Three patients died during follow-up for reasons unrelated to the tumor.

GROWING TUMORS

Twenty-four tumors (38%) in 21 patients (20 women, 83%) grew during follow-up (mean follow-up in this subgroup 63 ± 37 months, range 15–131 months). The mean age of this subgroup at diagnosis was 60 ± 11 years (range 40–79 years). Eighteen tumors (75%) were located in the convexital region. Mean tumor size increased from 18 ± 9 mm (range 5–45 mm) on the first diagnostic scan to 29 ± 15 mm (range 8–70 mm) on the last, for a mean growth rate of 4 ± 3 mm per

year (range 0.6–12 mm). Interestingly, three of the tumors started growing after several years of follow-up (2, 4 and 5 years). Three tumors (12% of total growing tumors) were partially calcified. Surgery was recommended because of tumor growth in 11 patients, 4 of whom agreed. The operation was performed after 15, 30, 36 and 82 months of follow-up and consisted of complete tumor excision in three cases; in the fourth, tumor infiltration of the sagittal sinus impeded complete extirpation. Tumor growth was not accompanied by clinical changes.

NON-GROWING TUMORS

During the follow-up 39 tumors (62%) in 35 patients (32 women, 91%) showed no growth (mean follow-up in this subgroup 66 ± 33 months, range 36–152 months). The mean age of this subgroup at diagnosis was 67 ± 9 years (range 39–83 years). Thirty tumors (77%) involved the convexital area. Mean tumor size was 18 ± 12 mm (range 3–70 mm). Calcification was found in 15 tumors (38%).

There was no statistically significant relationship of patient gender, tumor size, tumor location, or follow-up duration with tumor growth rate [Table 1]. The patients with growing tumors were significantly younger than those with non-growing tumors ($P = 0.007$). Every 1-year increase in age was associated with an 8% decrease in tumor growth risk. Non-growing tumors were more likely to be calcified than growing tumors (38% vs. 12%); this difference was statistically significant ($P = 0.02$).

DISCUSSION

Meningiomas account for 14–37% of all primary brain neoplastic tumors [1,9,10]. The incidence is higher in the elderly population and in autopsy studies [11–13]. A growing proportion of meningiomas are diagnosed when they are still asymptomatic. In these cases, the risk of intervention must be balanced against the possible morbidity associated with a conservative approach due to tumor growth. Today, the management of asymptomatic meningiomas is heterogeneous and based on the personal philosophy of the neurosurgeon in charge.

In the first study of the natural history and growth rate of untreated meningiomas, Firsching et al. [3] followed the course of 17 meningiomas for a median of 21 months and noted a median annual growth rate of only 3.6% of the tumor volume. Their consequent recommendation of a conservative management approach was later supported, particularly in the elderly, by a series of studies [Table 2] on the biological behavior of 294 meningiomas [2–4,6,7,13–15]. The findings showed growth in only one-third of the tumors. Only in rare cases did the enlarged tumors become symptomatic [3,6,7,16,17]. Tumor size at presentation is a risk factor for the development of new symptoms; meningiomas smaller

Table 1. Clinical data of 56 patients with 63 meningiomas

	Growing	Non-growing	Total	<i>P</i>
Patients				
No.*	21	35	56	
Gender (male/female)	3/18	7/28	10/46	NS
Age (yrs)†	60 ± 11	67 ± 9	64 ± 10	0.007
Follow-up (mos)†	63 ± 37	66 ± 33	65 ± 34	NS
Tumors				
No.	24	39	63	
Location (cortical/skull base)	18/6	30/9	48/15	
Calcifications	3	30/9	48/15	
Size (mm) first scan†	18 ± 9	15	18	NS
Size (mm) last scan†	29 ± 15	18 ± 12	18 ± 11	0.02
Growth rate (mm/yr)†	4 ± 3	18 ± 12	22 ± 14	NS

*One patient had both a growing and a non-growing meningioma.

NS = not significant ($P \geq 0.05$)

† Mean \pm standard deviation

than 2.5 cm usually remain silent during the next 5 years of follow-up [18].

The results of the present study of 63 meningiomas followed in a major tertiary center are similar to the findings in the literature. Thirty-eight percent of the tumors grew by 4 mm per year over an average 65 months of follow-up. Some of the tumors first started to grow several years after diagnosis. In no case did tumor growth result in a neurological problem. However, in one patient who was ultimately operated on, tumor growth into the sagittal sinus made complete resection impossible.

The identification of tumor features associated with growth would be extremely helpful in the selection of patients for surgery. In the literature, neither patient gender nor tumor location was found to predict tumor growth [6,14,15]; the predictive value of large tumor size at diagnosis remains controversial [3,5,6,8]. In the present study, none of these factors was related to tumor development. Furthermore, similar to other studies [8,14,15], we found that older age was significantly related to a low incidence of tumor growth: every increase of one year in age decreased the risk of tumor growth by 8%. In women, this relationship may be at least partly attributable to hormonal changes after menopause, given earlier findings that estrogen increases cell proliferation in meningiomas whereas gonadotropin inhibits it [19,20].

Several studies have associated tumor calcifications with no growth [4-6,8]. This finding, confirmed in our study, was supported by immunohistochemical MIB-1 staining, which indicated that calcified meningiomas have a reduced proliferation rate [21].

The outcome of surgery of asymptomatic meningiomas has been described in several studies. Nishizaki and colleagues [9] reported a poor outcome in 4 of 75 patients: 2 had severe disability and 2 died. In a study of 213 surgically treated incidental meningiomas, Yano et al. [16] noted a surgical morbidity rate of 4.4% in the younger patients and 9.4% in the patients older than 70 years. Reinert and team [22] reported a 4.9% risk of permanent postoperative neurological morbidity in patients treated surgically for 102 asymptomatic meningiomas.

Radiosurgery is an alternative mode of therapy for small meningiomas, particularly in older or high-surgical risk patients [23]. Kondziolka et al. [24] described the radiosurgical results for 1045 meningiomas (symptomatic or asymptomatic): the control rate was 93% during a median follow-up of 4 years. Surgery was necessary in 5% of patients, and the overall morbidity rate was 8%. Chang and co-authors [25], in a study of 140 meningiomas treated with radiosurgery, reported a 97% control rate during a mean follow-up of 37 months. Radiological complications occurred in 24% and clinical complications in 10%; in most of these cases the lesions were located in the cerebral hemisphere.

On the basis of the cumulative data, we propose the following guidelines for asymptomatic meningiomas:

Table 2. Growth rate of untreated meningiomas in the literature

Studies (year [ref])	No. of tumors	Growing tumors (%)	Annual growth rate	Mean follow-up (mos)
Firsching et al. (1990) [3]	17	59	3.6%	21
Olivero et al. (1995) [7]	45	29	2.4 mm/yr	32
Braunstein & Vick (1997) [2]	12	8	3 mm/yr	105
Go et al. (1998) [4]	35	11	3.1 mm/yr	74
Niironen et al. (2000) [6]	40	35	4.4 mm/yr	32
Yoneoka et al. (2000) [14]	37	9	5.3 mm/yr	50
Nakamura et al. (2003) [15]	41	92.5	14.6 %	43
Yano et al. (2006) [16]	67	37	1.9 mm/yr	90
Rubin et al. (2010) [present study]	63	38	4 mm/yr	65

- Patients aged 70 years or older should be treated conservatively owing to their higher surgical morbidity and mortality [5,10] and lower incidence of tumor growth (as in the present study). If significant tumor growth occurs during follow-up, definitive treatment should be considered.
- In younger patients (under 70 years), surgery is the recommended treatment modality because the growth rate is higher (as in the present study), the follow-up is longer, and the surgical morbidity is minimal [16]. However, if the patient is reluctant to undergo surgery or is not in optimal medical condition, observation may be acceptable as tumor growth is usually not associated with morbidity [3,6,7,16,17]. During the radiological follow-up, any change in the tumor should be taken as an indication that it is "active," and interventional treatment should be reconsidered.
- Other factors must be considered before reaching a final management decision:
 - ▶ If the tumor has calcifications or the patient has major medical problems, a more conservative approach is recommended.
 - ▶ If the meningioma is located adjacent to the optic tract, aggressive management is indicated since even slight growth may cause a neurological change.
 - ▶ Surgery should always be considered for meningiomas located close to the vascular structures (such as dural venous sinuses) because their involvement may impede complete resection.
 - ▶ Radiosurgery as an alternative procedure may be less preferable in patients under age 60 because data on its long-term malignant complications are still sparse.

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