Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI: 10.21474/IJAR01/6253
DOI URL: http://dx.doi.org/10.21474/IJAR01/6253

RESEARCH ARTICLE

THE NATURAL COURSE OF INCIDENTAL INTRACRANIAL MENINGIOMAS: SYSTEMATIC REVIEW AND META-ANALYSIS.

Mohammed Hammad EltantawyMD[1], Ahmed Mohamed Nabeel MD[1] and Hanaa Bayomy Ph.D[2].
1. Department of Neurosurgery, Benha University.
2. Department of Public Health & Community Medicine, Benha University.

Manuscript Info

Manuscript History

Received: 08 November 2017
Final Accepted: 10 December 2017
Published: January 2018

Key words:-
Asymptomatic meningiomas; Natural course; Systematic review.

Abstract

Background: With the increasing availability of radiological imaging, detection of incidental intracranial meningiomas in asymptomatic patients has increased dramatically. The best management of incidentally found meningiomas is not as clear. A systematic review and meta-analysis of the studies currently available allows for a better understanding of the natural course of asymptomatic meningiomas, a platform for more research, and a foundation on which a standardized guideline for following these tumors may be built.

Methods: A systematic review of the English language literature published before October 2017 with no lower date limit was carried out. Data collected from the articles included years of the study, study location, study design, number of patients with asymptomatic meningiomas with follow-up, number of meningiomas, inclusion of NF2 patients, mean age, gender, whether tumor was defined as growing or not, tumor location, MRI characteristics, initial size of the tumors, growth rates, and outcome of follow-up. Meta-analysis of the collected data was carried out.

Results: Twenty studies were identified and included in the meta-analysis (1108 patients, 1175 meningiomas). Meta-analysis results revealed an inverse relationship between age of patients and tumor growth (P<0.001). There was no significant correlation between tumor growth and gender (P=0.15). The presence of calcification was associated with significant reduced risk of growth (P<0.001). Meanwhile, growth was associated with the presence of edema (P=0.005) and T2 hyperintensity (P<0.001). Also, the tumor growth was associated with initial tumor size P=0.01. The outcome of follow up for 1154 tumors in all included studies revealed that 551 (47.7%) had grown, 283(51.4%) of them grown asymptomatically and 153 (27.8%) underwent surgery. 149 out of 1093 patients in the whole analysis developed symptoms during their follow-up (13.6%). The mean follow-up duration for the whole analysis was 60.7 months.

Conclusion: Regarding incidentally discovered meningiomas, an initial follow-up within 3-6 months of initial diagnosis with both clinical and radiological exam followed by another exam at 9-12 months. After the

Corresponding Author:- Mohammed Hammad Eltantawy.
Address:- Department of Neurosurgery, Benha University.

initial observation period, annual radiological exams may be sufficient with special consideration between years 5-10 post-diagnosis.

…….....

Introduction:-

Meningiomas are the most common primary intracranial tumors accounting for 25-30% of all primary intracranial tumors with an incidence of 0.55 per million/year [18,20]. With the increasing availability of computerized tomography (CT) and magnetic resonance imaging (MRI), the detection of incidental intracranial meningiomas in asymptomatic patients has increased dramatically. Typically, they are obtained for justifiable indications such as headaches or neurological deficits, but many parts of the developed world offer "imaging checkups" to private consumers [15,21]. With the increasing number of incidentally found asymptomatic meningiomas, the question of management has been under debate.

In general, if symptoms are being caused by the meningioma, surgical resection or stereotactic radiosurgery are methods considered to alleviate patient suffering. Risks versus benefits of performing the procedure are weighed and factors such as advanced age, anatomic accessibility of the tumor, loss of neurologic function secondary to surgery, and severity of symptoms are taken into consideration [21,22].

The best management of incidentally found meningiomas is not as clear. Although, it is widely accepted that most asymptomatic meningiomas are relatively safe to monitor with an observation period, no standardized guideline exists for follow-up with imaging and clinical exams. Various studies have measured different aspects of meningiomas attempting to correlate findings to outcomes such as age of the patient, gender, initial size of the tumor, growth rates (planimetric versus volumetric versus tumor doubling time or combination), location of the meningioma, initial CT or MRI findings, and development of symptoms. Published reports are often limited by a retrospective study design, small sample size, and short follow-up period. [1-14,16,17,19,21-23] A systematic review and meta-analysis of the studies currently available allows for a better understanding of the natural course of asymptomatic meningiomas, a platform for more research, and a foundation on which a standardized guideline for following these tumors may be built.

Methods:-

Inclusion/Exclusion Criteria and Search Strategy

We performed a systematic review of the English language literature published before October 2017 with no lower date limit. A primary MEDLINE literature search was performed using the terms: "asymptomatic", "incidental", "growth rate", "natural history", and "meningioma". The "related articles" function and the references from the articles were utilized to obtain other relevant articles. The search was performed by two independent members of the study team (Eltantawy MH and Nabeel AM). Inclusion criteria included studies that conservatively followed patients with incidental meningiomas. Patients who were initially treated with open surgery or stereotactic radiosurgery were excluded from our analysis although they may have been included in the original articles. Studies on optic nerve sheath meningiomas were excluded due to differences in the aims and measurements of the studies. Autopsy studies were also excluded from this analysis.

Data from the articles obtained were extracted independently by the second author (Nabeel AM) and were reviewed by a first author (Eltantawy MH). Statistical analysis was done by Bayomy H. Twenty articles were identified that met our inclusion and exclusion criteria. Data collected from the articles included years of the study, study location, study design, number of patients with asymptomatic meningiomas with follow-up, number of meningiomas, inclusion of NF2 patients, mean age, gender, whether tumor was defined as growing or not, tumor location, MRI characteristics, initial size of the tumors, growth rates, and outcome of follow-up. If no data was reported on a certain variable of interest, they were recorded as not available.

Statistical Analysis

The retrieved data were reported as means ± standard error of the mean and range for quantitative data, and frequency and percentage for qualitative data. Meta-analysis of the included studies was carried out using STATA/SE version 11.2 for Windows (STATA Corporation, College Station, Texas). The estimated Effect Size (ES), Standardized Mean Difference (SMD) and Odd Ratio (OR) and the corresponding 95% CI were calculated as

appropriate and demonstrated using the forest plot. The Funnel plot was used to test for publication error and most of data points were under the funnel. A P-value less than 0.05 was considered statistically significant.

Results:-

Study demographics of the 20 studies [1-14,16,17,19,21-23] included in our meta-analysis (1108 patients, 1175 meningiomas) are presented in Table 1 All but one of the studies included in this meta-analysis were retrospective chart reviews with one prospective observational consecutive series [2]. All were published on or after 1990 and the charts reviewed ranged from 1975 to 2015. Only those patients found with initial asymptomatic meningiomas were included in this analysis. The mean age of patients found with asymptomatic meningiomas was 63.09 ± 0.13 years old with a male: female (M:F) ratio of 204:866. Two studies included patients diagnosed with neurofibromatosis 2 (NF2) while two specifically excluded them from their studies, others did not mention that.

Nine studies indicated the mean age of patients with growing versus non-growing tumors [6,7,9,11,14,16,17,21,22]. The mean age of patients in these nine studies with growing tumors was 59.74 ± 0.15 years (range of 17 to 83 years) while the mean age of patients with non-growing tumors was 63.95 ± 0.09 years (range of 22 to 88 years). Eleven studies reported M: F ratios in growing versus non-growing tumors [3,4,5,7,9,10,11,13,16,17,22]. In these studies, the M: F ratio in patients with growing tumors was 33:143 with males comprising 18.75% of the population with growing meningiomas. The ratio in patients with non-growing tumors was 22:162 with males comprising 11.96% of the population.

Meta-analysis for age in growing vs. non-growing tumors (Figure 1A) revealed inverse relationship between age and growth (SMD; 95%CI: -0.43; -0.54 to -0.31) P<0.001. Figure 1B shows no significant correlation between tumor growth and gender (OR; 95%CI: 1.36; 0.89 to 2.07) P=0.15.

Most of the studies reported tumor location according to dural origin (falcine, parasagittal, sphenoidal, etc), which was not applicable for doing statistical analysis due to difference in definition of tumor location specially in large tumors in each individual study. Hashimoto etal in 2012, divided tumor location into: skullbase origins (olfactory grove, planum sphenoidal, cavernous sinus, sphenoid wing , clinoidal , tuberculum and petroclival) and non-skull base origin, tentorial meningiomas where considered non skull base lesions.[6].

Only 4 studies correlated growth to tumor location [6,7,17,21]. Only Hashimoto etal found that incidentally discovered skull base meningiomas tend not to grow compared with non-skull base (P=0.009). Even when the skull base meningiomas grow, the rate of growth is significantly lower than for non-skull base tumors (P=0.002). [6].

MRI findings are another characteristic that has been investigated to differentiate meningiomas. Table 2 shows the three most common MRI findings reported in the literature and the percentage of either growing or non-growing tumors in the study that showed these characteristics [4,5,7,9,11,13,16,17,21]. Meta-analysis results showed that calcification was associated with significant reduced risk of growth (0.34; 0.23 to 0.50) P<0.001 (Figure 2A). Meanwhile, growth was associated with the presence of edema (2.67; 1.35 to 5.28) P=0.005 (Figure 2B) and T2 hyperintensity (2.7; 1.72 to 4.24) P<0.001 significantly. (Figure 2C).

Ten studies measured initial tumor size in diameter, only six of them correlated this to risk of tumor growth [7,13,14,16,17,21]. Eight studies measured the initial tumor size in volume, four of them only correlated this to risk of growth [5,9,11,22](Table 3). The overall average initial size in diameter of asymptomatic meningiomas was calculated to be 2.15± 0.02 cm. In non-growing tumors, the average initial size was 1.94± 0.01 cm while in growing tumors, the average initial size was 2.13 ± 0.01 cm. The overall average initial size in volume of meningiomas was found to be 9.6 ± 0.08 cm^3. In non-growing tumors, the average initial size in volume was 6.11 ± 0.21 cm^3 while growing tumors initially measured 6.61 ± 0.19 cm^3. Meta-analysis results showed significant association between tumor growth and initial tumor diameter (0.15; 0.04 to 0.27) P=0.01 (Figure 3A), and initial tumor volume (0.28; 0.06 to 0.51) P=0.01 (Figure 3B).

Thirteen studies measured various aspects of the growth rate[3,4,5,6,7,10,11,14,17,19,21,22,23] (Table 4). Six measured growth rate in diameter. The average growth rate in diameter of asymptomatic meningiomas was calculated to be 0.64 ± 0.05 cm/year. Another six studies measured relative annual growth rates by volume which was calculated to average 14.15± 0.4%. Two studies measured the absolute growth rates by volume with an average rate of 0.8 ± 0.001 cm^3/year. Two different studies indicated the absolute growth rate by volume in growing tumors

while only one of these studies indicated it for non-growing tumors (did not meet their requirement to be considered a "growing" tumor although there was growth). The average absolute annual growth rate in volume for growing tumors was found to be 3.78 ± 0.27 cm^3/year. Four studies indicated tumor doubling time with an average tumor doubling time of 13.15 ± 0.61 years.

Table 5 shows the outcomes of follow up for 1154 tumors in all included studies, 551 (47.7%) had grown, 283(51.4%) of them grown asymptomatically, and 153 of them (27.8%) underwent surgery either open or radio-surgical. 149 patients among 1093 patients in the whole analysis developed symptoms during their follow-up (13.6%). The mean follow-up duration for the whole analysis was 60.7 months (range 6 to 240). The frequency of follow-up and significant findings are presented in Table 6. So, the risk of growth on follow up was unlikely (ES; 95% CI: 0.46; 0.44 to 0.49) P<0.001(Figure 4A). The development of symptoms was also unlikely (ES; 95% CI: 0.11; 0.09 to 0.14) P<0.001 (Figure 4B).

Discussion:-

General Demographics

In general, it is believed that younger patients have a higher propensity for their tumors to be more aggressive in nature.[8]. Studies by Yoneoka et al , Herscovici et al ,Oya etal and Nakusa etal found patients with growing tumors were younger than those with non-growing tumors. Regarding growth curve analysis Nakusa reported that majority of benign meningiomas began to slow their growth before age of 80 years [12]. From our meta-analysis, we found that the overall effect suggests that growth was more likely in young age patients (P<0.001).

It is also generally accepted that females are more likely to have meningiomas than males. Our analysis discovered that indeed males were more likely to have growing meningiomas than females. Males consisted 19.4% of the population with growing meningiomas but only 15.6% of the population with non-growing meningiomas. However, there was no significant statistical association between tumor growth and gender (P= 0.15).

Location:-

Due to the varying ways of categorizing locations in the different studies, it was difficult to statistically analyze the combined data. For instance, one study may have categorized a specific location whereas a second study may have listed the same location under the general heading of "other" [5,11,21]. Due to this discrepancy in labeling of location between studies, statistical analysis of the combined data was not performed.

Four out of the twenty studies reported the locations of growing and non-growing tumors [6,7,17,21]. Data was not enough which limit the power of statistical calculation. Only Hashimoto etal found that incidentally discovered skull base meningiomas tend not to grow compared with non skull base (P= 0.009). Even when the skull base meningiomas grow, the rate of growth is significantly lower than for non skull base tumors (P= 0.002). [6].

MRI Findings

The available literature shows that non-growing tumors show a significantly higher percentage presenting with calcifications. Eleven studies reported significant difference in tumors presenting with calcifications. Nine of them could be statistically evaluated in our meta analysis[4,5,7,9,11,13,16,17,21], calcification was associated with significantly reduced risk of growth (P= 0.001). Furthermore Nakusa etal and Jadid etal [8,12] concluded the same results with different way of calculation. Only Hashiba et al reported that the presence of calcifications was more frequently observed in lesions that followed a linear growth pattern than in those following an exponential pattern (P= 0.05) [5] .

Edema was associated with increased risk of growth in the four studies that reported peritumoral edema. Only Oya etal [16] found statistical significance for edema regarding factors that favor tumor growth (P= 0.018). Our results showed that growth was associated with peritumoral odema (P= 0.005) which coincides with the study done by Oya which was the largest regarding the number of cases and number of tumors.

Five studies reported MRI T2 hyperintinsity as a factor favoring tumor growth [6,9,13,16,21]. Our meta analysis concluded that T2 hyperintensity was associated with significant increased risk of growth (P= 0.001).

Correlating MRI findings to the likelihood of growth in asymptomatic meningiomas may be of interest to pursue in future studies to aid with decisions about follow-up and treatment.

Initial tumor Size:-

It is well accepted that volumetric measurement of tumor size is more accurate than planimetric measurements. This is due to the fact that tumors are 3-dimensional in nature and may grow in any direction. Measuring volume incorporates the multi-dimensional shape of the tumor while planimetric measures only a one-dimensional diameter. The advantage of measuring tumor diameter is the ease and speed with which it can be done. But the difference between the two different types of measurements is significant. Zeidman et al found a 3.82% per year difference between relative growth in planimetric versus volumetric measures with a $p<0.0001$. [23]

Ten out of the twenty studies utilized planimetric measurements of initial size of tumor while eight studies used volumetric measures. Niiro et al found a significant different in initial size in diameter between growing and non-growing tumors reporting a p-value of 0.016 [13]. Oya etal also found that tumor diameter larger than 25mm associated with significant growth [16]. Yano et al reported no significant difference in initial size in diameter between growing and non-growing tumors indicating a p-value of 0.737 [21]. Robin etal and Jadid etal also found it insignificant [8,17]. In our meta analysis we found that tumor growth was associated with larger initial diameter ($P= 0.01$).

In the studies that measured size in volume, Yoneoka et al was the only one who reported statistical significance using multivariate analysis that larger initial tumor volume increases the chance that the tumor will grow [22]. Three other studies that measured volume did not find a significant difference in initial size between growing and non-growing tumors. Our analysis of the available combined data shows Tumor growth was associated with large initial volume ($P= 0.01$)

Again, the small number of studies with either planimetric or volumetric measurements limits the power of our analysis.

Growth Rates:-

Different studies utilized different definitions of growth for meningiomas. Go et al and Niiro et al utilized a definition of increase in diameter greater than or equal to 0.5cm/year as for tumor growth [4,13] while Herscovici et al, Oya etal and Jadid etal defined growth as an increase in diameter greater than or equal to 0.2 cm [7,8,16]. Yoneoka et al used volumetric measures with an annual growth rate greater than $1cm^3$/year indicating tumor growth [22]. Hashiba et al and Hashimoto etal also measured tumor volume and defined growth as a relative volume change greater than 15% [5,6], but Nakuso etal and Oya etal defined tumor growth as volume change more than 8.2%. It should be noticed that Oya etal used both planimetric and volumetric measurements in their study [16]. Other studies such as Firsching et al, Olivero et al, Kuratsu et al, Nakamura et al, Yano et al, and Zeidman et al, measured growth rates under the assumption that any increase in size would be considered growth.[3,9,10,14,21,23]

The majority of asymptomatic meningiomas were found to be slow-growing with an average growth rate in diameter of 0.64 cm/year. The relative annual growth rate in volume was found to be 14.15 % with an absolute growth rate in volume of 0.8 cm^3/year. Tumor doubling time was calculated to be 13.5 years.

Outcome:-

On average, 47.7% of meningiomas were found to grow during the mean follow-up period of 60.7 months. Of the 1093 patients with follow-up, 13.6% of patients with meningiomas developed symptoms during the follow-up period. Five studies did not report whether patients developed symptoms or not. In patients with growing tumors, 51.4% remained asymptomatic throughout the follow-up period, which prove that routine radiological follow-up in such cases is really mandatory.

Twelve studies reported patients that ultimately underwent surgery [1,4,5,6,7,8,13,14,16,17,21,23]. Among patients with growing tumors, 27.8% underwent surgery, either open, radiosurgery, or both. Studies where patients underwent both open and radiosurgery were counted twice, once for their open procedure and again for their radiosurgery. The decision treat a patient with surgery depended on multiple factors including surgeon and patient factors that differed between studies. With multiple surgeons in multiple countries, the decision to operate was not

based on uniform criteria. Also, patient factors such as concomitant health issues and patient's right to choose influenced a surgeons decision on management.

Our meta-analysis specifically targeted studies that included patients who had initially asymptomatic meningiomas so that we could assess for differences in various characteristics between growing and non-growing tumors. Above all, we wanted to give a thorough analysis of the published data regarding the natural history of asymptomatic meningiomas to challenge generally accepted notions about this type of tumor and discover any gaps of evidence in the published literature.

We would like to acknowledge the short-comings of this type of analysis. We have attempted to analyze numerous studies performed in many different countries by many different neurosurgeons. Each study was performed with different goals in mind emphasizing different aspects of their data. Not every study presented each and every category of data that we sought. Due to the nature of this meta-analysis, the power of our analysis depends solely on the available data in these studies and any limitations that may have been introduced in the initial studies are now compounded by combining them. But by combining the information in the published literature thus increasing the total number of patients and number of tumors being analyzed, we attempted to give our study greater power than within each individual study.

It is generally accepted that it is safe to manage asymptomatic meningiomas conservatively. The slow growth of asymptomatic meningiomas is important to consider when determining a follow-up schedule for patients. Bindal et al found that at 1 year follow-up, 100% of tumors were unchanged; at 2 year follow-up, 97% of tumors were unchanged; at 5 year follow-up, 80% of tumors were unchanged; and at 10 year follow-up 42% of tumors were unchanged. According to their data, the time for the most change in size was between 5 and 10 years. [1]

Conclusion:-

Our meta-analysis supported that factors significantly favor tumor growth are younger patients age, larger initial tumor size, T2 hyper intensity, peri-tumoral edema. While only intra-tumoral calcification significantly favor slow or even no tumor grows. Other factors like sex, tumor location were not statistically associated with tumor growth.

We would like to propose universal criteria for following incidentally found asymptomatic meningiomas. An observation period of close follow-up within the first year seems prudent to ensure that the meningioma is not a rare-fast-growing type. An initial follow-up within 3-6 months of initial diagnosis with both clinical and radiological exam was followed by another exam at 9-12 months. After the initial observation period, annual radiological exams may be sufficient with special consideration between years 5-10 post-diagnosis.

Table 1: General Study Demographics

Authors & Year	Study Period	Study Location	No. of pts	No. of meningiomas	Included NF2 pts	Mean age in years (range)			M: F ratio		
						All	Growing tumors	Non-growing tumors	All	Growing tumors	Non-growing tumors
Firsching et al (1990)	1979-1989	Koln, Germany	17	17	Unknown	64.4 (46-83)	NA	NA	3:14	3:14	NA
Olivero et al (1995)	1987-1995	Peoria, Illinois	60 (45)	66 (45) *******	Unknown	66.0 (38-84)	60.7	63.5	15:45	NA	NA
Braunstein et al (1997)	NA	Evanston, Illinois	12	12	Unknown	63.0 (45-75)	NA	NA	4:8	NA	NA
Go et al (1998)	1975-1993	Olmsted County, Minnesota	35	38*	Yes	67.0 (10-93)	NA	NA	3:32	1:3	2:29
Yoneoka et al (2000)	1986-1997	Niigata, Japan	37	37	No	61.0 (21-82)	53.2	60.5	5:32	3:6	2:26
Kuratsu et al (2000)	1989-1996	Kumamoto, Japan	63	63	Unknown	66.8 (22-88)	67.5	66	11:52	5:15	6:37
Niiro et al (2000)	1995-2000	Kagoshima, Japan	40	40	Unknown	76.1 (70-95)	NA	NA	8:32	5:9	4:22
Van Havenbergh et al (2003)	1985-1996	Hannover, Germany Leuven, Belgium	21	21	Unknown	56.8 (36-78)	NA	NA	5:16	NA	NA
Nakamura et al (2003)	1978-2000	Hannover, Germany	47	47	No	57.6 (33-84)	NA	NA	5:42	5:42	NA
Bindal et al (2003)	1975-1998	Indianapolis, Indiana	40	40	Unknown	54.0 (37-79)	NA	NA	5:35	NA	NA
Herscovici et al (2004)	1989-1999	Tel Aviv, Israel	44	51**	Unknown	65.0 (39-83)	61	67	8:36	3:13	5:23
Nakasu et al (2005)	NA	Shiga, Japan	7	18***	Yes	56.3 (18-77)	49.2	74	2:5	2:3	0:2
Yano et al (2006)	1989-2003	Kumamoto, Japan	67	67	Unknown	64.4 (17-88)	63	65.8	NA	NA	NA
Zeidman et al (2008)	1987-2004	Evanston, Illinois	21	22	Unknown	61.0 (36-74)	NA	NA	4:17	NA	NA
Hashiba et al (2009)	1993-2005	Osaka, Japan	70	70	Unknown	61.6 (28-83)	64	60.5	9:61	6:38	3:23
Oya et al (2011)	2003-2009	Cleveland, USA	244	273****	No	60.5 (29-88)	56	63	53:220	24:96	29:124
Nakusa et al (2011)	2001-2004	Shiga, Japan	52	52	Unknown	57.6*****	NA	NA	13:39	NA	NA
Rubin et al (2011)	1994-2008	Ramat Aviv, Israel	56	63	Unknown	64 (39-83)	60	67	10:46	3:18	7:28
Hashimoto et al (2012)	1993-2009	Osaka, Japan	110	113******	Unknown	66.8 (37-91)	NA	NA	17:93	NA	NA
Jadid et al (2015)	1991-1998	Karolinska, Sweeden	65	65	Unknown	66.6 (27-84)	NA	NA	24:41	NA	NA
TOTALS			1108	1175		63.09 (0.13) [s]	59.74 (0.15) [s]	63.95 (0.09) [s]	204:866	60:257	58:314

*1 pt with 2 tumors, 1 pt with 3 tumors; **4 pts with 2 tumors, 2 pts with 3 tumors; ***1 pt with 3 tumors, 1 pt with 10 tumors. Both patients had NF2; **** 273 meningiomas in 244 patients; ***** median not mean; ****** 2 patients had multiple tumors, ******* among 60 patient had demographic data ,only 45 had follow-up; S: Standard error of the mean; NA: Not Available

Table 2:- Comparison of MRI Findings in growing tumors versus non-growing tumors

Authors & Year	Calcifications (%)		Edema (%)		T2 Hyperintensity (%)	
	Non-growing	Growing	Non-growing	Growing	Non-growing	Growing
Go et al (1998)	19/19 (100)	0/0 (0)	NA	NA	NA	NA
Kuratsu et al (2000)	21/38 (55.3)	2/18 (11.1)	NA	NA	6/24 (25)	8/9 (88.9)
Niiro et al (2000)	16/26 (61.5)	3/14 (21.4)	7/26 (26.9)	2/14 (14.3)	3/13 (23.1)	7/14 (50)
Herscovici et al (2004)	10/19 (52.6)	2/32 (6.3)	NA	NA	NA	NA
Nakasu et al (2005)	2/2 (100)	3/16 (18.8)	NA	NA	NA	NA
Yano et al (2006)	19/25 (76.0)	6/21 (28.6)	3/25 (12)	5/21 (23.8)	9/25 (36)	11/18 (61.1)
Hashiba et al (2009)	16/44 (36.4)	16/26 (61.5)	3/44 (6.8)	5/26 (19.2)	24/44 (54.5)	12/26 (46.2)
Oya et al (2011)	42/111 (37.8)	19/101 (18.8)	3/150 (2)	13/107 (12.2)	17/128 (13.3)	32/86 (37.2)
Rubin et al (2011)	15/39(38)	3/25(12)	NA	NA	NA	NA
TOTAL	145/284 (51.1)	51/228 (22.4)	16/245 (6.5)	25/168 (14.9)	59/234(25.2)	70/153(45.8)

NA: Not Available

Table 3:- Comparison of Growing vs. non-growing tumors as regard initial size of the tumor

Authors & Year	Average initial diameter in cm (range)			Average initial volume in cm^3 (range)		
	All	Non-growing tumours	Growing tumours	All	Non-growing tumours	Growing tumours
Olivero et al (1995)	2.15	2.19 (0.5 to 5.0)	1.7 (0.8 to 3.0)	NA	NA	NA
Yoneoka et al (2000)	NA	NA	NA	NA	3.7 (3.0 to 4.4)	6.7 (4.9 to 8.5)
Kuratsu et al (2000)	NA	NA	NA	NA	9.49 (-6.11 to 25.09)	9.75 (-0.25 to 19.75)
Niiro et al (2000)	2.6 (1.0 to 6.0)	2.33 (0.8 to 4.0)	3.09 (1.8 to 6.0)	NA	NA	NA
Herscovici et al (2004)	1.7 (0.3 to 4.5)	1.5 (0.3 to 3.0)	1.85 (1.0 to 4.5)	NA	NA	NA
Nakasu et al (2005)	NA	NA	NA	2.76 (0.2 to 17.4)	9.46 (1.53 to 17.4)	1.92 (0.2 to10.9)
Yano et al (2006)	NA	2.3 (1.0 to 4.4)	2.4 (0.5 to 6.0)	NA	NA	NA
Hashiba et al (2009)	NA	NA	NA	10.4 (0.63 to 69.2)	4.0 (0.75 to 45.9)	4.2 (0.63 to 69.2)
Oya et al (2011)	2 ±1.1	1.9 ±0.9	2.1 ±1.3	NA	NA	NA
Rubin et al (2011)	1.8±1.1 (0.3-7)	1.5	1.8±0.9	NA	NA	NA
Total	2.15 (0.02) [s]	1.94 (0.01) [s]	2.13 (0.01) [s]	9.6 (0.08) [s]	6.11(0.21) [s]	6.61(0.19) [s]

S: Standard error of the mean
NA: Not Available

Table 4:- Growth Rates

Authors & Year	**Ave. Growth in Diameter (cm/year)**	**Relative Annual Growth Rates in Volume (%)**	**Ave Absolute Annual Growth Rates in Volume (cm^3/year)**	**Non-growing tumors Absolute Annual Growth Rates in Volume (cm^3/year)**	**Growing tumors Absolute Annual Growth Rates in Volume (cm^3/year)**	**Tumor doubling time (years)**
Firsching et al (1990)	NA	3.6 (0.5 to 21.0)	NA	NA	NA	NA
Olivero et al (1995)	0.24 (0.013 to 1.0)	NA	NA	NA	NA	NA
Go et al (1998)	0.32	12	NA	NA	NA	NA
Yoneoka et al (2000)	NA	NA	NA	0.1 (0 to 0.2)	5.3 (3.2 to 7.4)	NA
Van Havenbergh et al (2003)	0.081	NA	0.81	NA	1.10	NA
Nakamura et al (2003)	NA	14.6 (0.48 to 72.8)	0.796 (0.03 to 2.62)	NA	NA	21.6 (1.27 to 143.5)
Herscovici et al (2004)	0.4	NA	NA	NA	NA	NA
Nakasu et al (2005)	NA	NA	NA	NA	NA	18.4 (1.35 to 250.41)
Yano et al (2006)	0.19 (0.042 to 1.147)	NA	NA	NA	NA	NA
Zeidman et al (2008)	NA	5.82 (0 to 24.3)	NA	NA	NA	NA
Hashiba et al (2009)	NA	20	NA	NA	NA	7.8 (1.08 to 11.17)
Rubin et al (2011)	**2.2 ± 1.4**	NA	NA	NA	NA	NA
Hashimoto etal (2012)		Skull-base 6.84, non-skull-base 13.78				Skull-base 13.4, non-skull-base 9.3
Total	0.64(0.05)^s	14.15(0.4)^s	0.8(0.001)^s	0.1	3.78(0.27)^s	13.15(0.61)^s

S: Standard error of the mean
NA: Not Available

Table 5:- Outcomes

Authors & Year	No. tumors	No. of growing tumors	No. of non-growing tumors	No. of cases developed symptoms	No. asymptoms growing tumors	No. of growing tumors to undergo surgery*	No. of death during f/u related to meningioma	Mean duration of follow-up in months (range)
Firsching et al (1990)	17	17	0	NA	NA	NA	NA	25.06 (2 - 89)
Olivero et al (1995)	45	10	35	0	10	0	1	32 (6 - 180))
Braunstein et al (1997)	12	1	11	7	0	NA	NA	105.6 (39.6 - 153.6)
Go et al (1998)	38	4	34	1	3	3	NA	74 (5-182)
Yoneoka et al (2000)	37	9	28	2	7	NA	NA	50.4 (42 - 58.8)
Kuratsu et al (2000)	63	20	43	NA	NA	NA	NA	NA
Nirro et al (2000)	40	14	26	5	9	9	1	38.4 (6 - 97)
Van Havenbergh et al (2003)	21	16	5	17	0	NA	2	82 (48-120)
Nakamura et al (2003)	47	47	0	NA	NA	NA	NA	43 (6 to 105)
Bindal et al (2003)	40	7	33	11	0	17	0	76 (10-312)
Herscovici et al (2004)	51	19	32	0	19	3	NA	67
Nakasu et al (2005)	18	16	2	NA	NA	NA	NA	93.8 (45.8 - 168.2)
Yano et al (2006)	67	25	42	11	25	35	NA	60
Zeidman et al (2008)	22	20	2	6	14	0	NA	43.7 (25.2 - 129.6)
Hashiba et al (2009)	70	44	26	3	41	3	NA	39.3 (12-123)
Oya et al (2011)	273	120	153	72	48	49	NA	45.6
Nakusa et al (2011)	52	44	8	NA	NA	NA	NA	92.4
Rubin et al (2011)	6**3**	24	39	0	24	11	0	65±**34**
Hashimoto etal (2012)	113	71	42	7	71	7	NA	46.9 (12-121)
Jadid et al (2015)	65	23	42	7	12	16	11	74 (6-240)
Total	1154**	551(47.7%)	603(52.3%)	149(13.6%)	283(51.4%)	153(27.8%)	15	60.7

*Numbers include open and radiosurgery. Patients who underwent both open and radiosurgery were counted twice

** 1154 tumors in 1093 patients in all included studies, these numbers are different from the demographics table due to Olivero etal study (14).

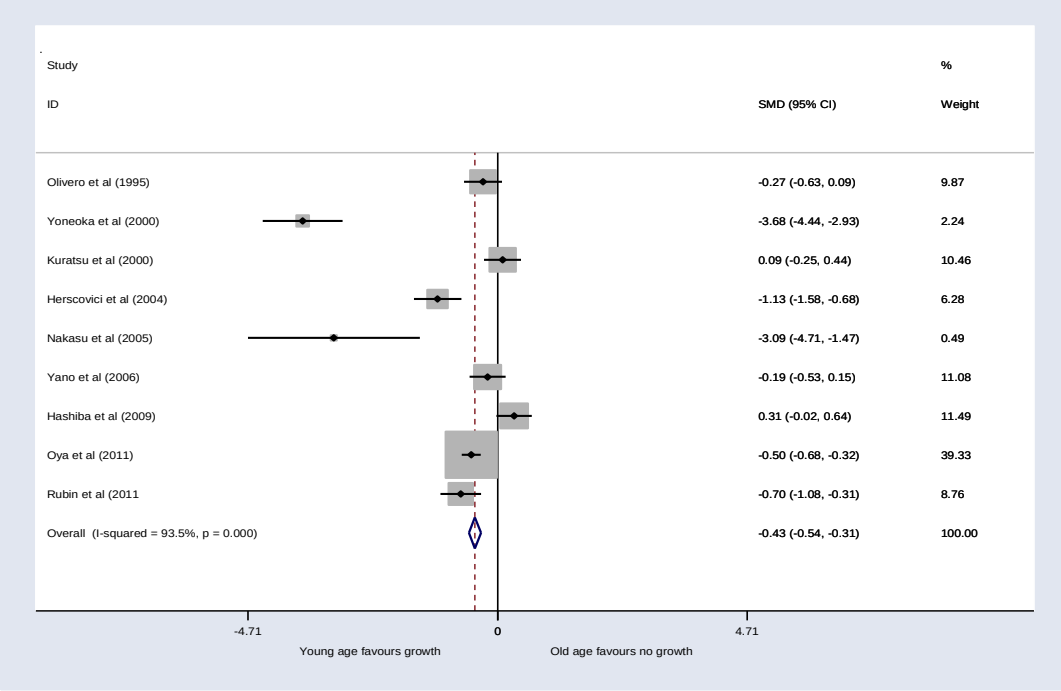
NA: Not Available

Table 6:- Follow-up

Authors & Year	Frequency of clinical follow-up	Frequency of radiographical follow-up	Significant difference found
Firsching et al (1990)	NA	Variable from 1980 to 1989	Calc.
Olivero et al (1995)	3 months and 9 months Post-diagnosis, then every 6 months to 1 year thereafter	3 months after initial diagnosis, then 9 months post-diagnosis, and yearly or every other year thereafter	NA
Braunstein et al (1997)	NA	4 or 6-month intervals for first year or two after diagnosis. Then, 12 months for most patients thereafter	NA
Yoneoka et al (2000)	NA	NA	Age, Initial size in volume
Kuratsu et al (2000)	NA	NA	Calc., T2 hyperintensity
Niiro et al (2000)	NA	NA	Calc., Initial size in diameter,
Van Havenbergh et al (2003)	Approximately every 2 years	Approximately every 2 years	NA
Nakamura et al (2003)	NA	6 months and yearly after initial diagnosis depending on location	NA
Bindal et al (2003)	NA	Yearly	NA
Herscovici et al (2004)	NA	6 to 9 months after diagnosis and yearly thereafter	Age
Nakasu et al (2005)	NA	NA	NA
Yano et al (2006)	NA	NA	Calc., T2 Hyperintensity
Zeidman et al (2008)	NA	NA	NA
Hashiba et al (2009)	NA	NA	Calc.
Oya et al (2011)	NA	NA	Calc., edema, T2 Hyperintensity
Rubin et al (2011)	NA	6-9 months after diagnosis then annually after that	Calc.
Nakusa et al (2011)	NA	>4 images during study period	Calc.
Hashimoto etal (2012)	NA	>3 MRI over more than 1 year	NA
Jadid et al (2015)	NA	Annual	Calc.

NA: Not Available

A.



B.

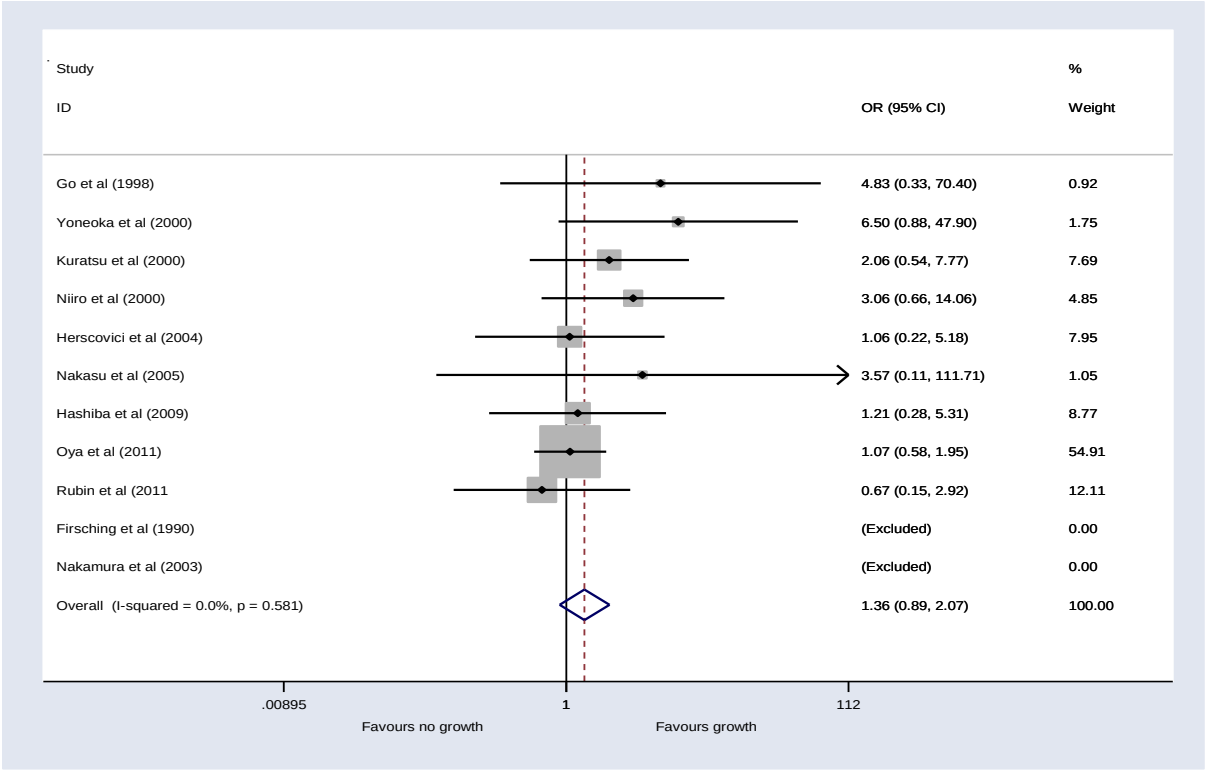
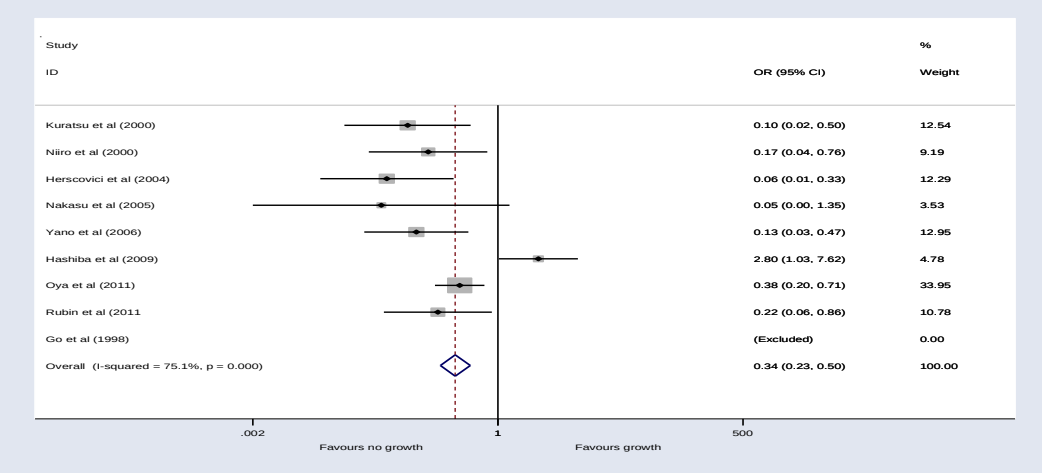


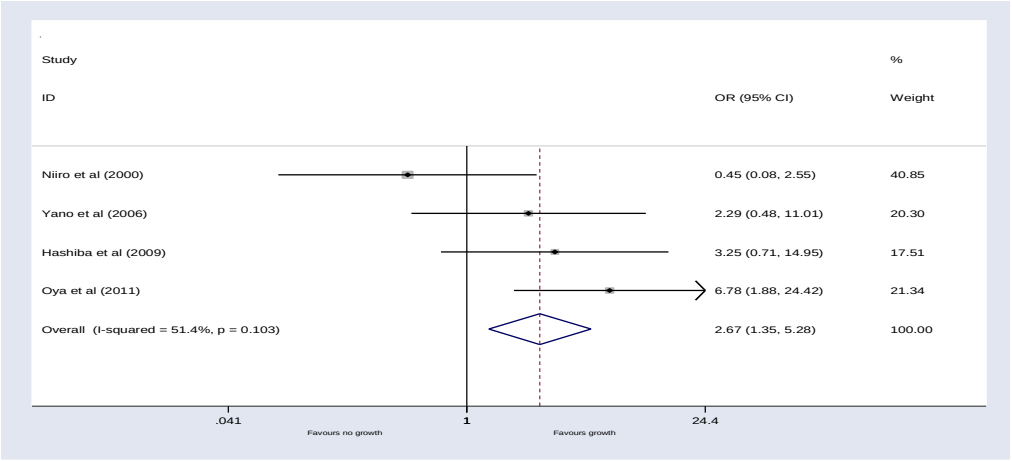
Figure 1:- Growing vs. non-growing tumors as regard age (A) and M: F ratios (B)

A

A.



B.



C.

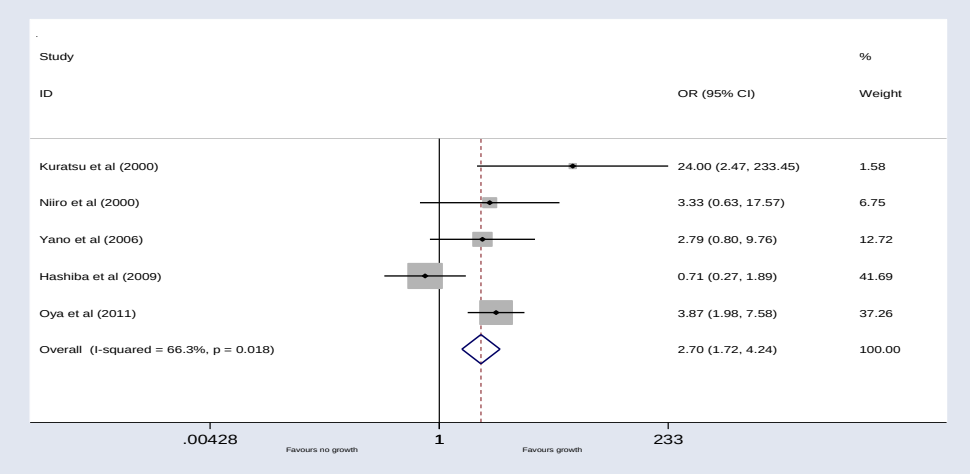
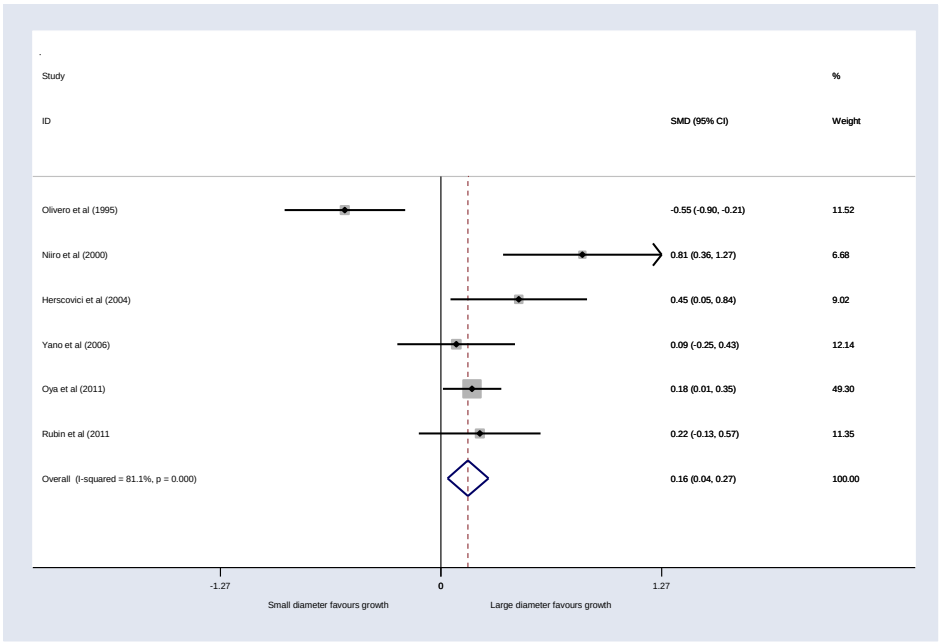
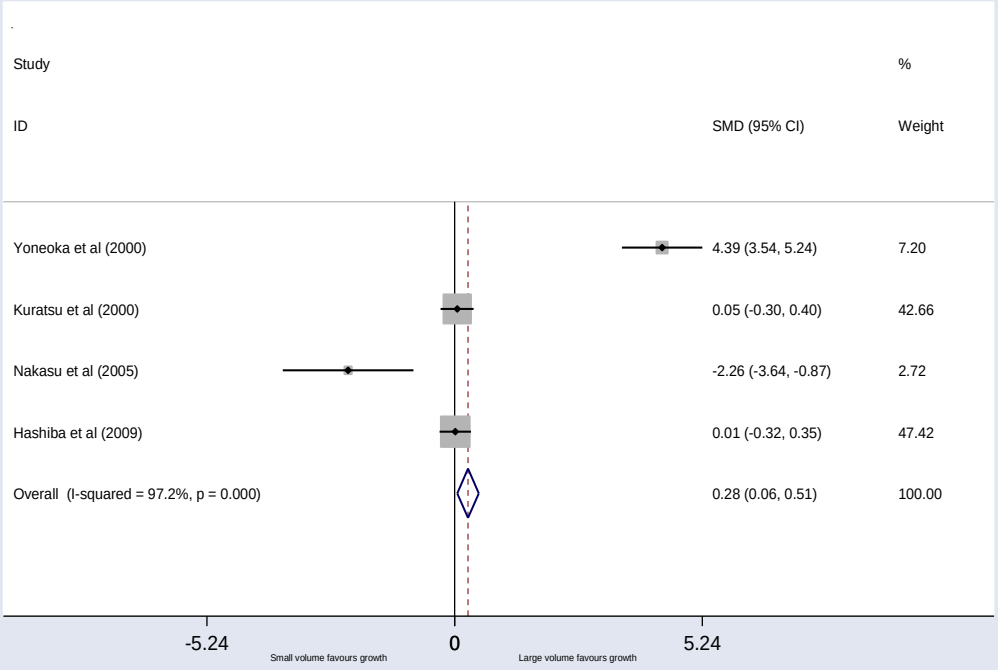


Figure 2:- Growing vs. non-growing tumors regarding MRI findings: calcification (A), edema (B) and T2 hyperintensity (C)

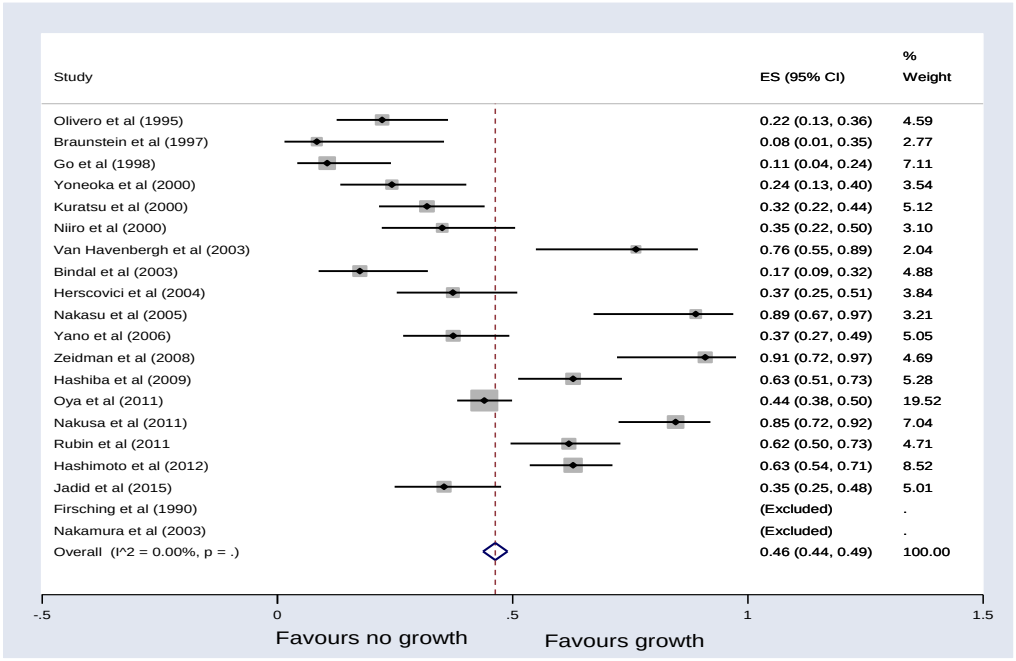


A

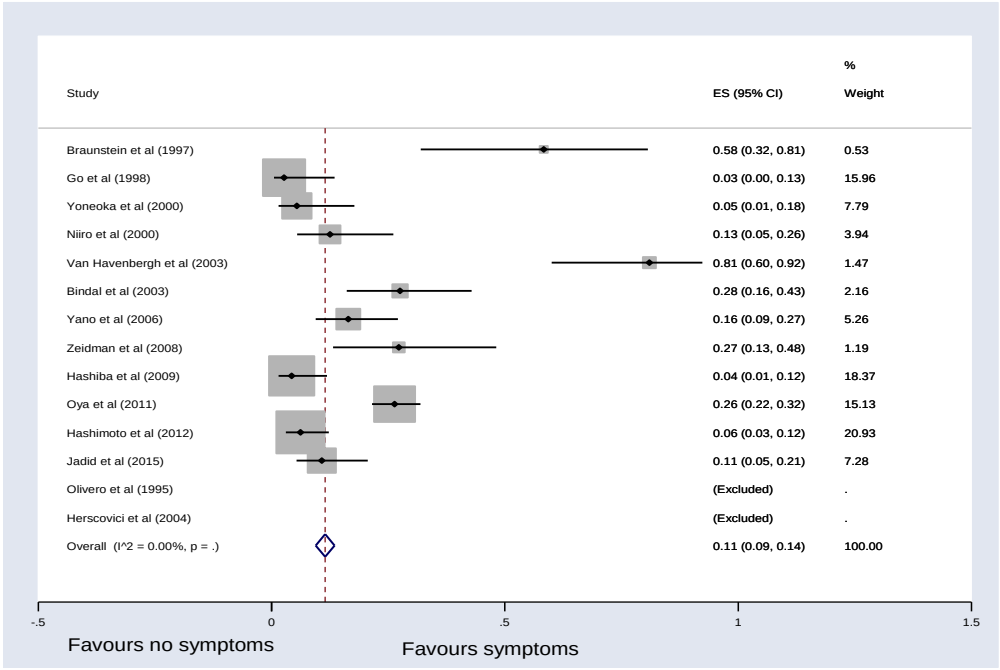


B

Figure 3:- Growing vs. non-growing tumors regarding initial size in cm (A) and cm^3 (B)



A



B

Figure 4:- Occurrence of growth (A) and the development of symptoms (B) on follow up

References:-

1. Bindal R, Goodman JM, Kawasaki A, Purvin V, Kuzma B. The natural history of untreated skull base meningiomas. Surg Neurol. 2003 Feb;59(2):87-92
2. Braunstein JB, Vick NA. Meningiomas: the decision not to operate. Neurology 1997;48(5):1459–1462
3. Firsching RP, Fischer A, Peters R, Thun F, Klug N. Growth rate of incidental meningiomas. J Neurosurg 1990;73(4):545–547
4. Go RS, Taylor BV, Kimmel DW. The natural history of asymptomatic meningiomas in Olmsted County, Minnesota. Neurology 1998; 51(6):1718–1720
5. Hashiba T, Hashimoto N, Izumoto S, et al. Serial volumetric assessment of the natural history and growth pattern of incidentally discovered meningiomas. J Neurosurg 2009;110(4):675–684
6. Hashimoto N, Rabo CS, Okita Y, et al. Slower growth of skull base meningiomas compared with non-skull base meningiomas based on volumetric and biological studies. J Neurosurg 2012;116 (3): 574–580.
7. Herscovici Z, Rappaport Z, Sulkes J, Danaila L, Rubin G. Natural history of conservatively treated meningiomas. Neurology 2004; 63(6):1133–1134
8. Jadid KD, Feychting M, Höijer J, Hylin S, Kihlström L, Mathiesen T. Long-term follow-up of incidentally discovered meningiomas. Acta Neurochir (2015) 157:225–230
9. Kuratsu J, Kochi M, Ushio Y. Incidence and clinical features of asymptomatic meningiomas. J Neurosurg 2000;92(5):766–770
10. Nakamura M, Roser F, Michel J, Jacobs C, Samii M. The natural history of incidental meningiomas. Neurosurgery 2003;53(1): 62–70
11. Nakasu S, Fukami T, Nakajima M, Watanabe K, Ichikawa M, Matsuda M. Growth pattern changes of meningiomas: long-term analysis. Neurosurgery. 2005 May;56(5):946-55
12. Nakasu S, Nakasu Y, Fukami T, Jito J, Nozaki K. Growth curve analysis of asymptomatic and symptomatic Meningiomas. J Neurooncol 2011, 102:303–310
13. NiiroM, Yatsushiro K, Nakamura K, Kawahara Y, Kuratsu J. Natural history of elderly patients with asymptomatic meningiomas. J Neurol Neurosurg Psychiatry 2000;68(1):25–28
14. Olivero WC, Lister JR, Elwood PW. The natural history and growth rate of symptomatic meningiomas: a review of 60 patients. J Neurosurg 1995;83(2):222–224
15. Onizuka M, Suyama K, Shibayama A, Hiura T, Horie N, Miyazaki H. Asymptomatic brain tumor detected at brain check-up. Neurol Med Chir (Tokyo). 2001 Sep;41(9):431-4.
16. Oya S, Kim SH, Sade B, Lee JH. The natural history of intracranial meningiomas. J Neurosurg 114:1250–1256.
17. Rubin G, Herscovici Z, Laviv Y, Jackson S, Rappaport ZH. Outcome of untreated meningiomas. Isr Med Assoc J 2011;13(3): 157–160.
18. Schaller BJ, Ludwig HC, Buchfelder M. Molecular imaging by positron emission tomography in diagnosis and treatment follow-up of brain tumor. In: Trends in brain research, Editior: Chen FJ, Nova science publishers 2006: ch 1, p8.
19. Van Havenbergh T, Carvalho G, Tatagiba M, Plets C, Samii M. Natural history of petroclival meningiomas. Neurosurgery. 2003 Jan;52(1):55-62
20. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A. Incidental findings on brain MRI in the general population. N Engl J Med. 2007 Nov 1;357 (18):1821-8.
21. Yano S, Kuratsu J; Kumamoto Brain Tumor Research Group. Indications for surgery in patients with asymptomatic meningiomas based on an extensive experience. J Neurosurg 2006;105(4): 538–543
22. Yoneoka Y, Fujii Y, Tanaka R. Growth of incidental meningiomas. Acta Neurochir (Wien) 2000;142(5):507–511
23. Zeidman LA, Ankenbrandt WJ, Du H, Paleologos N, Vick NA. Growth rate of non-operated meningiomas. J Neurol. 2008 Jun;255(6):891-5.