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Original article

Atypical meningioma: a study of prognostic factors.

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Objective: Atypical meningiomas now represent 20% 0f all meningiomas. This retrospective study aims to analyze the prognostic factors, the effect of different methods of treatments and the behavior of atypical meningioma.
Patients and methods: Forty four patients diagnosed with atypical meningioma according to the 2007 WHO classification in the period between January 2007 and December 2010 presented to the departments of Clinical Oncology & Nuclear Medicine and Neurosurgery. Data were collected including patients' age, gender, tumours' location, presenting symptoms and treatment received. Patients were followed up to detect recurrence and assess survival.
Results: Median overall survival (OAS) was 60 months ranged from 9-181 months, with a 5-year survival of 42%. Significantly better survival was observed for patients < 50 years than those above 50 years (65 versus 46 months, *P*=0.033) , and patients with total resection over subtotal or biopsy (75,46 and 24 months respectively, *P*<0.0001). Patients with a tumour located in brain convexity had better survival with statistical significance (*P*=0.019). Multivariate analysis showed prognostic significance with age (*P*=0.030) and extent of resection (*P*<0.000). Progression free survival (PFS) ranged from 7-83 months with a median value of 39 months, it showed significant relation with subtotal resection when compared to biopsy (*P*=0.007) . Recurrences were less in patients who received postoperative radiotherapy and was statistically significant (*P*=0.007).
Conclusion: Long term survival is possible for patients with atypical meningiomas treated with surgery and post-operative radiation. Multivariate analysis confirmed that age (< 50 years) and total surgical excision were independent prognostic factors for survival. Adjuvant radiotherapy reduces tumour recurrence especially after incomplete surgery.

Key words: atypical meningioma, prognostic factors, adjuvant radiotherapy.
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INTRODUCTION

Meningiomas are tumours that arise from meninges of the brain and the spinal cord. They represent approximately 20% of all primary intracranial tumours, and these tumours have been divided into benign, atypical and malignant subtypes based on histopathologic criteria[1].

Benign meningiomas are typically slow growing tumours with 5 year survival reported to range from 90% to 100% in the era of modern imaging and treatment modalities[2]. Malignant meningiomas display a more aggressive clinical course with 5 year survival rates ranging between 50 and 60%[3].

The 2000 and 2007 WHO classifications defined the most frequent subtypes as grade I meningioma ,atypical and anaplastic neoplasms as grades II and III meningiomas, respectively[4,5].

Atypical meningioma,which represented only 5-7% of meningiomas before the 2007 WHO classification, now accounts for more than 20% of all meningiomas[5-7]. Because of their aggressive behavior, grades II and III meningiomas have an unpredictable outcome[6,8,9] and reported series have consisted of only a few patients[10-15]. As a consequence, prognostic factors and therapeutic strategy are not clear and considerable controversy remains.

AIM OF WORK

This retrospective study aims to analyze the prognostic factors, the effect of different treatments and the behavior of atypical meningioma.

PATIENTS AND METHODS

Patients populations:

This retrospective study included 44 patients with atypical meningioma (after revision of 186 pathological slides of meningiomas) presented to the departments of

Clinical Oncology & Nuclear Medicine and Neurosurgy, Mansoura University Hospital between January 2007 to December 2010.

The criteria for inclusion were adult patients with age > 18 years, presenting with GII intracranial meningioma according to WHO (2007) pathological classification. Patients included were operated for the first time. They were followed up clinically every two months and radiologically by CT or MRI every 6 months.

Clinico-radiological data:

Data were collected including patient's age at surgery, gender and presenting symptoms (increase of intracranial tension, focal neurological {e.g sensory, motor, extra pyramidal, mental and speech disorders} or others. Initial imaging was either by computed tomography (CT) scan or magnetic resonance imaging (MRI). Tumor location was divided into three groups (convexity, cranial base and others).

Treatment modalities:

Surgical treatment was divided to total excision, subtotal excision or biopsy only, which was determined from the operation notes for all the cases.

Postoperative radiotherapy was given only to patients who underwent subtotal excision or biopsy except for two patients (as decided by the treating panel then). Patients were immobilized using aquaplast mask. Following thin cut CT scan in treatment position, target and critical non-target tissues were delineated and 3D-treatment planning was performed.

In all patients, dose volume histograms of target as well as non-target tissues were obtained. All treatments were delivered as 5 fractions per week, 1.8–2.0 Gy/ per fraction, 1 fraction per day. CT-based conformal beam arrangements were done. The clinical target volume (CTV) included gross disease, operative bed and areas of dural thickening with approximately 1 cm margin. Boost volume RT was not given to any of the cases. Total prescribed target doses ranged ranged from 4500-6000 cGy with a median value of 5500cGy. Two patients only had a dose of RT less than 5000cGy.

Recurrences were confirmed by the radiological data. The outcome of patients after treatment was obtained from registry.

Pathological examination:

Revision of 186 pathological slides of meningiomas during the period between January 2007 and December 2010 was done. Routine H&E stained paraffin sections were retrieved from the archives of Pathology department, Mansoura Faculty of Medicine, Mansoura University and reviewed without knowledge of patient outcome. New sections were cut if lost or when staining had faded. An Olympus CX-21 light microscope was used, and a HPF was defined using the 40x objective.

The tumours were classified according to the 2007 WHO grading system criteria[1]. Atypical meningioma was diagnosed if the tumour has four or more mitoses per 10 HPF, or if three of the following five features are present: high cellularity, high nuclear/cytoplasmic ratio, prominent nucleoli, necrosis, sheet-like growth pattern and or brain invasion.

Mitotic count was assessed in areas with high mitotic activity by summing the highest number of mitotic figures in ten consecutive non-overlapping HPFs. Brain infiltration, defined as irregular, tongue like protrusions of tumour cells infiltrating underlying brain parenchyma without an intervening layer of leptomeninges (which was found only in 5 slides).Increased cellularity was evaluated semi-quantitatively as present or not. Sheeting defined as lack of typical meningioma growth pattern, was noted as present when this covered more than half of the field of vision at the 10x magnification. Macronucleoli were recognized as present when easily observed with the 10x objective. Cells with an increased nuclear cytoplasmic ratio were characterized as small-cell formations.

Survival calculation:

Overall survival (OAS) was calculated from the date of diagnosis to the date of death or the last follow –up, disease free survival (DFS) was calculated from the day of the total surgical excision to the first documentation of recurrence and progression free survival (PFS) was detected from time of subtotal excision or biopsy to the time of the disease progression.

Statistical analysis:

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data was presented as number and percent. Chi-square test was used for comparison between groups. Non-parametric data was presented as min – max and median. Mann-Whitney test and Kruskal-Wallis test were used for comparison between groups. Kaplan- Meier survival curve was used to estimate survival. Cox regression and hazard ratio were used to test the effect of different risk factors on survival. *P* value is considered significant if it is < 0.05.

RESULTS

This retrospective study included 44 patients with atypical intracranial meningioma, patients characteristics are listed in Table (1). The age ranged from 26-68 years

with median 52 years. Gender presented equal number (22 male and 22 famale patients). The commonest presenting clinical sign was the symptoms of increase of intracranial tension (↑ICT) in 26patients (59.1%), followed by focal neurological manifestations in 12 patients (27.3%).

Brain convexity was present in 31.8% (14 cases). Total excision was performed in 16 cases (36.4%), subtotal in 22 cases (50%), and biopsy only in 6 cases (13.6%). In 26 of patients (59.1% of all patients) were treated with RT, the patients were treated after surgery because of incomplete surgical resection or no surgery performed at all. The dose of RT ranged from 4500-6000 cGy with a median value of 5500cGy. Two patients only had a dose of RT less than 5000 cGy .

Period of follow up ranged from 6-179 months with median value of 49 months. On follow up, 16 patients (36.4%) developed recurrence and ten of them (62.5%) underwent total excision and didn't receive postoperative radiotherapy which showed significant relation (*P*=0.001).

Survival time ranged from 9-181 months with median duration of 60 months, and the 5-year survival rate was (42%) (Figure1). On univariate analysis (Table 2) age < 50 years was associated with greater median survival than patients with age > 50 years (65 vs 46 months) and was statistically significant (*P*=0.033). Median survival was better in patients not presented with symptoms of increased intracranial tension or focal neurological manifestations, and it showed significant relation (*P*=0.008). Complete surgical resection showed better survival(75 months) than subtotal (46 months) or biopsy (24 months), and was highly statistically significant (*P*<0.0001). Tumours located in brain convexity had a better survival comparing to cranial base, and showed a statistical significance (*P*=0.019). Multivariate analysis confirmed the prognostic significance of age <50years (*P*=0.030; HR, 0.294; CI,0.97 to 0.888), and total resection (*P*<0.0001; HR,0.022; CI,0.005 to 0.102).

Progression free survival (PFS) ranged from 7-83 months with a median value of 39 months. On univariate analysis (Table 3), subtotal excision was found to be associated with a longer PFS when compared to biopsy only (median 44 months, *P*=0.007).

The disease free survival (DFS) in patients who were treated with complete excision ranged from 17-178 months with a median value of 52 months.

Table 1: Patients characteristics:

Character	Number (NO)	Percent (%)
Age		
<50years	18	40.9
>50years	26	59.1
Gender		
Male	22	50%
Female	22	50%
Clinical signs		
↑ICT	26	59.1%
Neurological	12	27.3%
others	6	13.6%
Location		
Convexity	14	31.8%
Cranial base	8	18.2%
Others	22	50%
Surgery		
Total	16	36.4%
Subtotal	22	50
Biopsy	6	13.6%
Radiotherapy		
Yes	26	59.1%
No	18	40.9%
Dose of RT		
<5000cGy	2	4.54%
>5000cGy	42	95.45%
Recurrences		
Yes	16	36.4%
No	28	63.6%

Table 2: Median overall survival in months for atypical meningioma as a function of possible prognostic factors.

Prognostic factor	Median OAS (in months)	*P* value
Age		
<50 years	65 (18)	0.033
>50 years	46 (26)	
Clinical signs		
↑ICT	60 (26)	0.008
Neurological	24.5 (12)	
Others	92.5 (6)	
Location		
Convexity	77 (14)	0.019
Cranial base	59 (8)	
Others	46(22)	
Surgery		
Complete	75(16)	<0.0001
Subtotal	46 (22)	
Biopsy	24 (6)	

Table 3: Median progression free survival in months for atypical meningioma as a function of possible prognostic factors.

Prognostic factor	median PFS (in months)	*P* value
Surgery		
Subtotal	44 (22)	0.007
Biopsy	10 (6)	

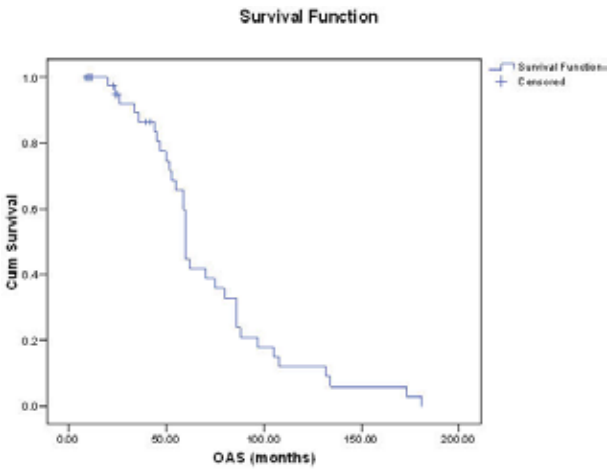

Figure 1: Overall survival of patients.

DISCUSSION

Meningioma grading has been a subject of debate. The first classifications introduced a significant degree of subjectivity, due to selected criteria. Later, more reproducible factor (such as mitotic rate, macronuclei, prominent nucleoli, sheet-like growth patterns and hypercellularity) were studied[5,16,17,18].

In the 2000 WHO classification, a mitotic rate >4 per 10 HPF was considered as the most significant factor for defining atypical meningioma. In patients with a lower mitotic rate, the presence of at least three of the following variables is necessary: increased cellularity, macronuclei, prominent nucleoli, sheet-like growth pattern, and necrosis[19].

The prognostic role of brain invasion has been widely discussed in the recent literature. In the latest revision of the WHO classification (2007), brain invasion has become a criterion for atypical meningioma[5].

There is no consensus on the management of grades II and III meningiomas. Surgical resection is recognized as a determinant prognostic factor in all meningiomas[20,21]. Concerning WHO grade III meningiomas, radiotherapy (RT) is considered necessary because of their potential for recurrence and aggressive behavior[22,23]. This combined treatment is more controversial in the treatment of WHO grade II meningiomas. Some surgeons favour repeated surgical resections. In contrast, there appears to be general support for the RT following incomplete or complete resection for malignant meningiomas and for clinically aggressive atypical meningioma. Chemotherapy (CT) has not shown any convincing effect on atypical and anaplastic meningiomas and should be reserved for recurrent meningiomas when all standard therapies have failed[21,23,24].

In this retrospective study, data of forty four patients diagnosed with atypical meningioma (after revision of 186 pathological slides of patients diagnosed with meningioma) according to WHO classification (2007) criteria, were analyzed. Statistical analysis was performed to determine whether age, preoperative clinical status, tumors' location, extent of surgery or postoperative RT affected OS or PFS.

A predominance of males in patients presenting with atypical meningiomas was not confirmed by our study, in which 50% of the patients were female. This is different from that reported in the literature that GII meningiomas seem to be more frequent in men[6].This result, however could be attributed to the relatively small study size which is much similar to that found in a study done by Palma *et al*. on 42 patients only[11].

Analysis of the patient's age showed that grade II meningiomas were diagnosed at around 52 years of age ranging from 25-68 years. This finding is consistent with the reported series stating that these tumours occur primarily in middle-aged or elderly patients but can also occur in younger patients, typically with neurofibromatosis Type II[25].

Atypical meningioma was found more common in brain convexity and it seems that tumours located in the skull base and spine are less often grades II and III meningiomas[26].

In six different studies done on patients with grade II and III meningiomas, the 5-year overall survival rates ranged from 28% to 91%[3,6,17,27,28,29].Our study showed a 5-year survival rate of 42% (Figure 1), and a median duration of OAS of 60 months. Patients with either subtotal resection or biopsy only had a median PFS of 39 months. However, comparisons between published series are not easy because of the different histological grading systems used by the WHO before and after 2000. Brain invasion was not retained as a malignant criterion in the 2000 WHO grading system. The significance of brain invasion has been widely debated and is nowadays one of the criteria used for grading tumors[17,5].

Age was a good prognostic factor, with a better overall survival when the patient was under 50 years of age. This result is similar to that found by a multicentric retrospective study done on patients with malignant and atypical meningioma[26]. Other authors have defined 65 years as the cut-off for a poor prognosis[6,25], which could be attributed to the relatively larger number of patients over the age of 60 years in these studies.

In this study, tumour location in the convexity was associated with better survival than other sites and this

was may be related to the total excision usually done to meningiomas at this site. This finding meets with that found by a study done on 71 cases of atypical and malignant meningiomas by Palma, *et al.*[11].

Extent of surgery has been reported as one of the most significant predictors of outcome in patients with meningiomas. Surgery provides an anatomopathological diagnosis, reduces the effect of the tumour mass and improves the symptoms[30]. The radicality of surgical excision, in turn, depends mainly on the meningioma site and it is subjectively assessed by the surgeon. In this study complete excision was associated with better local control and survival and was statistically significant. Multivariate analysis showed prognostic significance with age (P=0.033) and extent of resection (P<0.000). In addition to that, PFS was better with subtotal excision rather than surgical biopsy only. These results are in consistent with many series done on atypical and malignant meningiomas[11,25,26].

However, in a recent study, Pasquier *et al*.[6] reported that the extent of surgical resection was not a significant prognostic factor for grades II and III meningiomas, but their statistical analysis was performed on the whole group, with no distinction between the grades. In addition, in their retrospective study, the extent of surgery was not checked by post-operative imaging, as was the case in our series.

Adjuvant radiotherapy after incomplete resection (benign or aggressive meningioma) has not been evaluated in a prospective study to date[31]. Some retrospective trials promote combined radiotherapy after incomplete resection in patients with atypical meningioma, and independently of the status of resection in malignant meningioma[22,23]. This study showed that the use of combined radiotherapy significantly reduces the incidence of recurrence but was used only after tumour incomplete resection or biopsy. That is why we found that 62.5% of the recurrences were found in patients with total excision and didn't receive radiotherapy. However the role of combined radiotherapy in completely resected atypical meningioma is still unclear.

In our study two patients only had radiotherapy at a dose less than 50 GY, so the effect of the dose of radiotherapy on the outcome couldn't be assessed statistically, whereas in certain series dose was a prognostic factor[22,29]. In Milosevic al, dose >50 Gy and age <40 years were the two prognostic factors associated with a favourable outcome on multivariate analysis[3].

Despite a course of conventional megavoltage photon radiation treatment, the majority of patients with atypical or malignant meningioma will ultimately experience local recurrence. Dose escalation (dose >55-60 Gy) was accomplished by Hug *et al.* by 3D-treatment planning assisted combined photon and proton beam RT with significantly better local control. This technique was usually chosen for tumours with large irregular shapes or near critical structures[29].

The role of radiosurgery in aggressive meningioma have not been evaluated in a controlled, prospective study. Some retrospective series report benefit in terms of local control after fractionated or single-dose stereotactic radiotherapy or after proton radiotherapy[32,33]. It is nevertheless important to prospectively evaluate such techniques in this respect. The Phase II 22042 European Organization for Research and Treatment of Cancer trial is assessing the impact of high-dose radiotherapy on progression-free survival, treatment tolerance and post-treatment global cognitive functioning in patients with resected atypical or malignant meningioma[34].

Conclusion: "atypical meningiomas" have a limited signs of histological anaplasia as recently introduced into the WHO classification 2007. Long term survival is possible for patients with atypical meningiomas treated with surgery and post-operative radiation. On univariate analyses, age less than 50years, total surgical excision and absence of symptoms of increase intracranial tension were significantly associated with better OAS. Multivariate analysis confirmed that age (< 50 years) and total surgical excision were independent prognostic factors for survival. Adjuvant radiotherapy reduces tumour recurrence especially after incomplete surgery. Other therapeutic options to be considered are radiation dose escalation using3D-conformal radiation therapy,hyper- fractionated radiotherapy,radiosugery or brachytherapy.

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