International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Original Research Article.

A Retrospective Critical Analysis of Intracranial Atypical Meningiomas Managed At a Tertiary Care Centre with a Rural Set up in Rural Area of India

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ABSTRACT

Background: Atypical meningiomas are World Health Organization - Grade II tumours, which have higher local recurrence rates and lower survival rates than their benign counterparts. The aim of this study is to review the outcome of newly diagnosed patients with atypical meningioma after therapy.

Aim: To study the incidence and clinical outcome of patients with atypical meningiomas managed at a tertiary care centre with rural set up in rural area of India.

Methods and Materials: We conducted a retrospective review of the medical records of patients having atypical meningiomas who were treated in our hospital between January 2008 to December 2017. Their age, sex, initial presentation, tumor location, tumor size, extent of resection, tumor recurrence or tumor progression, duration of follow up, adjuvant therapy, and outcome were reviewed in detail.

Results: There were 34 consecutive patients (19 male and 15 female) having newly diagnosed intracranial atypical meningiomas treated in our hospital between January 2008 and December 2017. Their mean age at diagnosis was 60.81 years. Twenty nine patients (85.29%) underwent total resection of the tumor, whereas five patients (14.71%) had partial resection of their tumors during their first time of surgery. Twenty patients (58.82%) had received adjuvant radiotherapy. 12 patients (35.29%) had tumor progression or recurrence during follow up, and five of them were proved to have malignant transformation to anaplastic meningiomas in the following operations. The mean time to tumor progression or recurrence of these nine patients was 17.67 months. Twenty three patients (67.65%) had a favorable outcome, ten patients (29.41%) had an unfavorable outcome, and we lost one patient (2.94%) due to disease progression.

Conclusion: Surgery remains the standard treatment for atypical meningioma, and postoperative adjuvant radiotherapy is still controversial especially to those who undergo total surgical resection of the tumors. Our study reveals that early postoperative adjuvant radiotherapy seems to play a role in local control. Atypical meningioma can have malignant transformation to anaplastic meningioma, so aggressive treatment and regular follow up are essential to manage this particular tumor.

Key words: Atypical Meningioma, Anaplastic Meningioma, Local Control, Malignant Transformation, Post-Operative Adjuvant Radiotherapy.

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Article History:

Received: 11-02-2018, **Revised:** 02-03-2018, **Accepted:** 27-03-2018

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2018.4.2.072	

INTRODUCTION

In 1614, Felix Plater first described a meningioma in an autopsy report.[1-4] A French surgeon, Antoine Louis, published the first report in 1754 that dealt specifically with meningiomas.[1,2,4,5] In 1847, Virchow described meningiomas as psammonas (sandlike) because of the presence of tumoral granules. In 1864, Bouchard termed meningiomas as epitheliomas, and in 1869 Golgi described them as endotheliomas. In 1922, Harvey Cushing first used the term meningioma. Pathologists subsequently have demonstrated the origin of meningiomas as arachnoid cap cells commonly found in association with arachnoid villi at the dural venous sinuses and veins.[2,4]

Hospital-based brain tumor series indicate that the incidence of meningiomas is approximately 20% of all intracranial tumors (the most common nonglial primary intracranial tumor), whereas

autopsy-based studies indicate an overall incidence of 30%. Furthermore, 2% of autopsies reveal incidental meningiomas. There is an age-dependent incidence of meningiomas (0.3/100,000 in childhood and 8.4/100,000 in the elderly). Ninety percent of all meningiomas occur in the supratentorial compartment.[1,2,4-6] Intracranial meningiomas are most common in adults in their fourth through sixth decades of life and are rare in children (2% of all meningiomas present in childhood).[1,2,4-9] Meningiomas are more common in African-Americans and in females. There is a 2:1 female to male ratio in intracranial meningiomas.[1,2,4-6]

A female preponderance for meningioma correlates with an endogenous hormone level and exogenous hormone replacement in postmenopausal women (in whom an increased incidence of meningioma is seen) as compared with postmenopausal women who have not taken exogenous hormone replacement therapy.[1,2,4,6]

Increased growth of meningiomas during pregnancy as well as postpartum clinical regression has been reported but remains poorly understood.[10] Recently, however, no associations with reproductive or hormonal factors were observed in a case–control study of 151 meningiomas in female patients.[11] The literature does not support any association between the development of meningiomas and oral contraceptives.[12]

Meningiomas arise from the arachnoid cap cells and account for 13–26% of all primary intracranial tumors.[13-16] They are histologically classified as benign World Health Organization (WHO) Grade I, atypical (WHO Grade II), and anaplastic (WHO Grade III).[15] Atypical meningiomas and anaplastic meningiomas are aggressive which constitute about 4.7–7.2% and 1.0–2.8% of meningiomas, respectively.[14,17] In 2000 WHO classification, the pathological criteria for the diagnosis of atypical meningiomas are: ≥4 mitoses/10 HPF or at least three of the following features are present: Sheeting, macronuclei, small cell formation, hypercellularity, foci of spontaneous necrosis;[13,14,17,18] and in 2007, the WHO definition of atypical meningioma added brain invasion as an alternative criterion.[18,19] Immunohistochemistry plays a role in meningioma variants dominated by unusual features. The most commonly used marker is epithelial membrane antigen, sometimes vimentin staining is also helpful in meningioma diagnosis. However, they are not specific. Another important role for immunohistochemistry in meningioma diagnostics lies in the assessment of the proliferative index, which is usually measured with the antibody MIB-1. Raised MIB-1 labeling indices are associated with increased risk of recurrence. MIB-1 labeling indices above 5% suggest a greater chance of recurrence and can be helpful as an adjunct to grading in borderline atypical cases.[1] The extent of surgical resection and the aggressiveness of the tumor cells are the key factors to the tumor recurrence.[17,18,20-22] There is no general consensus for the management of atypical meningiomas. Surgery is recognized as the standard and effective treatment to all meningiomas.[14,21-23] For anaplastic meningiomas, radiotherapy is considered necessary because of the potential for recurrence and aggressive behavior,[14,21-23] but this adjuvant therapy is controversial in the treatment of atypical meningiomas, especially for those who undergo total surgical tumor resection.[17,18,22,23] The objective of this clinical study is to review the outcome of newly diagnosed patients with atypical meningioma after therapy.

METHODS AND MATERIALS

We conducted a retrospective review of the medical records of patients newly diagnosed with atypical meningiomas, who were treated in our hospital between January 2008 to December 2017. We excluded those who underwent their first surgery at other hospitals, patients who lost in follow up and those who were diagnosed with a malignant transformation from previously resected benign meningiomas (WHO Grade I). Their age at diagnosis, sex, initial clinical presentation, tumor location, tumor size, extent of resection, tumor recurrence or tumor progression, duration of follow-up, adjuvant therapy, and outcome were reviewed and analyzed. The extent of resection was determined from the operative records and imaging (CT or MRI). Recurrence or tumor progression was diagnosed if re-growth or tumor enlargement was detected on a follow-up brain magnetic resonance imaging (MRI). Progression-free period was determined by calculating the length of time from the end of the first treatment (date of surgery) to the appearance of tumor recurrence or tumor enlargement on follow up imaging. We used Glasgow outcome scale (GOS) which is a global scale for functional outcome of the patients having brain damage, and it was initially described in 1975 by Jennett and Bond [Table 1] to score the outcome of our patients.

Table 1: Glasgow Outcome Scale

GLASGOW OUTCOME SCALE
1. Dead
2. Vegetative State
3. Severe Disability
Able to follow commands/unable to live independently
4. Moderate Disability
Able to live independently; unable to return to work or school
5. Good Recovery
Able to return to work or school
Jennett B, Bond M. “assessment of outcome after severe brain damage.” Lancet 1975 Mar 1;1(7905): 480-4

RESULTS

There were 34 consecutive patients having newly diagnosed intracranial atypical meningiomas treated in our hospital between January 2008 to December 2017. Nineteen of them (55.88%) were male and fifteen patients (44.12%) were female with the male to female ratio 1.27:1. Their age at diagnosis ranged from 36-year- old to 80-year-old with a mean age of 60.81 years. Their initial clinical presentations include focal neurological deficits, signs of increased intracranial pressure, neuropsychological decline, seizure, and asymptomatic. The locations of tumors were as follows: Convexity = 10; falcine/parasagittal = 15; sphenoidal ridge = 8; foramen magnum = 1. We had 20 patients whose tumors were ≥5 cm in dimension. These 34 patients had been followed up for 1–84 months (median = 50 months) [Table 2]. Twenty nine patients (85.29%) underwent total resection of the tumor, whereas five patients (14.71%) had partial resection of their tumors during their first time of surgery. All patients who had partial tumor resection received postoperative adjuvant radiotherapy after their surgical wounds had been healed. The

further treatment modality of those patients having total tumor resection was based on the preference of the surgeons. During follow-up, we arranged regular postoperative brain MRI to all patients. If tumor recurrence or residual tumor with progression had been detected, reoperation followed by postoperative adjuvant radiotherapy was recommended if there was no contraindication.

Twenty patients (58.82%) had finished adjuvant conventionally fractionated radiation therapy, and their radiation dose ranged from 50 to 60 Gy. Of these 20 patients, nine (26.47%) of them were treated by having total surgical resection of their tumors followed by immediate postoperative adjuvant radiotherapy, and they showed no tumor recurrence during follow-up; five cases underwent partial resection of the tumors followed by immediate postoperative adjuvant radiotherapy; six patients received radiotherapy after tumor recurrence, and all of them had total surgical resection of the tumor in their first operation. 12 patients (35.29%) had tumor progression or recurrence during follow-up and their progression-free period ranged from 7 to 27 months with an average 17.67 months. Of these twelve patients, seven of them underwent total resection of the tumor in their first surgery without immediate postoperative adjuvant radiotherapy; five cases underwent partial resection of tumors with immediate postoperative adjuvant radiotherapy [Table 3]. The tumor locations of these eleven patients were as follows: Convexity = 2; falcine/parasagittal = 8; sphenoidal ridge = 1. We notice that falcine/parasagittal atypical meningiomas recur more frequently, probably due to superior sagittal sinus involvement which hinders the absolutely complete removal of the tumor. Five of these nine patients were proved to have malignant transformation to anaplastic meningiomas in the subsequent operations; in this particular group, one patient had expired due to disease progression.

Within these 34 patients, 23 patients (67.65%) had favorable outcome with GOS score 4 or 5, ten patients (29.41%) had unfavorable outcome with GOS score 2 or 3, and one patient (2.94%) had expired 5 years and 3 months after the diagnosis due to disease progression [Table 3].

Table 2: Clinical Characteristics of Patients

Characteristics	Value
A) Patients (*n*)	34
B) Male/Female (ratio)	19/15 (1.27:1)
C) Mean age of diagnosis (years) (range)	60.81 (36-80)
D) Follow-up period (months) (range)	50 (1-84)
E) Initial clinical presentation, frequency (%)	
▪ Focal neurological deficits	12 (36.36)
▪ Signs of increased intracranial pressure	10 (30.31)
▪ Neuropsychological decline	7 (21.21)
▪ Seizure	2 (6.06)
▪ Asymptomatic	1 (3.03)
F) Tumor location, *n* (%)	
▪ Convexity	10 (29.41)
▪ Falcine/Parasagittal	15 (44.12)
▪ Sphenoidal ridge	8 (23.53)
▪ Foramen magnum	1 (2.94)
G) Dimension of tumor (cm), *n* (%)	
▪ ≥5	20 (58.82)
▪ <5	14 (41.18)

Table 3: Treatment Modalities of Patients

Treatment Modalities	Total Resection Only	Total Resection And Immediate Radiotherapy	Partial Resection And Immediate Radiotherapy
Number of patients	20	9	5
Tumor recurrence	7	0	0
Residual tumor with progression	0	0	5
Anaplastic transformation in the following surgery	3	0	2
GOS=5	14	6	0
GOS=4	1	2	0
GOS=3	0	1	4
GOS=2	5	0	0
GOS=1	0	0	1

GOS= Glasgow outcome scale

DISCUSSION

Most meningiomas are benign but some of them are aggressive with high recurrence rate as well as increased rate of mortality and atypical meningiomas belong to the aggressive one.[15,19,21] In 2000, the WHO classified atypical meningiomas as WHO Grade II.[15] Benign meningiomas are female predominance, but atypical meningiomas seem to be more common in male patient;[14,17] our series showed the same with male to female ratio 1.25:1. Cerebral convexity is reported to be the common site of atypical meningioma,[14,23,24] but we had more at the region of falcine/parasagittal. Surgical resection remains the standard and effective treatment modality to meningiomas, and the extent of resection plays an important role in the tumor recurrence.[17,18,20-22] Simpson proposed a grading system based on the degree of surgical excision [Table 4].

Table 4: Simpson Grading System on Meningioma Resection

Simpson Grade	Definition
I	Macroscopically complete tumor resection with removal affected dura and underlying bone
II	Macroscopically complete tumor resection with coagulation of affected dura only
III	Macroscopically complete tumor resection without removal affected dura or underlying bone
IV	Subtotal tumor resection
V	Decompression with or without biopsy

Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957;20:22-39

The recurrence rate at 5 years was 9% for Simpson Grade 1 resection, 19% for Simpson Grade 2 resection, and 29% for Simpson Grade 3 resection.[15,20] Simpson Grade 1 resection is the ideal goal; however, some tumors cannot be totally excised because their anatomical locations and their close relationship to the surrounding vital neural or vascular structures.[15] In cases of incomplete resection of atypical meningioma, administration of adjuvant radiotherapy is included in the treatment algorithm.[14,18,19] However, for those who have undergone complete surgical resection of the atypical meningiomas, postoperative adjuvant radiotherapy is debatable.[17,18,22,23] There are several studies showing the promising results on local control by adjuvant radiotherapy.[24-26]

In our series, we had nine patients having total surgical tumor resection with immediate adjuvant radiotherapy, and none of them demonstrated tumor recurrence during follow-up; 20 patients underwent total surgical tumor resection only at initial presentation, but seven of them revealed tumor recurrence during follow- up. Because of small case numbers, the data for radiotherapy are difficult to analyze, but it seems that surgery with immediate adjuvant radiotherapy at initial presentation is superior to surgery only in local control. Multicenter, prospective trials are necessary to evaluate the potential impact of radiotherapy on local control and survival in patients with atypical meningioma. Our follow-up period ranged from 1 to 84 months with median 50 months is too short to draw a comment on the longterm value of adjuvant radiotherapy for atypical meningioma, also the possible side effects of radiation such as radiation necrosis, deterioration of neurological function, and induction of further tumors need longterm observation.[24]

In our series, 3 men and 2 women (5 patients, 14.71%) were proved to have malignant transformation to anaplastic meningioma from atypical meningioma during the following operations to their recurrent disease. Their tumors were all located at falcine/parasagittal and were bigger than 5 cm in dimension. The initial treatment modality of these five patients was as follows: Two patients underwent partial resection of the tumor with immediate postoperative adjuvant radiotherapy; three patients underwent total tumor resection only. The average time interval between the last surgery to their atypical meningiomas and the first surgery to their malignant transformed anaplastic meningiomas was 14.25 months. Their clinical outcome became poor after malignant transformation to anaplastic meningiomas was established, and one of them died 5 years and 3 months after the initial presentation. Malignant progression of recurrent meningiomas has been reported previously.[14,16,27] Computed tomography (CT) and MRI play important roles in the diagnosis of meningioma. Typically, meningiomas are sharply demarcated and hyperdense on CT. On MRI, the tumor is iso- or hypointense on noncontrast T1-weighted image, and iso- or hyperintense on T2-weighted image; homogeneous enhancement is observed after contrast administration. Tomura et al. pointed out that in their study, partial or complete disappearance of the peritumoral band had been seen in a majority of atypical meningiomas; more than half of the atypical meningiomas exhibited lack of dural tail sign and a relatively large amount of perifocal edema.[28] Filippi et al. reported that atypical and malignant meningiomas tend to be markedly hyperintense on diffusion-weighted MR images and exhibit marked decreases in the diffusion constant (D_{av}) or apparent diffusion coefficient values when compared with normal brain parenchyma.[29] Although atypical meningioma is diagnosed based on the histological criteria, if the radiological characteristics of a meningioma give the possible diagnosis of atypical meningioma before surgery, neurosurgeons should prepare to remove the tumor completely as possible as they can. Despite advances in imaging, neuropathology, microsurgery, and radiotherapy, meningiomas remain a challenging clinical problem, especially the recurrent disease. Recurrent meningiomas bring the subsequent operations or radiotherapy which may increase the morbidities and worsen the quality of life of patients. Besides this, recurrent meningioma can have malignant biological progression which sometimes is responsible for grave prognosis. In some situations, there are conflicts between the preservation of optimum function and the need to treat the tumors. Understanding the nature of meningioma of different WHO grading, the immediate and delay risks and benefits of surgery and radiotherapy including long-term possible risks of the second neoplasm induced by radiotherapy are crucial for physicians to create individualized treatment strategy for meningioma patients at their initial presentation to achieve the best outcome.

CONCLUSION

The decision to treat a meningioma is dependent on tumor size and associated symptoms. Many small incidentally discovered intracranial meningiomas may be observed expectantly. Evidence for meningioma development and growth associated with reproductive and hormonal factors, especially in premenopausal women is not compelling. Contrast-enhanced cranial CT and MR imaging are the predominant imaging techniques used in the diagnosis and management of meningiomas; however, in selected cases, MR spectroscopy and octreotide scintigraphy may be useful. Surgery, when complete and image-verified, results in the best long-term survival and freedom from disease recurrence. Radiotherapy is recommended for tumors incompletely resected or recurrent following initial surgery. Stereotactic radiosurgery is increasingly used both as primary therapy (for example, in an elderly patient with a tumor in an eloquent brain location) and as salvage therapy for recurrent meningioma. Long term outcome studies, however, are lacking. Hormonal, immunotherapy, and chemotherapy for recurrent meningioma having failed surgery and radiotherapy is only partially effective. Of the agents studied, hydroxyurea appears the most effective. However, there is a paucity of clinical trials on which to make decisions regarding these agents. In summary, meningiomas are benign extra-axial CNS tumors, which when symptomatic are typically treated with definitive resection. However, small asymptomatic meningiomas may be observed and followed by sequential MR and CT imaging. Radiation therapy is suggested for residual and recurrent disease following surgery and for symptomatic meningiomas in surgically hazardous locations (for example, the cavernous sinus). Our study reveals that early postoperative adjuvant radiotherapy seems to play a role in local control. Atypical meningioma can have malignant transformation to anaplastic meningioma, so aggressive treatment and follow up are essential to manage this particular tumor.

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Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Milan K. Senjaliya, Ankur Bhupendrakumar Pachani, Mayur Mhatre, Parth D. Lalakia. A Retrospective Critical Analysis of Intracranial Atypical Meningiomas Managed At a Tertiary Care Centre with a Rural Set up in Rural Area of India. Int J Med Res Prof. 2018 Mar; 4(2):318-22. DOI:10.21276/ijmrp.2018.4.2.072