Original Article

Long term outcome analysis of role of radiotherapy in Grade I meningiomas: A single centre experience from North India

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Abstract

Background: Intracranial meningiomas are the second most common tumor of the central nervous system. Grade I tumors are the most common variety of meningioma and have a benign course. Surgery is the mainstay of treatment. Radiotherapy (RT) decreases the local recurrence rates and progression in patients with subtotal excision (STE). The authors present our institute's experience in combined modality management of 18 successive patients of Grade I meningioma. **Materials and Methods:** We retrospectively reviewed 18 patients of Grade I meningioma treated in our institute from 2003 to 2011. Clinical characteristics and treatment modality in form of surgery and RT were noted. Statistical analysis was done with regards to recurrence free survival and overall survival using Kaplan–Meier survival analysis. **Results:** The median age of the patients was 52.5 years. Seven patients were males and 11 patients were females. The median duration of symptoms was 8 months. Headache was the most common presenting symptom followed by vomiting, seizures, motor weakness and visual deficits. Five patients underwent complete excision while 13 had STE. 11 patients received early RT while 5 patients received RT at recurrence. Median RT dose delivered was 50 Gy. RT had significant effect on local control especially in subtotal resections, with overall 93.75% local control rates. **Conclusions:** Grade I meningiomas represent a benign neoplasm. The mainstay of therapy is gross total resection at the initial surgery. Postoperative adjuvant RT should be offered to patients with subtotal resection. Long-term follow-up is important as local recurrences and progression can develop years after the initial treatment.

Key words: Meningioma, radiotherapy, recurrence

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Introduction

Intracranial meningiomas are the second most common tumor of the central nervous system, accounting for 15–20% of all primary brain tumors in adults.[1] Meningiomas are histopathologically classified as Grade I, II, or III according to the 2000 World Health Organization (WHO) classification system.[2] Ninety percent of meningiomas are WHO Grade I benign tumors.[3] Evidence in the literature comes mainly from retrospective studies carried out over long periods in which diagnostic workup changed dramatically and therapeutic modalities in form of surgical techniques and radiotherapy (RT) techniques have also evolved significantly. The optimal method of treatment consists of maximal safe resection (MSR). Postoperative adjuvant RT decreases progression of tumor in incompletely resected tumors.[4] It decreases the local recurrence and progression and can be used as a adjuvant treatment modality after incomplete surgical resection.[4] We herein report our institutional experience of 18 successive patients of intracranial Grade I meningiomas being treated from 2003 to 2011.

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Materials and Methods

Patient population and initial evaluation

We retrospectively reviewed the patients of Grade I meningioma from March 2003 to April 2011 treated in our institute. Total number of patients was 18. We reviewed the records of these patients to extract the following information: Age, sex, clinical symptoms, histology, radiology (computed tomography/magnetic resonance imaging [MRI]), tumor extent, and extent of surgical resection, radiation (technique, total dose, dose per fraction, number of fractions), toxicity, response, recurrence, progression and death.

Surgico-pathological review

Operative notes were reviewed to determine intraoperative suspicion of invasion, gross tumor extension into adjoining structures, and completeness of resection. Pathology reports were obtained for all patients and the tumors were graded as per WHO histopathological grade.[2]

Treatment

Surgery and RT were used in the treatment. MSR was the surgical approach and RT was delivered in conventional 1.8–2 Gy per fraction. Median RT dose was 50.0 Gy which ranged from 45 to 54 Gy. RT planning evolved with time and expertise and patients were planned with two-dimensional and three-dimensional conformal radiotherapy (3DCRT) techniques. Six patients received RT with two-dimensional technique and the ten patients received RT with 3DCRT technique.

Follow-up

The period between the first complaint and diagnosis was registered as symptom duration. Survival, recurrence and progression information were collected through chart review, patient or relative contact. Response evaluation was noted both clinically and radiologically and RECIST criteria were applied.[5]

Statistical analysis

SPSS version 15 was used for statistical analysis. The Kaplan–Meier survival analysis was done for analyzing recurrence free survival (RFS) and overall survival (OS).[6]

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Between March 2003 and April 2011, 18 patients of Grade I intracranial meningioma were registered in our department. The median age of the patients was 52.5 years and ranges from 24 years to 66 years. Seven patients (38.9%) were males and 11 patients (61.1%) were females. The tumor was located at the convexity in 8 patients (44.4%), at the skull base in 5 patients (27.7%), parasagitally or along the falx in 3 patients (16.6%), and in other locations including the intraventricular regions or orbit in 2 patients (11.1%). The median duration of symptoms was 8 months. Headache was the most common presenting symptom manifesting in all 18 patients followed by vomiting, seizures, motor weakness and visual deficits. No patient had a history of neurofibromatosis.

Table 1: Patient characteristics, treatment details and outcome

Age	Sex	Surgery	Early postoperative RT	Progression/recurrence	T/t of progression	Status
36	Female	STE	Yes	No	-	Alive, asymptomatic
29	Male	STE	Yes	No	-	Alive, asymptomatic
34	Female	GTE	No	No	-	Alive, asymptomatic
40	Female	STE	No	Yes	S+RT	Alive, asymptomatic
60	Female	STE	No	Yes	S+RT	Alive, asymptomatic
24	Male	STE	No	Yes	S+RT	Progressive disease
62	Female	STE	Yes	No	-	Alive, asymptomatic
32	Female	STE	Yes	No	-	Alive, asymptomatic
62	Male	STE	Yes	No	-	Alive, asymptomatic
40	Female	GTE	No	Yes	S+RT	Alive, asymptomatic
53	Female	STE	Yes	No	-	Alive, asymptomatic
66	Male	GTE	No	Yes	S+RT	Alive, asymptomatic
58	Female	STE	Yes	No	-	Alive, asymptomatic
63	Male	STE	Yes	No	-	Alive, asymptomatic
56	Female	GTE	No	No	-	Alive, asymptomatic
49	Male	STE	Yes	No	-	Alive, asymptomatic
54	Female	STE	Yes	No	-	Alive, asymptomatic
52	Male	GTE	Yes	No	-	Alive, asymptomatic

RT: Radiotherapy; STE: Subtotal excision; GTE: Gross total excision

Treatment details

Treatment modalities consisted of surgery and RT. All patients underwent primary surgery, out of which 5 patients underwent gross total excision (GTE) and 13 underwent subtotal excision (STE). The reasons for STE were adherence to dura and adjacent brain matter, and proximity to vital neural structures. Early postoperative RT (within 6 weeks of surgery) was delivered in 11 patients and 7 patients were kept on regular follow-up. 5 out of these 7 patients had recurrence and received RT when they had recurrence of disease, while 2 patients did not receive any RT [Table 2]. For RT planning, gross tumor volume (GTV) was defined as the macroscopic lesion visible on the contrast-enhanced imaging and/or the resection cavity. The planning target volume was calculated from the GTV using a uniform three-dimensional expansion of 1 cm. Median RT dose was 50.0 Gy which ranged from 45 to 54 Gy.

Clinical and radiological response

After treatment completion, patients were assessed for response both clinically and radiologically. All were asymptomatic and had significant improvement in symptoms. Eleven patients who received early postoperative adjuvant RT were alive and did not have recurrence or progression irrespective of the extent of resection. Of these eleven patients, ten patients had initial STE while only one patient had initial GTE.

But, five out of seven patients who did not receive postoperative adjuvant RT had recurrence and progression. Of these five, three had initial STE only while two had initial GTE. All the five recurrence cases were managed with re-excision and further localized RT. Four of them are alive with clinical and radiologically free from disease while further disease progression was seen in 1 patient.

Table 2: Treatment details

Treatment modality	Number of patients (%)
Extent of resection	
Complete (GTE)	5 (27.8)
Subtotal (STE)	13 (72.2)
Initial treatment approach	
Surgery only	7 (38.9)
Surgery+RT	11 (61.1)
RT	
Adjuvant (early)	11 (61.1)
After progression	5 (27.7)
No RT	2 (11.1)
Dose (median)	50.0 Gy
Dose (range)	45-54 Gy
RT modality	
Two-dimensional	6
Three-dimensional	10

RT: Radiotherapy; STE: Subtotal excision; GTE: Gross total excision

Overall survival and recurrence free survival

Median duration of follow-up was 77 months (range, 15–126). Mean OS was 119.7 months.

Mean RFS was 95.76 months. 5 year overall RFS was 78% and 10 year overall RFS was 60% [Figure 1]. Early adjuvant postoperative RT had significant impact on RFS. Mean RFS for patients with early postoperative RT was 119.7 months while for patients who did not received early postoperative RT was 58.14 months only (P = 0.2).

Total number of patients who received RT (early or after recurrence) was 16 and only 1 of them had progression even after RT. Thus the local control rate after RT for patients in this study was 93.75%.

Treatment toxicity and compliance

There were no surgical complications in form of postoperative deaths or wound complications. RT toxicity occurred in all patients in form of Grade I-II dermatitis and there was no Grade III or higher toxicity. All patients completed treatment with no significant toxicity or treatment interruption.

Discussion

Intracranial meningiomas are the second most common tumor of the central nervous system, accounting for 15–20% of all primary brain tumors in adults.[1] Meningiomas are derived from nonneuroepithelial progenitor cells known as arachnoid cap cells.[3] Risk factors for developing meningiomas range from hereditary syndromes, chromosomal deletions, and previously ionizing RT.[3] No patients in our series had any history of these risk factors. The incidence of these tumors increases with age and is most commonly seen in sixth and seventh decades of life.[7] The median age of patients in our series was 52.5 years.

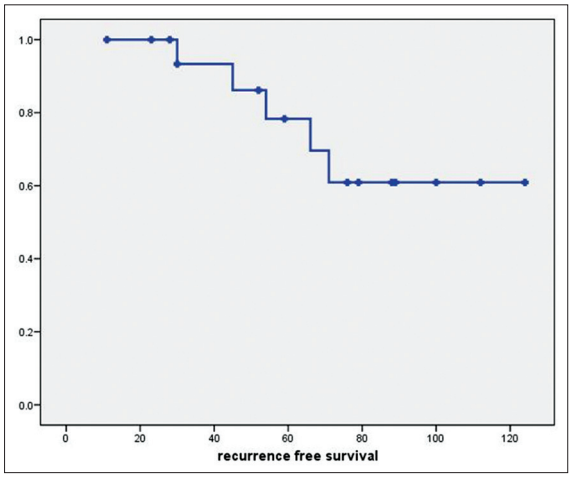

Figure 1: Kaplan–Meier curve showing recurrence free survival

Histologically they are classified as Grade I, II, or III according to the 2000 WHO classification system.[2] Ninety percent of meningiomas are WHO Grade I benign tumors.[3] Most of the Grade I meningiomas asymptomatic and discovered incidentally, thereby earning the name incidentaloma.[3] However, if the meningioma growth causes secondary compression of vital structures, then the patient becomes symptomatic. The most common locations of meningiomas, in descending order of frequency, are convexity (19–34%), parasagittal (18–25%), sphenoid and middle cranial fossa (17–25%), frontal base (10%) and posterior fossa (9–1 5%), cerebellar convexity (5%), cerebellopontine angle (2–4%), intraventricular (1–5%), and clivus (1%).[8] In our series, the most common location was the convexity (44.4%) followed by the skull base (27.7%) and parasagital (16.6%). The clinical presentation in these patients is determined by tumor location and size. Typical clinical presentations have been extensively described in the literature, the most common of which are headache, seizures, visual symptoms, motor weakness and mental status changes.

The optimal method of treatment consists of MSR.[9] Surgery offers immediate relief of mass effect and allows histopathological confirmation of diagnosis. Gross total resection (GTR) is preferred approach but the frequent association with vital neural structures often makes GTR challenging. In our series, only 27.7% of patients underwent complete (GTR) surgical excision while the rest 72.3% of patients underwent STE only. The reasons for STE were adherence to dura and adjacent brain matter, and proximity to vital neural structures. The extent of surgical resection is the most important factor in the prevention of recurrence. In 1957, Simpson retrospectively reviewed the postoperative course of 265 patients who had meningiomas, 55 of whom experienced recurrences (21%). Recurrence rates were higher in patients with subtotal resection as compared to GTR.[9] Mathiesen *et al*. also reported decreased recurrence rates with increasing extensiveness of resection.[10] Soyuer *et al*. reported 92 patients treated at M. D. Anderson Hospital and found that patients who had a GTR had a favourable PFS at 5 years of 77% compared to 52% in patients who received a subtotal resection.[4]

However, their anatomic location near vital neural structures and at the base of skull makes complete resection of the tumor difficult and for that reason, a subtotal resection and adjuvant RT is frequently the optimal treatment regimen. Because of the well-circumscribed nature and slow progression rate of WHO Grade I tumors, surgery is a reasonable option for symptomatic lesions that are completely resectable with acceptable morbidity. Otherwise, subtotal resection followed by postoperative RT is an effective treatment option.[11] Definitive RT may be offered to patients with tumors that are not amenable to surgery and to those who are medically inoperable.[12]

Patients with Grade I benign diseases have a favorable long-term survival, which can increase to more than 90% by adding RT. Condra *et al*. examined 229 patients treated with external-beam RT for benign and atypical disease at the University of Florida between 1964 and 1992. The 10-year local control improved to 90% with the addition of RT, compared with 80% and 40% in those receiving gross total and subtotal resection alone, respectively.[13] Brell *et al*. treated 30 cavernous sinus meningiomas with fractionated RT in Barcelona, Spain, between 1997 and 2001. Patients were treated with a once-daily fraction of 2 Gy to a median of 52 Gy. The actuarial local PFS was 93% at 4 years.[14] In our series, RFS was significantly increased with addition of early postoperative adjuvant RT which was more effective in patients with subtotal resection. Of the 13 patients who had subtotal resection, 3 did not receive RT and all three had progression. Overall the local control rate after RT for patients in our study was 93.75%.

Radiosurgery may be used for patients who have recurrent or residual tumors or as a primary treatment in patients unwilling or unable to undergo surgery and who possess a lesion with the typical imaging characteristics of a meningioma. Radiosurgery for meningiomas is usually performed with the gamma knife (GK).[15] Modified linear accelarators or proton beam can also be used. This method of treatment is designed for smaller tumors ≤3 cm, located more than 3 mm from radiosensitive structures, such as the optic nerve.[16] Stafford *et al*. treated 178 patients with radiosurgery at the Mayo Clinic. The 5-year cause-specific survival rate was 100%, and local control was 98%.[17] Kreil *et al*. treated benign skull-base meningiomas with GK radiosurgery and reported 5 year and 10 year PFS of 98.5% and 97.2%, respectively.[18] Hasegawa *et al*. reported on 115 patients with benign cavernous sinus meningiomas treated with GK radiosurgery. The local control rates at 5 and 10 years were 94% and 92%, respectively.[19]

The present literature and evidence argues in favor of early RT in patients with subtotal resections.[4] In our series also, 3 out of 13 patients of initial subtotal resection had progression when early RT was not given. One main argument commonly used against early RT was the development of neurocognitive deficits. However, with modern RT techniques the risk of RT related neurocognitive deficits is very low because of sparing of normal tissues.[20,21]

Extent of surgical excision and early RT are important prognostic factor in local control.[22,23] In our series also, early adjuvant RT had a significant impact on local control

and recurrence. Long term follow-up with periodic MRI and thorough neurological examination is recommended because meningiomas may recur years after treatment.

The management of Grade I meningiomas is a paradigm of cooperation between clinicians, surgeons and pathologists from establishing diagnosis to organizing the therapeutic strategy. With new techniques, there is a significant improvement of therapeutic standard and meningiomas represent a model of therapeutic implementation and achievement in oncology. Novel strategies including advanced RT techniques such as IMRT, SRS, SRT and proton therapy should be prospectively investigated

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