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Clinical Study

The role of radiotherapy in the treatment of subtotally resected benign meningiomas

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Summary

Thirty-six patients with benign meningioma were treated for primary or recurrent disease by subtotal resection and external beam irradiation from 1968–1986 at Massachusetts General Hospital. Comparison is made with 79 patients treated by subtotal surgery alone from 1962–1980.

Progression-free survival for 17 patients irradiated after initial incomplete surgeery was 88% at 8 years compared with 48% for similar patients treated by surgery alone ($p = 0.057$). 16 patients incompletely resected at time of first recurrence were irradiated and 78% were progression-free at 8 years while 11% of a similar group treated by surgery alone were progression free ($p = 0.001$). Long term overall survival was high and similar in both control and study groups. Two patients were irradiated at second recurrence and 1 patient at third recurrence.

Twenty-five patients were treated with photons alone and have a median follow-up of 57 months, 6 patients have recurred at doses 45–60 Gy. Eleven patients were treated with combined 10 MV photons and 160 MV protons utilizing 3-D treatment planning. These patients have been followed for a median of 53 months and none have failed to date. Eight of 11 received 54–60.4 Gy and $3/11 > 64.48$ Gy. Sex, age, pathology grade and score, surgery and timing of radiation therapy were not associated with significant differences in failure patterns within the irradiated study group ($p < 0.1$). Complications have been seen in 6 irradiated patients.

Introduction

Meningiomas are usually benign tumors originating in the brain and spinal cord meningeal surfaces. They represent approximately 15–20% of all CNS neoplasms and are rarely a cause of death. They have, however, a high tendency for post-surgical recurrence especially after incomplete excision. Certain tumors invading bone or major vessels may preclude a complete excision.

Several authors have studied the value of radiotherapy after primary or salvage incomplete excision. Conflicting reports on efficacy exist, some suggesting only marginal benefit with significant and unacceptable morbidity [1–4] while other reports strongly favor its use [5–14]. In order to better assess the indications for adjuvant irradiation following subtotal resection in benign meningioma we have reviewed the experience at our institution, the Massachusetts General Hospital. As a secondary goal, we wished to look for a dose-response relationship and to assess complications of radiotherapy in these patients.

Clinical material and methods

From 1968 to 1986, 36 patients diagnosed with benign meningioma were treated with radiation at the Massachusetts General Hospital for primary or recurrent disease following subtotal resection or at the time of progression without surgical intervention. Their outcome was compared to a previously reported group of 79 patients (controls) treated at the same institution during the period 1962–1980 for primary benign meningioma with subtotal resection alone [15].

Radiotherapy was delivered to 17 patients immediately after primary incomplete resection, to 16 patients after first recurrence, to 2 patients after second recurrence, and to one patient after third recurrence. A curative surgical attempt before radiotherapy was performed in 21 patients as part of a primary or salvage treatment procedure. Fifteen patients underwent radiation after biopsy (6 pts.) or at time of progression without prior salvage surgery (9 pts.). The referral criterion for radiotherapy after first surgery, or at recurrence, or not at all, was referral physician preference.

The median age was 43.5 years (range 16–74). The male : female ratio was 1 : 2.3. The anatomical location of the 36 tumors are listed in Table 1. All patients were treated with Megavoltage gamma- or X-rays, and since 1980, 11 patients underwent treatment with combined 10 MV X-rays and 160 MV protons (Harvard Cyclotron Laboratory). This group of patients benefited additionally from a sophisticated 3-dimension planning system with CT imaging allowing dosimetric optimization (i.e. improvement in dose distribution to precisely designed treatment volumes).

Histological confirmation was obtained in all patients at the initial surgical resection or biopsy. The grading of tumors was based upon traditional criteria for diagnosing degree of anaplasia in meningiomas (i.e. the presence of hypercellularity, necrosis, mitotic figures, and brain invasion). Typical benign (31 pts.) and atypical benign (5 pts.) meningiomas were included. In 18 patients of the study group and in 53 of the control group in whom the slides of the first surgery could be reviewed, a score ranging from 0 to 3 was assigned based upon a number of histopathologic independent predictors of progression-free survival (i.e. the presence of sheeting: the presence of nucleoli; and less than 10% meningothelial pattern) [16]. The remaining slides were unavailable for review.

Tumor progression was assessed by radiological documentation of an increase in size of the tumor lesions with or without worsening of old symptoms or development of new symptoms. Median follow-up for the irradiated study group was 88 months (range 7–345) and 72 months (range 7–321) for the surgery alone group.

Progression-free survival was analyzed comparing patients who underwent radiotherapy immediately after primary incomplete surgery (17 pts.) versus the whole control group (79 pts.). Patients who underwent radiation treatment after first recurrence with or without additional surgery (16 pts.) were compared to a control subgroup composed of patients treated after first failure with surgery alone (18 pts). All analyses were performed using SAS statistical analysis package [17]. Progression-free survival curves were estimated using the Kaplan-Meier method and the logrank test was used to assess differences in these curves. Chi-square or Fisher's exact tests were used to test for association between treatment groups and possible prognostic factors (sex, pathologic score and grade, and location). A t-test was used to compare age in the 2 treatment groups. Cox proportional hazards model was used for multivariate analysis to assess the simultaneous effects of treatment group and age or pathologic score on progression-free survival.

Results

Figure 1, shows progression-free survival rates of those patients who underwent radiotherapy immediately after primary incomplete resection versus the whole control group. The irradiated patients fared better than the surgical only group (88% versus 48%, 8-year progression-free survival) ($p = 0.057$). The radiotherapy group was significantly younger than the surgery only group (average age = 46 and 55 years, respectively, $p = 0.02$). A

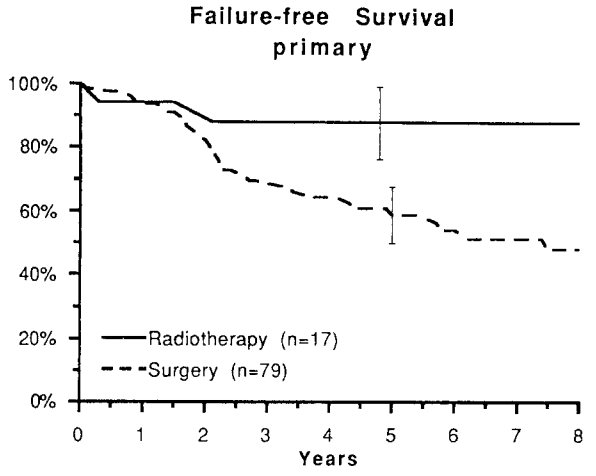


Fig. 1. Comparative progression-free-survival rates after primary subtotal excision with or without postoperative radiotherapy.

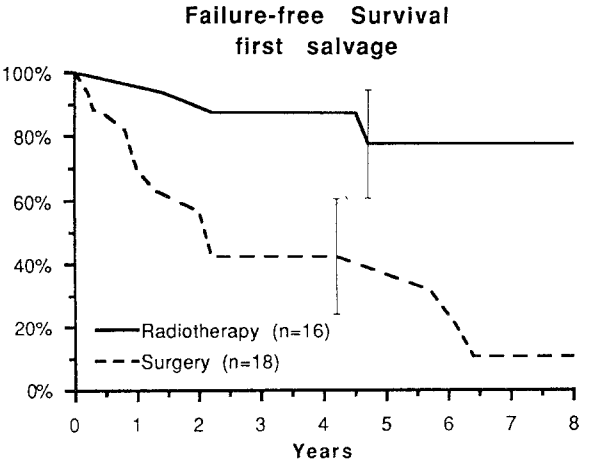


Fig. 2. Comparative progression-free-survival rates after first salvage subtotal excision with or without postoperative radiotherapy.

multivariate analysis found age to have little effect ($p > 0.1$) and treatment group to have a marginally significant effect on time to first failure ($p = 0.07$). Figure 2 shows the progression-free survival rates of those patients who underwent radiotherapy alone or combined with surgery as part of a salvage procedure after first recurrence. Again, the irradiated patients performed significantly better than the surgery only group (78% versus 11%, 8-year progression-free survival, $p = 0.001$). More radiotherapy patients had pathology scores of 2 or 3 (12/16 or 75%) than the surgery alone group (2/11 or 18%, $p = 0.006$). A multivariate analysis found both treatment group ($p = 0.06$) and score ($p = 0.03$) to have substantial effects on time to second failure. However, it is necessary to emphasize that pathology scores were only available in 18/36 of the study group and in 55/79 of the control group.

The two patients who underwent radiotherapy as part of their salvage after second failure are controlled 240 and 48 months after treatment, respectively. The only patient who was salvaged with radiation after third failure died of a myocardial infarction 52 months later without evidence of tumor progression.

Intercurrent disease (i.e. lung cancer) was the cause of death of one patient 60 months after completing radiotherapy; there was no progression of meningioma. One patient died of a stroke 57 months after completing radiation treatment for a recurrent tumor encasing the right carotid artery and the optic chiasm; this was consistent with tumor progression and was considered a disease related death. The disease also progressed in five other patients after radiotherapy. Two are alive with regrowth. Of these, one patient treated for a recurrent left parasellar tumor presented a progression of symptoms and radiological hydrocephalus which was considered consistent with tumor progression and recently has required a shunt. The other patient was treated for a recurrent sphenoid wing meningioma and presented 24 months later with radiological progression of his disease; he looks clinically stable 24 months after the last failure. Two additional failures are stable after surgical salvage. One of these patients presented regrowth of a right parasellar tumor 104 months post-radiotherapy and was salvaged with a subtotal removal; no progression has been detected 37 months after surgery. The second patient presented a recurrence of a large posterior fossa tumor 25 months post-radiation; a subtotal resection was performed and no progression has been detected 22 months after surgery. One patient with a sphenoid ridge tumor presented a symptomatic progression 4 months post-radiotherapy; even though there was no radiological proof of recurrence it was considered a failure. This patient has since died of

Table 1. Tumor location of 36 patients treated with subtotal excision and/or radiotherapy for benign meningioma

Location	Number patients
Parasellar	14
Sphenoid ridge	14
Posterior fossa	6
Brain convexity	1
Cervical spine	1
	—
	36

biliary cirrhosis. Two patients showed stable disease when lost to follow-up 49 and 18 months after radiotherapy. Table 2 shows the 6 post-radiotherapy failures.

Univariate analysis revealed that none of the possible prognostic factors studied (see Table 3) had a significant effect on progression-free survival ($p > 0.1$). However, proton-3-Dimension-planning showed a slight trend for better progression-free survival (0/11 failures, $p = 0.14$). Long-term overall survival was high and similar for both study and control groups 94% and 93% at 8 years, respectively. The median follow-up for 25 patients treated with photons alone is 57 months (range 4–239) and for 11 patients treated with protons and photons is 53 months (range 26–100). Figures 3 & 4 show examples of treatment planning incorporating the beams eye view concept.

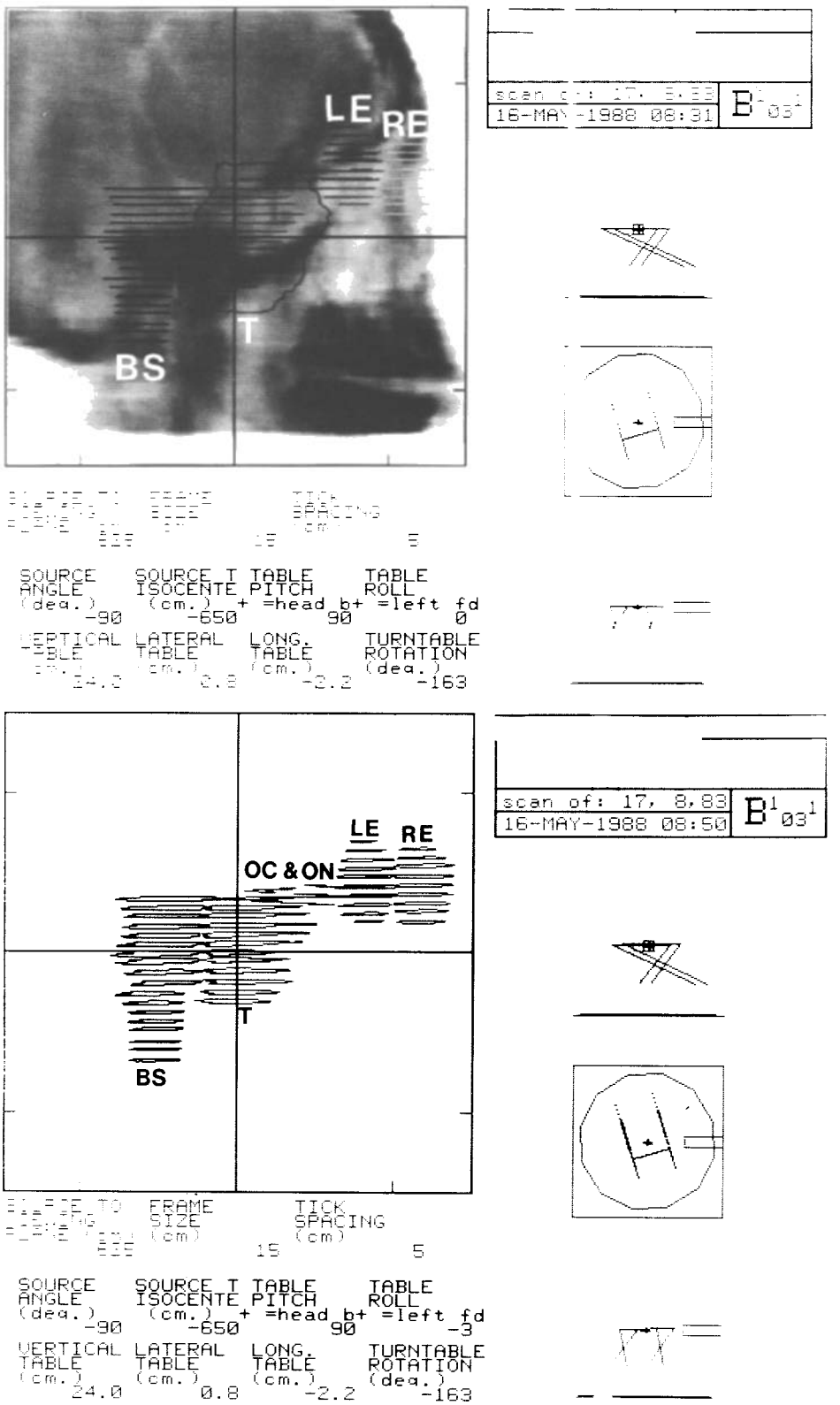
Morbidity seen after surgery was most frequently permanent cranial nerve disturbance. Radiation therapy was associated with hearing loss in 2 patients receiving 52 and 69.6 Gy. One additional patient treated with 55.8 Gy complained of memory loss and had hypogonadism. One patient treated with combined 10 MV x-rays and protons as a salvage for a large recurrent meningioma growing in the cerebello-pontine angle and invading the left parapharyngeal wall developed brain stem and cerebellar necrosis (proved surgically) after receiving a tumor dose of 71.6 CGE (Cobalt-Gray-Equivalent). The patient is living with involvement of several cranial nerves on the left side (i.e. V, VII, IX, X, XI, and XII) and marked cerebellar dysfunction 96 months after treatment. Table 4 lists complications of irradiation.

Discussion

Analysis of survival and recurrence in benign meningioma requires long-term follow-up because of the slow growing nature of these lesions. A relatively low failure rate ranging from 6 to 20% has been published involving the 60 to 80% of patients where a complete excision is technically feasible [1, 2, 3, 4, 5, 13, 14, 18]. Progressive or recurrent disease is most usually associated with an incomplete excision with a frequency of 30–74% in other published series [6, 9, 11, 12]. Salvage surgery, when undertaken, may yield additional morbidity in these circumstances. Tumors located at the sella, on the sphenoid ridge or posterior fossa account for nearly 40% of all locations but are only amenable to compete resection in 50% of those patients [19]. This contrasts with 85–90% total excision probability for much more accessible lesions such as those located in the brain convexity or the parasagittal-falx region [19].

Table 2. Local failure in 6 patients with benign mengioma treated by subtotal excision and external beam irradiation

Location current status	Pathology	Time to failure		
		Dose gray	Months	Status
Parasellar	–	45	17	Alive and well
Parasellar	Atypical	45	104	Alive with recurrent disease
Sphenoid ridge	Atypical	45	26	Alive with recurrent disease
Sphenoid ridge	Benign	51.3	57	Dead of disease
Sphenoid ridge	Atypical	60	4	Dead of disease
Posterior fossa	Benign	45	25	Alive and well



Figs. 3 & 4. Beam's eye view concept in treatment planning.

Although the reported perioperative mortality rates in meningioma range from 4 to 16% [1, 2, 4, 15, 18], state of the art neurosurgical techniques have lowered mortality and morbidity risks. Yamashita *et al.* [4], reviewed 336 patients treated from 1942 to 1980 and reported a 29% perioperative mortality rate for subtotally resected meningiomas. This contrasted with a 7% treatment related death rate after complete excision. Even analyzing the more recently treated subgroup of patients (i.e. after 1975), the perioperative mortality rate for subtotally resected lesions still was found to be high (i.e. 30%). Thus, those patients at higher risk for recurrence are also subjected to a relatively higher surgical related death risk. An adjuvant treatment such as radiation could play a role in preventing regrowth and thus avoiding a high-risk surgical procedure.

In our study we chose to compare the results after radiation therapy with a non-irradiated group of patients treated in the same institution with similar techniques during a similar period of time. The control group outcome was reported in a former paper [15] and has been updated for the present study.

To further validate the comparison we controlled for variables such as sex, age, tumor location and pathology grade and score. We observed better progression-free survival rates in irradiated patients whether they were treated after primary surgery or after second surgery for recurrence when surgery was subtotal in nature.

Formerly, a study was performed at our institution to identify histologic features associated with tumor recurrence and decreased progression-free survival in patients with subtotally resected benign meningiomas [16]. A significantly abbreviated progression-free survival was associated with the presence of 2 of the following features; sheeting of tumor cells, prominent nucleoli, or the presence of less than 10% meningothelial pattern. Thus, we assigned a score 0 to 3 to the surgical specimens available for review (18/36 irradiated and 58/79 control patients) based upon the number of the above defined independent histological predictors present.

Progression-free survival after primary treatment was markedly influenced by the pathology scores of both study and control groups, pooled together (59% scores 0 or 1 versus 20% scores 2 or 3; 8-year progression-free survival, ($p = 0.005$). No significant differences concerning progression-free survival between pathology scores were seen within the group of 18 irradiated patients indicating radiocurability of meningiomas irrespective of their pathology scores. Three out of 14 patients scored 0 or 1 failed, while 2/4 scored 2 or 3 progressed. (This may be explained simply by the small number of patients for whom the slides could be scored). These data suggest that local control

Table 3. 8-year actuarial analysis

		N	Local control (%)	Logrank p-value
Sex	M	11	91	0.9407
	F	25	81	
Age (yrs)	50	22	84	0.7760
	50	14	86	
Pathology score	0 & 1	14	74	0.7325
	2 & 3	4	75	
Pathology grade	Typical	15	75	0.6978
	Atypical	4	75	
Surgery	Resection	19	79	0.5541
	None	17	88	
Tumor	Primary	17	88	0.8569
	Recurrent	19	81	
Dose (Gy)	54	23	80	0.4054
	54	13	92	
XRT Technic	Protons	11	100	0.1421
	Photons	25	78	

Table 4. Complications of radiation therapy

Age/gender	Dose Gy	Complication
48 F	48.66	Chronic otitis
70 F	52.00	Hearing loss
74 M	55.8	Bilateral blindness
66 F		Memory loss hypopituitarism
33 F	69.5	Hearing loss*
38 F	71.62	Cerebellar/brainstem necrosis*

* Photon/proton/3-D planning.

6 patients with complications – average dose = 58.9 t-test.

30 patients complication free – average dose = 49.6 $p = 0.003$.

rates can be improved by the addition of radiation, and this may be of most benefit to those with high pathological scores. It is interesting that 3 of 5 atypical meningiomas progressed after irradiation suggesting increased biologic aggression in this category.

Resection or no-resection prior to radiotherapy did not influence the outcome of the patients in our study. Although a significant dose-control relationship was not evident, 5/6 failures received 45–51.3 Gy. No patients treated with combined x-rays and protons failed; 8/11 patients received 54–60.4 Gy while the remaining 3 patients were treated with 64.48 Gy or more. When comparing the outcome of the proton patients with the rest of patients treated with more 'standard' radiotherapy methods only a trend towards better control could be seen. We are unable to separate the effects of improvements in defining the tumor volume using CT and a computerized 3-dimension planning system from the relatively high doses delivered with protons.

According to the present study, radiotherapy after primary incomplete resection or at time of recurrence is equally effective. Thus, one could consider waiting until tumor regrowth has been documented to initiate radiotherapy as a salvage procedure. Carella *et al.* [8] and Wara *et al.* [14] observed better control rates when irradiation followed the first resection rather than at the time of recurrence which supports that rationale, but conflicts with our findings.

Conclusion

While long follow-up and large numbers of patients are required to clarify optimal timing of adjuvant irradiation in benign meningioma, our data appears to show the usefulness of such treatment in selected clinical settings. Since recurrences were seen at lower doses, doses greater than 54 Gy seem indicated, yet complications have been seen at ≥ 55.8 Gy. We believe that better treatment planning may allow higher dose delivery to tumor with sparing of critical normal tissue and we are currently studying the question of dose in patients with benign meningiomas randomized between 50.6 and 59.4 Gy given primarily with protons utilizing 3-D planning.

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