

Nonsurgical treatment options in the management of intracranial meningiomas

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1. ABSTRACT

Surgical resection is the treatment of choice for most intracranial meningiomas. We review the current state of adjuvant therapies, including radiation and chemotherapy. Conventional external beam radiation and stereotactic radiosurgery remain second-line options for patients unwilling or unable to undergo surgery. Radiation therapy is most useful in the setting of recurrent or residual tumor after surgical resection, where it is associated with a clear increase in the length of progression-free survival. This survival advantage is most pronounced with high-grade meningiomas, which have a much higher recurrence rate than low-grade meningiomas, even after gross total resection. In contrast, the role of chemotherapy in the treatment of meningiomas is limited. This treatment modality is often reserved for inoperable tumors or those refractory to radiation treatment. Furthermore, the choice of chemotherapy agents is limited. Hydroxyurea, a ribonucleotide reductase inhibitor, has modest clinical activity in meningiomas. In recent small clinical trials, somatostatin analogues have been moderately effective in controlling tumor growth.

2. INTRODUCTION

Surgical resection is the treatment of choice for most intracranial meningiomas. We review the current state of adjuvant therapies, including radiation and chemotherapy.

3. RADIATION THERAPY

Early clinical series showed little benefit from radiation for intracranial meningiomas (1). However, studies from the last 30 years have shown a clear role for radiation therapy in the treatment of meningiomas. Radiotherapy can take the form of either conventional external-beam radiation therapy delivered in a fractionated schedule or stereotactic radiosurgery.

4. CONVENTIONAL EXTERNAL-BEAM RADIATION THERAPY

Though surgical resection remains the first-line treatment for meningiomas, radiation therapy can be considered for patients unwilling or medically unable to

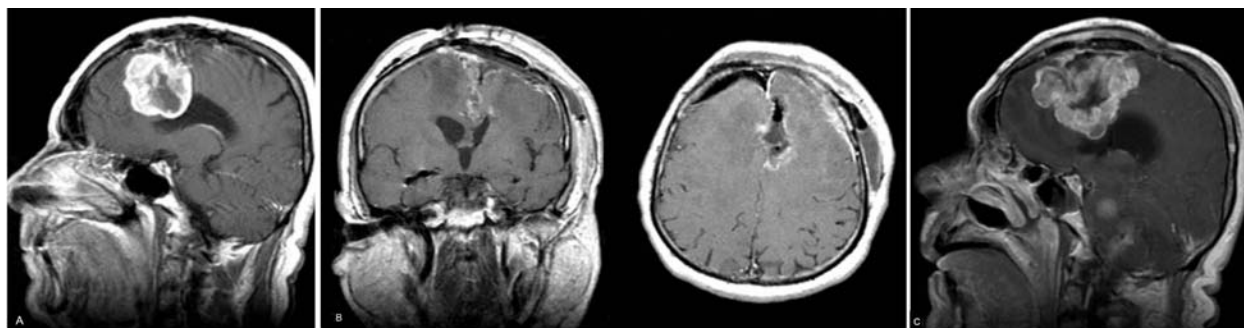


Figure 1. Postcontrast T1-weighted MR images of a 56-year-old man presenting with a rapidly growing extraaxial lesion (A) found to be consistent with a Grade II anaplastic meningioma (B) after gross total resection. Six months later, the patient had a massive recurrence at the site of resection (C) and diffusely in the posterior fossa (D). Despite aggressive surgical resection and radiation treatment, he died of his disease within 3 months.

undergo surgery. Glaholm and colleagues reported 186 patients with intracranial meningiomas who underwent external-beam radiation at the Royal Marsden Hospital between 1963 and 1983 (2). Wide-field radiation was used at doses of 50 to 55 Gy. Of their 186 patients, 32 were deemed inoperable and received only radiation therapy. Their 15-year actuarial rate of cause-specific survival was 46 percent. After radiotherapy alone, the Karnofsky performance scale score improved in 12 of these 32 (38 percent) patients with inoperable disease. At New York University Medical Center, Carella and colleagues reviewed their experience with radiation therapy at doses of 50 to 55 Gy in the management of meningiomas (3). All 11 patients who received radiation therapy as the primary treatment were alive in the follow-up period of 3 to 6 years. Of the 11 patients, neurological function had improved in nine.

Radiation therapy has also been validated for the control of residual tumor after surgery. The length of progression-free survival increases in patients who receive adjuvant radiation therapy after subtotal resection of a meningioma. The advantage of local control appears to hold true in cases where radiation was first administered after tumor recurrence. In 1975, Wara and colleagues published the initial series from University of California–San Francisco (UCSF), which consisted of 92 patients who underwent subtotal resection of a meningioma (4). During the 5 to 20 years of follow-up, the length of progression-free survival was significantly longer in the patients who received adjuvant radiation compared to those who did not. The recurrence rate of the former was 24 percent compared to 74 percent for the latter.

Subsequently, Barbaro and colleagues reported their experience with 84 patients with partially resected meningiomas (5). Of 30 patients who underwent subtotal resection alone, 18 (60 percent) had a recurrence compared to 17 of 54 (32 percent) patients who received postoperative radiation therapy. Between 1968 and 1986 at Massachusetts General Hospital, Miralbell and colleagues treated 36 patients with primary or recurrent benign meningiomas by subtotal resection and external beam irradiation (6). These patients were compared with 79 patients treated by subtotal surgery alone. The rate of progression-free survival at 8 years for 17

patients irradiated after a first incomplete surgery was 88 percent compared with 48 percent for similar patients treated by surgery alone. The rate of progression-free survival of 16 patients who underwent radiation therapy at the time of their first recurrence was 78 percent at 8 years compared to 11 percent for a similar group of patients treated by surgery alone.

Goldsmith and colleagues retrospectively analyzed 140 patients treated at UCSF from 1967 to 1990 to evaluate the results of radiation therapy after subtotal resection of intracranial meningiomas (7). Their median follow-up period was 40 months, with 5-year progression-free survival rates of 89 percent and 48 percent for benign and malignant meningiomas, respectively. For 117 patients with a benign meningioma, the 10-year progression-free survival rate was 77 percent. An improved progression-free survival rate was associated with higher radiation doses, a younger age, and treatment after 1980 but not with tumor size. Morbidity (3.6 percent) included sudden blindness or cerebral necrosis and death.

The group at the Mayo Clinic in Rochester reported 581 patients who underwent surgical resection of an intracranial meningioma from 1978 to 1988 (8). Twenty percent of these patients underwent subtotal resection. In those who underwent subtotal resection, the progression-free survival rates at 5 and 10 years were 61 percent and 39 percent, respectively. During the follow-up period, tumor recurred in 106 of the 581 patients. Progression-free survival tended to improve after the first recurrence with radiation with or without operation compared to patients undergoing only surgical treatment, but the difference was not significant ($P = 0.058$).

Atypical (World Health Organization [WHO] grade II) and anaplastic or malignant (WHO grade III) meningiomas pose a more formidable challenge than their benign counterparts (Figure 1). Recurrence rates are significantly higher for higher-grade meningiomas even after gross total resection. Engenhart and colleagues reported a 37 percent recurrence rate after a mean period of 27.2 months after gross total resection of atypical meningiomas (9). Interestingly, in four cases undergoing repeat operation for atypical meningioma, the proliferation



Figure 2. The Gamma Knife stereotactic radiosurgery unit. A fixed headframe system allows radiation to be delivered precisely to targeted intracranial regions.

rate associated with the recurrent tumors was higher than the proliferation rate associated with the first tumor in three cases. Jaaskelainen and colleagues reported recurrence rates of 38 percent and 78 percent for grade II and grade III meningiomas, respectively (10).

In the UCSF study, Goldsmith and colleagues reported 23 patients with a malignant meningioma treated with adjuvant radiation therapy (median dose, 54 Gy) after subtotal resection (7). The overall 5-year survival rate for these patients was 58 percent. The 5-year rate of progression-free survival was 48 percent compared with 89 percent for patients with benign meningioma. The 5-year survival rate of patients receiving more than 53 Gy was 63 percent, which was significantly better than the 17 percent rate associated with patients who received a lower dose. Coke and colleagues reported a comparable 60 percent 5-year survival rate for patients undergoing surgery and adjuvant radiation therapy (61 Gy) for malignant meningioma (11).

Because of such high recurrence rates, strong consideration must be given to adjuvant radiation therapy after surgical treatment of atypical meningiomas. Alternatively, these patients can be followed very closely with serial scans. In general, all malignant meningiomas should be treated with postoperative radiation regardless of the extent of resection. It also appears that higher radiation doses (greater than 50 Gy) significantly increase the length of survival.

5. STEREOTACTIC RADIOSURGERY

Radiosurgery can be administered by linear accelerator, Leksell Gamma Knife, Novalis Tx, or Cyberknife (Figure 2). Stereotactic radiotherapy has been advocated instead of surgery for high-risk or elderly patients and for patients with meningiomas in eloquent or surgically inaccessible locations (12). Lee and colleagues reviewed the University of Pittsburgh experience with 964 patients who underwent Gamma Knife radiosurgery for

intracranial meningioma between 1987 and 2004 (13). Their 10-year actuarial rate of tumor control was 93 percent for benign meningiomas. Their 5-year actuarial control rates for patients with atypical and malignant meningiomas were 83 percent and 72 percent, respectively. The incidence of radiation-related morbidity ranged between 5 percent and 16 percent. Over the course of the study, morbidity gradually decreased. The authors attributed this trend to lower doses and better treatment planning based on magnetic resonance (MR) imaging.

Kollova and colleagues reviewed their experience with Gamma Knife radiosurgery in 368 patients with meningioma treated between 1992 and 1999 (14). The median tumor volume was 4.4 cm³. The median tumor margin dose was 12.5 Gy to the 50 percent isodose line. The 5-year actuarial progression-free survival rate was 98 percent. In 70 percent of the cases, the volume of the treated tumor decreased. A margin dose of more than 12 Gy was associated with a significantly higher tumor control rate compared to a lower dose. Fifteen percent of the patients developed peritumoral edema, which was evident on MR imaging. The rate of permanent morbidity was 5.7 percent.

Salvage therapy with stereotactic radiosurgery is a particularly appealing option for treating the recurrence of atypical and malignant meningioma. Kano and colleagues reported a significantly higher rate of tumor control in patients undergoing salvage therapy with a marginal dose of more than 20 Gy for high-grade meningioma (63 percent vs. 29 percent for patients receiving lower doses) (15).

Stereotactic radiosurgery is a valuable option for the treatment of primary and recurrent meningiomas. This modality is an effective adjunct to surgical management, particularly when tumors are large or in areas difficult to access surgically. Bambakidis and colleagues reported their experience with 64 petroclival meningiomas. In some cases, aggressive surgical resection was limited in an effort to minimize perioperative morbidity. Their rate of progression-free survival was excellent (16). In this series, 12 patients underwent postoperative stereotactic radiosurgery, none of whom showed evidence of a recurrence at a mean follow-up of 4 years.

Large size and diffuse spread are limitations for radiosurgery. In the future, fractionated radiosurgery may make treating larger tumors possible. Studies on the effectiveness of such modalities are in progress. Fractionated radiosurgery with devices such as the CyberKnife is especially useful near radiosensitive areas, such as the optic apparatus, and can be used in areas that are difficult to target with the Gamma Knife, such as the foramen magnum (17,18).

At Barrow Neurological Institute, we offer surgery as the first-line of treatment for most meningiomas. Older patients with small tumors are given the option of observation with serial scans. Radiosurgery is seldom used as a primary treatment in the absence of a definitive diagnosis. Repeat surgery is usually offered to patients with

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recurrent disease. Patients whose tumor recurrence is amenable to stereotactic radiosurgery are given that option. Patients with large tumors or an *en plaque* extension are more likely to be treated with repeat operation and possible adjuvant radiation therapy. We are aggressive with early salvage radiosurgery for high-grade meningiomas.

6. CHEMOTHERAPY

The mainstay of treatment for meningiomas is surgical resection. Patients with an unresectable or partially resectable lesion or patients who develop a recurrence after gross total resection and re-resection are treated with fractionated conformal radiotherapy, stereotactic radiosurgery, or both. When the limits of surgery and radiation for particularly recalcitrant lesions are reached, additional treatment options are sought. For most intracranial neoplasms, these options include locally or systemically administered chemotherapy. For meningiomas, however, the role of chemotherapy is extremely limited. Multiple small clinical trials have consistently been associated with disappointing outcomes. Either the efficacy of a given chemotherapeutic agent has been unconvincing, or favorable results have not been reproducible in subsequent investigations. To date, attention has focused on hormonal therapy, immunomodulators, and anti-neoplastic agents.

7. HORMONAL THERAPIES

The use of antiestrogens and antiprogesterones for the treatment of meningiomas is a rational approach based on the observations that these tumors are more common in women, demonstrate growth fluctuations during pregnancy and other states of hormonal fluctuations, and express estrogen surface receptors and, to a much greater degree, progesterone receptors (19,20). In a 1985 pilot study, 6 patients with a recurrent inoperable meningioma were treated with tamoxifen for 8 to 12 months; only one patient showed an objective response after 4 months of treatment (21). In a larger, phase II study conducted by the Southwest Oncology Group (SWOG) (22), 21 patients with recurrent meningiomas refractory to resection and radiotherapy were treated with tamoxifen (40 mg/m² twice daily for 4 days) followed by a maintenance schedule (10 mg twice daily). Among 19 evaluable patients, one partial response and two minor responses were noted. In six patients, the disease was stable for a mean duration of 31 months. However, in more than half of the patients (53 percent), the disease progressed during therapy. The investigators concluded that the evidence did not support the use of tamoxifen therapy for the treatment of this disease. The use of higher doses, such as those used in the experimental treatment of glioblastoma multiforme (23), has not been reported. In a Japanese case report, a patient exhibited a 73 percent reduction in tumor size on computed tomography after 2 years of treatment with the anti-estrogen agent, megestrol acetate, for an unrelated disease (24).

There has been considerable interest in the use of anti-progesterone therapy for the treatment of meningiomas. Numerous clinical trials have been conducted using these agents to treat refractory meningiomas. In a pilot study, Markwalder and colleagues

treated 15 patients with brain and spinal meningiomas preoperatively with medroxyprogesterone acetate to measure the effect of binding to progesterone receptors, thereby producing a competitive blockade. Effective binding was demonstrated, but the effect on tumor growth rate was not measured (25). Grunberg and Weiss treated nine patients with a meningioma with megestrol acetate, a progesterone agonist for 1 to 12 months. They documented responses, suggesting that progesterone antagonists might be more active than agonists (26). Grunberg and colleagues then reported the results of a clinical trial using the antiprogestosterone agent, mifepristone, to treat 14 patients with a recurrent meningioma (27). Patients received 200 mg/day for 2 to 31 months. Twelve patients received treatment for more than 6 months. Of 13 evaluable patients, 5 experienced either objective radiographic evidence of tumor shrinkage or objective improvement of their vision based on examination of their visual field. Therefore, the response rate was 38 percent.

However, the prospect of significant efficacy of mifepristone in the treatment of meningioma ended with a large phase III, double-blind, placebo-controlled study conducted by SWOG. In this study 193 patients with nonmalignant recurrent meningioma were treated with mifepristone (28). Of the 160 evaluable patients (80 in each treatment arm), two patients and one from a placebo group had unconfirmed responses. The median times of freedom from progression were 10 months in the treatment group and 12 months in the placebo group.

8. IMMUNOGRAPHY AND BIOLOGICAL RESPONSE MODIFIERS

At the M.D. Anderson Cancer Center, six patients with recurrent, unresectable, and malignant meningiomas were treated with interferon alpha-2B, 5 days per week. There were five objective responses: The disease was stable in four patients, and one patient showed a minor response that lasted 6 to 14 months (29). Given the relative tolerability of this therapy, it was suggested that a larger study be pursued. However, with the exception of another small study of 12 patients from Sweden (30), with equally efficacious results (9 responders, 5 with durable responses treated from 9 months to 8 years), no large patient series have been reported.

In a pilot trial, 16 patients with a recurrent meningioma, most of whom had previously undergone radiotherapy and chemotherapy, were treated with long-acting somatostatin (31). The presence of receptors in all patients was confirmed using In-111 octreotide single photon emission-computed tomography scanning. After 2 to 15 cycles of treatment, four patients showed a partial response. The disease was stable in five patients and progressed in seven patients. At 6 months, the rate of progression-free survival was 44 percent. A large clinical trial is in the planning stages.

9. ANTI-NEOPLASTIC CHEMOTHERAPY AND HYDROXYUREA

The rationale for chemotherapy has been the basis of treatment of soft-tissue tumors, sarcomas, and other intracranial tumors, such as gliomas. Sarcoma-based

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chemotherapy regimens of ifosfamide, cyclophosphamide, adriamycin, and dacarbazine have been used, but toxicity is a problem (32).

Chamberlain and colleagues conducted a prospective, phase II clinical trial using temozolomide as salvage therapy for patients with treatment-refractory, recurrent meningiomas (33). In this study, 16 patients were treated for 42 consecutive days (75 mg/m²/day), with a 4-week break, repeated as 10-week cycles. All 16 patients were deemed evaluable for response. At the end of the first cycle, the disease was stable in 13 patients and had progressed in three patients. However, by the end of the second cycle of treatment, the disease had progressed in those same 13 patients. The primary endpoint—a 6-month progression-free survival rate of 40 percent—was not achieved. The authors concluded that this treatment was ineffective for recurrent meningiomas.

The same investigators conducted another phase II trial using Irinotecan (CPT-11) for salvage treatment of nonmalignant meningiomas (33). Sixteen patients were treated with intravenous CPT-11 every 3 weeks, with appropriate dose adjustments for those on enzyme-inducing antiepileptic drugs. None of these patients had received prior chemotherapy. The treatment cycle was defined as three infusions during a 9-week period. All 16 patients were evaluable. There were no complete or partial responses. Initially, the disease was stable in 13 patients, but it progressed after two cycles. The results of this study were considered negative.

Hydroxyurea, a ribonucleotide reductase inhibitor, exerts antiproliferative activity in meningiomas by inducing apoptosis (34,35). Furthermore, in studies of malignant tumors, hydroxyurea has been used as a radiosensitizer (36). Several small clinical trials have used hydroxyurea to treat meningiomas. Schrell and colleagues treated four patients with recurrent meningiomas with a standard dose of hydroxyurea (20 mg/kg/day) (37). Three of these patients had undergone multiple surgical resections and radiotherapy. After 5 to 10 months of treatment, three patients with a WHO grade I meningioma, were reported to have 15 percent to 74 percent tumor shrinkage with associated improvement in clinical symptoms. In one patient with a WHO grade III (malignant) meningioma, the disease was stable for 24 months. In a pilot study, the same investigators treated 21 patients with conformal radiotherapy and concurrent chemotherapy with hydroxyurea (38). Clinical improvement and a minor response on neuroimaging were seen in three patients, and the disease was stable in 14 patients. The median time to progression was 59 weeks, and progression-free survival rates at 1 and 2 years were 84 percent and 77 percent, respectively.

Newton and colleagues treated 17 patients with unresectable or residual meningioma with the same hydroxyurea dose schedule as used in the studies summarized above (39). Of 16 evaluable patients, the disease was stable in 14 with a median durable response of 80 weeks. After 10 weeks of treatment, the disease had progressed in two patients, resulting in a response rate of 88

percent. Hematologic toxicity required a dose reduction in 53 percent of the patients. In general, however, the treatment was well tolerated. The concluding recommendation was to consider this treatment for patients with a refractory meningioma.

Mason and colleagues treated 20 patients with a recurrent or unresectable meningioma, including one malignant meningioma, with hydroxyurea (20 mg/kg/day) (40). All 20 patients were evaluable for response. The disease was stable in 12 patients for a median treatment duration of 122 weeks. Two of these patients exhibited clinical improvement. After 39 weeks of treatment, one patient showed a minor response. After 24 weeks of treatment, the disease progressed in the patient with the malignant meningioma. The 1-year progression-free survival rate was 93 percent. The findings confirm that though reduction in the actual size of a tumor may be limited, there is value in stabilization of otherwise progressive meningiomas.

Loven and colleagues treated 12 patients with a progressive unresectable meningioma using hydroxyurea (20 mg/kg/day) continuously for 2 years (41). In nine patients, the median time to progression was 13 months. No clinical improvement was reported, and two patients withdrew from treatment because of grade 3 and 4 hematologic toxicity. The authors concluded that this regimen failed to stabilize the disease in this group of patients.

10. CONCLUSIONS

Efforts to find effective treatments for recurrent meningioma have met with minimal success. The data are limited to small individual series with a wide range of results that do not appear to be reliably reproducible. As with other neoplasms, the future of treating meningiomas lies in translational research and the delineation of molecular genetics and signal transduction pathways with the development of therapies specifically designed to target growth factor receptors that modulate angiogenesis and growth.

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Abbreviations: MR, magnetic resonance; SWOG, Southwest Oncology Group; UCSF, University of California-San Francisco; WHO, World Health Organization

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