Factors affecting outcome following treatment of patients with cavernous sinus meningiomas

Clinical article

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Object. Although there is a considerable volume of literature available on the treatment of patients with cavernous sinus meningiomas (CSMs), most of the data regarding tumor control and survival come from case studies or single-institution series. The authors performed a meta-analysis of reported tumor control and survival rates of patients described in the published literature, with an emphasis on specific prognostic factors.

Methods. The authors systematically analyzed the published literature and found more than 3000 patients treated for CSMs. Separate meta-analyses were performed to calculate pooled rates of recurrence and cranial neuropathy after 1) gross-total resection, 2) subtotal resection without adjuvant postoperative radiotherapy or radiosurgery, and 3) stereotactic radiosurgery (SRS) alone. Results were expressed as pooled proportions, and random-effects models were used to incorporate any heterogeneity present to generate a pooled proportion. Individual studies were weighted using the inverse variance method, and 95% CIs for each group were calculated from the pooled proportions.

Results. A total of 2065 nonduplicated patients treated for CSM met inclusion criteria for the analysis. Comparisons of the 95% CIs for recurrence of these 3 cohorts revealed that SRS-treated patients experienced improved rates of recurrence (3.2% [95% CI 1.9–4.5%]) compared with either gross-total resection (11.8% [95% CI 7.4–16.1%]) or subtotal resection alone (11.1% [95% CI 6.6–15.7%]) (p < 0.01). The authors found that the pooled mixed-effects rate of cranial neuropathy was markedly higher in patients undergoing resection (59.6% [95% CI 50.3–67.5%]) than for those undergoing SRS alone (25.7% [95% CI 11.5–38.9%]) (p < 0.05).

Conclusions. Radiosurgery provided improved rates of tumor control compared with surgery alone, regardless of the subjective extent of resection. (DOI: 10.3171/2010.3.JNS091807)

Key Words • cavernous sinus meningioma • meningioma • surgery • radiosurgery • radiotherapy

Abbreviations used in this paper: CSM = cavernous sinus meningioma; SRS = stereotactic radiosurgery.
of tumor control and morbidity are highly variable in the literature. There are conflicting reports in the literature regarding the best method for achieving tumor control in cases in which the lesion is subjected to limited or even no attempts at resection. There are no Class I data supporting the superiority of SRS alone versus fractionated radiotherapy alone, or comparing either of these modalities combined with subtotal resection of the exophytic cavernous portion. Thus, most arguments advocating one treatment paradigm over another are largely theoretical, as definitive studies have yet to be published. To attempt to provide a data set that minimizes potential biases with as much statistical power as possible, we performed a meta-analysis of the existing literature regarding the treatment, prognosis, and outcome of patients treated for CSMs. Evaluated clinical end points included tumor control rate and the rate of postoperative cranial neuropathy.

Methods

Article Selection

Articles were identified via PubMed search using the key words “meningioma,” “cavernous sinus,” “radiotherapy,” “surgery,” “microsurgery,” “gamma knife,” and “radioisotopes” alone and in combination. We then searched all references in these papers to identify all available CSM patient-related data. Inclusion criteria for articles were as follows: 1) data for patients with CSMs must be presented separately from data from patients with other tumors, and 2) data for patients undergoing different treatments must be presented separately. We studied meningiomas primarily centered in the cavernous sinus, excluding middle and posterior fossa meningiomas invading the cavernous sinus secondarily. We excluded data presented in aggregate forms, which precluded meaningful disaggregated subset analysis. Finally, papers that did not clearly state their definition of CSM were excluded.

Data Extraction and Quality Assessment

Our search resulted in more than 3000 patients treated for CSMs. Of these, 2065 patients were disaggregated with treatment and follow-up data available. All of these studies were disaggregated, and all references for these articles were further scrutinized to ensure nonduplication of patients and completion of a thorough and comprehensive review of the entire English-language literature. The group of patients with incomplete resections includes all cases in which partial, subtotal, and near-total resections were performed. Tumor control was defined as lesion that shrank or remained the same size on follow-up imaging. Data were analyzed as a whole and stratified into 3 subgroups. We analyzed surgically treated patients divided into 2 groups based on the degree of resection: one group consisted of patients who had partial resection and the other group consisted of those patients who were reported to have had their meningiomas “completely excised.” A third group of patients analyzed underwent SRS (Gamma Knife, linear accelerator, or proton-beam radiotherapy) without prior resection. Given the limited number of individual studies with significant numbers of patients receiving either subtotal resection followed by radiotherapy or radiosurgery, or receiving fractionated radiotherapy alone, we could not accurately combine these studies in a statistically robust way and no further analysis was performed. Given that the majority of patients in this series did not receive gross-total resections, recurrence (defined as return of radiographically documented tumor after gross-total resection) and progression (defined as renewed growth or return of initial symptoms) were grouped together and analyzed as one group. To ensure data quality and statistical rigor, we eliminated all case reports or cases series describing fewer than 4 patients, as the between-report variability cannot reasonably be estimated from such small numbers. We also eliminated all individual patients for whom there were fewer than 36 months of follow-up, as well as all patients who did not undergo serial follow-up imaging.

Statistical Analysis

Separate meta-analyses were performed on calculated pooled rates of recurrence and cranial neuropathy after 1) gross-total resection, 2) subtotal resection without adjuvant postoperative radiotherapy or SRS, and 3) SRS alone. Results were expressed as pooled proportions (percentage) with 95% CIs, and these values were used. Heterogeneity across the studies was evaluated using the Cochrane Q statistic, and random-effects models were used to incorporate any heterogeneity present to generate a pooled proportion using methods published by DerSimonian and colleagues. Individual studies were weighted using the inverse variance method, and 95% CIs for each group were calculated from the pooled proportions using the inverse Zt transform of the proportion generated from random-effects model. Between-group hypothesis testing was performed on the calculated odds ratio of the pooled proportions. The possible effect of publication bias was assessed using funnel plots, which on visual inspection did not demonstrate obvious asymmetry (data not shown). Other between-group comparisons were performed using ANOVA or Pearson chi-square testing for continuous or categorical variables, respectively. Parametric statistics were performed only after the data were subjected to formal tests of normality. Significance was set at p < 0.05. Statistical analysis was performed using PASW version 17.0.

Results

Results of the Systematic Review

A total of 2065 nonduplicated patients with CSM met inclusion criteria for this study. Four-hundred thirty-five patients underwent surgery as the only treatment for their tumor with 217 patients undergoing subtotal resection, and 218 patients undergoing a reported gross-total resection. Seventy-one patients underwent subtotal resection followed by some form of postoperative adjuvant radiation-based treatment (SRS or fractionated radiotherapy). One thousand three hundred nine patients underwent SRS as the only treat-
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ment for their tumor, while 250 patients underwent fractionated radiotherapy alone. The overall tumor control rate among all patients was 93%, and the mean follow-up duration in these studies was 47 months (median 44 months). The overall survival rate was 99%.

Tumor Control Rates With Various Treatment Modalities

We identified 17 studies providing more than 36 months of follow-up data for patients undergoing a reported gross-total resection. Our analysis of these studies calculated a pooled random-effects recurrence rate of 11.8% (95% CI 7.4–16.1%) over a mean follow-up period of 51 ± 3.3 months. This follow-up period did not significantly differ from that of other groups. The forest plots and pooled estimate for this cohort are depicted in Fig. 1A. We identified 6 studies providing more than 36 months of follow-up data for patients undergoing a reported subtotal resection without adjuvant radiotherapy or radiosurgery. Our analysis of these studies calculated pooled random-effects recurrence rate of 11.1% (95% CI 6.6–15.7%) over a mean follow-up duration of 59 ± 3.2 months, which did not significantly differ from that in other groups. The forest plots and pooled estimate for this cohort are depicted in Fig. 1B. We identified 22 studies providing more than 36 months of follow-up data for patients undergoing SRS alone. Our analysis of these studies calculated a pooled random effects recurrence rate of 3.2% (95% CI 1.9–4.5%) over a follow-up period of 44 ± 2.6 months. This follow-up period did not significantly differ from that of other groups. The forest plots and pooled estimate for this cohort are depicted in Fig. 1C. Comparisons of the 95% CIs for recurrence of these 3 cohorts reveals that SRS-treated patients experienced more favorable rates of recurrence than either those who underwent gross-total or subtotal resection alone (p < 0.01).

Rates of Neurological Deficits After Treatment for Cavernous Sinus Meningioma

Due to differences in data presentation between various published reports, we had a limited ability to assess nonneurological morbidity following either surgical or radiosurgical treatment. We were able to calculate the rates of postsurgical cranial neuropathy for patients treated with either surgery or radiosurgery and found that the pooled mixed-effects rate of cranial neuropathy was markedly higher in patients undergoing resection (59.6% [95% CI 50.3–67.5%]) than in those undergoing radiosurgery alone (25.7% [95% CI 11.5–38.9%]) (p < 0.05).

Discussion

Although complete excision of a meningioma and its attachment remains ideal treatment for many of these tumors, it is often not the best approach for the patient, particularly because of attendant morbidity. In this study, we performed a meta-analysis of outcomes following treatment of CSMs and compared rates of morbidity and tumor control between those who underwent resection and those who underwent radiosurgery/radiotherapy. We found that radiosurgery appeared to outperform surgery alone. Furthermore, surgery-related morbidity was higher than that of SRS. More specifically, surgery in the cavernous sinus is associated with a high rate of cranial neuropathies referable to this region.

We found that the effect of resection on recurrence and overall survival in patients with CSM was frequently highlighted by authors of the literature. In our study, the estimated recurrence rate of both completely and incompletely resected CSMs was slightly greater than 11% during a mean follow-up interval of 46 months (median 44 months). Our results from the pooled analysis were comparable to those reported in the larger individual studies from the literature. For example, De Jesús and colleagues7 studied 119 patients and reported recurrence rates of 9.6 and 15.2% in completely and incompletely resected CSMs, respectively, in a mean follow-up period of 39 months. Another study of 41 patients with CSMs, carried out by DeMonte and colleagues,8 revealed a recurrence rate of 10.7% in patients who underwent incomplete tumor resection and a 20% recurrence rate in those in whom tumors were completely excised; the mean follow-up duration was 45 months. Taken together or individually, these results seem to emphasize the lack of significant benefit on local tumor control of aggressive CSM resection, and they suggest that a more limited approach is prudent. However, every patient is distinct, and there have been reports documenting improvement in cranial neuropathies after cavernous sinus decompression.6 Such cases will require further study within the context of quality of

![Fig. 1. Forest plots depicting 95% CIs for recurrence rates of studies in this analysis and the pooled proportion calculated from our analysis. Individual studies are indicated by PubMed identification number at the left: forest plots for patients receiving gross-total resection (A), forest plots for patients receiving subtotal resection (B), forest plots for patients receiving SRS alone (C).](image-url)
life assessments, and a practitioner-patient agreement on what acceptable trade-offs are.

Based on the published literature, patients receiving SRS experienced similar to lower rates of tumor recurrence compared with patients who underwent surgery alone. The principal qualifier of this statement is our lack of ability to control for tumor size, due to the failure of most studies in the literature to publish size data in a usable, disaggregated format. Additionally, the present rates of tumor control with radiosurgery may be further improved using current MR imaging–based targeting techniques. While SRS cannot cure these lesions, this modality is associated with excellent rates of tumor control. Accordingly, indications for surgical treatment of these lesions could include goals such as 1) relief of symptomatic extracavernous mass effect, 2) to provide tissue in cases when the diagnosis or histological tumor grade is in doubt, and 3) to limit radiation doses to sensitive extracavernous regions such as the optic nerves and brainstem. It should be acknowledged that any aggregation of data is only as good as its composite studies and may reflect source study biases. Due to the diverse range of data presentation, the number of variables able to be studied and controlled for is limited. Variables that might be of interest, such as tumor size and exophytic growth outside of the cavernous sinus, are inconsistently presented and cannot be studied. In addition, multivariate regression to control for the effects of important variables, such as age and initial size, is impossible to do across a large number of studies, which adhere to differing formats of data presentation. With these important limitations noted, it can be concluded from the results that purely intracavernous masses, without confounding medical histories to suggest other pathology, can be controlled with radiosurgery alone, potentially lowering morbidity and associated health care costs compared with aggressive resection.

While our analysis suggests that radiosurgery provides both better tumor control and lower rates of cranial neuropathy for patients with CSMs, a number of questions still remain. Notably, the question of which patients need tissue diagnoses still remains unanswered. This is an important point due to the relatively poor clinical response of WHO Grade II and III lesions to radiosurgery in published series and due to the nonneoplastic or malignant pathology that can mimic meningiomas in this region. While there are not definitive data to drive recommendations regarding indications for tissue diagnosis, we would suggest that immunosuppression, nasopharyngeal or infratemporal fossa extension, rapid onset of symptoms, cavernous sinus syndrome, or other synchronous lesions are indications for tissue diagnosis. The excellent rates of tumor control seen with radiosurgery suggest that the lack of a tissue diagnosis at least is not leading to large numbers of patients being harmed by empirical radiosurgery without tissue diagnosis.

Other important questions that need to be answered include the posttreatment prognosis of these patients following radiosurgery: Do symptoms resolve, improve, or worsen following treatment? How do these tumors behave relative to no treatment? Also, are there radiological pathoanatomical features (other than proximity to the optic nerve), for which surgery is indicated even for smaller lesions. Additionally, non–cranial nerve morbidity deserves additional analysis, as there presently is inadequate data to draw firm conclusions. Additionally, the rates of tumor control following simple tumor debulking of large exophytic lesions followed by radiosurgery deserve additional attention, as it is not implausible to postulate that these lesions behave differently than smaller lesions that can be contained by radiosurgery alone. Finally, what is the efficacy of 3D-conformal radiotherapy in cases in which radiosurgery is not an option due to proximity to the optic nerve. These questions form the foundation for future work in the field.

Conclusions

We present our findings of tumor control and survival from a large meta-analysis of the literature on the treatment of CSMs. The data seem to suggest that SRS should be the therapeutic modality of choice. We presently reserve surgery for cases involving large exophytic components or optic nerve compression, which would make treatment with radiotherapy or radiosurgery alone difficult and complicated, and for cases in which the diagnosis of meningioma is in question.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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