Plasmacytoma of the Skull Base: A Meta-Analysis

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Abstract

Objective Extramedullary plasmacytomas are rare tumors. In the current study we aim to characterize its clinical course at the skull base and define the most appropriate therapeutic protocol.

Methods We conducted a meta-analysis of articles in the English language that included data on the treatment and outcome of plasmacytoma of the base of skull.

Results The study cohort consisted of 47 patients. The tumor originated from the clivus and sphenoclivus region in 28 patients (59.5%), the nasopharynx in 10 patients (21.2%), the petrous apex in 5 patients (10.6%), and the orbital roof in 4 patients (8.5%). The chief complaints at presentation included recurrent epistaxis and cranial nerve palsy, according to the site of tumor. Twenty-two patients (46.8%) had surgical treatment; 25 (53.2%) received radiation therapy. Adjuvant therapy was administered in 11 cases (50%) with concurrent multiple myeloma.

The 2-year and 5-year overall survival rates were 78% and 59%, respectively. Clear margin resection was achieved in a similar proportion of patients who underwent endoscopic surgery and open surgery ($p = 0.83$). A multivariate analysis of outcome showed a similar survival rate of patients treated surgically or with radiotherapy.

Conclusions The mainstay of treatment for plasmacytoma is based on radiation therapy, but when total resection is feasible, endoscopic resection is a valid option.

Keywords

- plasmacytoma
- extramedullary
- base of skull
- clivus

Introduction

Solitary plasmacytoma is a rare tumor that constitutes < 10% of plasma cell neoplasms.^{1,2} The two forms of the disease, solitary bone plasmacytoma and extramedullary plasmacytoma, are distinguishable by sites of origin, prognosis, and the tendency to convert to multiple myeloma.¹ Approximately 5% of patients with multiple myeloma have an initial diagnosis of solitary plasmacytoma.³

Plasmacytoma of the skull base is rare, with very few cases described in the literature. The mainstay of treatment of these

lesions remains radiotherapy with the addition of chemotherapy when multiple myeloma (MM) is present. Nevertheless, with the increasing utilization of the minimally invasive approach to the skull base, the role of extended endonasal endoscopic surgery for these patients remains to be determined.⁴

We performed a meta-analysis of the characteristics and outcomes of patients with skull base plasmacytoma. We aimed to identify prognostic factors associated with outcomes of patients and to determine the best treatment regime in this population.

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Materials and Methods

Meta-analysis Search Strategy and Selection Criteria

During December 2014, we conducted a systematic electronic literature database search of studies published in PubMed up through December 2014, using the Medical Subject Heading terms (plasmacytoma) AND (skull base OR base of skull), limited to "Human." Reference lists of retrieved manuscripts were hand-searched for additional publications. Publications in a language other than English were excluded. Articles were excluded at the initial screening if their titles or abstracts showed that they were clearly irrelevant. Full texts of potentially relevant articles were reviewed to assess their suitability for inclusion in the meta-analysis. Inclusion criteria for study populations were histologically diagnosed or clinically suspected plasmacytoma of the base of skull, and availability of data about treatment and outcome including survival or recurrence.

Patients

Thirty studies documenting 46 patients were identified.^{4–31} One patient was diagnosed and treated for plasmacytoma of the skull base at our institution and was added to the analysis. The patients ranged in age from 28 to 85 years (mean: 56.3 years); 26 (55.3%) were men. The median follow-up was 19 months (range: 1.5–165 months). Concurrent MM was

present in 11 patients (23.4%) simultaneously when diagnosed with plasmacytoma; 5 patients were diagnosed with MM (10.6%) after the diagnosis of plasmacytoma and 3 (6%) were diagnosed before.

Statistical Analysis

Two-year overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier method. Differences in the survival rates were assessed by the log-rank test. OS was measured from the date of surgery to the date of death or the last follow-up. The DSS for patients who died from causes other than plasmacytoma was established as the time of death. All analyses were performed on JMP 10 software (SAS Institute, Cary, North Carolina, United States) and confirmed by an independent statistician on an IBM SPSS Statistics package (IBM Corp., Armonk, New York, United States). All *p* values were two sided, and a *p* value < 0.05 was adopted as the threshold for significance. The meta-analysis was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.

Results

The final study group consisted of 47 patients. ►Fig. 1 shows the flowchart of the study selection process. Demographic and clinical characteristics are presented in ►Table 1.

Fig. 1 Flowchart of the study selection process. Preferred Reporting Items for Systematic Reviews and Meta-Analysis: the PRISMA statement.

Table 1 Demographic and clinical characteristics of the cohort

Variable		No. of patients	%
Mean age, y	56.3 (28–85)	47	100
Gender, <i>n</i> = 44	Male Female	26 18	59 41
Site, <i>n</i> = 47	Sphenoclivar region Nasopharynx Petrous apex Orbital roof	28 10 5 4	59.5 21.2 10.6 8.5
Treatment modality, <i>n</i> = 47	Surgery Surgery and RT Surgery and C Surgery, C. and RT RT C and RT Chemotherapy	8 10 2 2 13 10 2	17 21.2 4.2 4.2 27.6 21.2 4.2
Median follow-up, mo	19	33	

Abbreviations: C, chemotherapy; RT, radiotherapy.

Table 2 Presenting symptoms of the cohort according to the site of disease

Site	Signs and symptoms	Cranial nerve involved
Sphenoclivar region	Diplopia Hemianopia Blurred vision Ocular pain	II, III, IV, VI, IX, X
Petrous apex	Hearing loss Vertigo Gait instability	VIII
Nasopharynx	Recurrent epistaxis Anosmia	I
Orbital roof	Orbital proptosis Epiphora Ptosis	III

Sphenoclivar plasmacytoma was present in 28 (59.5%) of the cases, nasopharyngeal in 10 (21.2%), petrous apex involvement in 5 (10.6%), and 4 patients (8.5%) had orbital roof involvement. ► **Table 2** describes the presenting symptoms of the patients according to the site of disease origin.

Analysis of treatment modalities revealed that 22 patients (46.8%) underwent surgery. Of them, 10 (45.4%) received adjuvant radiotherapy, 2 (9%) adjuvant chemoradiation, and 2 others (9%) received adjuvant chemotherapy indicated for MM. Radiotherapy was administered to 13 patients (27.6%) as a single modality, and chemoradiation was administered to 10 (21.2%) (► **Table 1**).

Of the patients who received radiation therapy, external-beam radiation therapy was administered to 31 (89%), and 4 (11%) were irradiated using stereotactic radiosurgery. The radiation dose ranged from 3,000 to 5,400 cGy (mean: 4458 cGy).

Of the 22 patients who underwent surgical resection, 10 (45%) underwent endoscopic surgery and 12 (55%) open surgery. R0 resection (all margins tumor free) was achieved in 10 patients (45%), R1 (microscopic positive margins) in 4

(18%), and 8 patients (37%) had R2 resection (residual gross disease). R0 resection was achieved in a similar proportion of patients who underwent endoscopic surgery (50.0%) and open surgery (41.6%) ($p = 0.83$).

Considering the entire cohort, the 2-year and 5-year rates of OS were 78% and 59%, respectively; the rates of DSS were 97% and 83%, respectively (► **Fig. 2**). The 2-year OS of patients who had MM was 53%, compared with 38% for those who had plasmacytoma only, yet this difference did not reach statistical significance ($p = 0.54$) (► **Fig. 3**).

We performed a multivariate analysis of the entire cohort to assess the effect of disease characteristics on survival. Age ($p = 0.6$), gender ($p = 0.8$), site of the disease ($p = 0.8$), R0 resection ($p = 0.6$), and chemotherapy administration ($p = 0.4$) were all tested and found to be insignificant as prognostic factors for OS.

Discussion

Plasmacytoma is a rare tumor that originates from the skull base. The diagnosis of skull base plasmacytoma is based on

Fig. 2 Kaplan-Meier survival analysis: 5-year overall survival (OS) (blue) and disease-specific survival (DSS) (red) of the entire cohort.

Fig. 3 Kaplan-Meier survival analysis according to multiple myeloma status. Two-year overall survival comparing patients with multiple myeloma (blue) and patients with solitary plasmacytoma (red).

the presentation and exclusion of other entities by a tissue sample from the suspicious site. Although findings from a computed tomography scan or magnetic resonance imaging may lead to the diagnosis of plasmacytoma, differentiating from other skull base tumors based only on radiologic findings is difficult. The differential diagnosis includes multiple myeloma, meningiomas, chordomas, metastatic carcinomas, and nasopharyngeal carcinomas.³² Four patients from our cohort were managed with a working diagnosis other than plasmacytoma (two misdiagnosed as chordoma and two as meningioma). Only total body imaging work-up, tissue diagnosis, and immunohistochemical staining determined the final diagnosis of plasmacytoma.

The administration of radiation therapy to more than half of the patients in the cohort concurs with the knowledge that plasmacytoma is a radiosensitive tumor. The radiation dose ranged between 3,000 cGy and 5,400 cGy, which compares with the radiation dose recommended of 5,000 to 6,000 cGy.^{33,34} Three patients received a total dose of 3,000 cGy, all of whom had MM, so they were treated with chemotherapy as well. For two patients, the disease recurred shortly after treatment completion, and the third patient was lost to follow-up after 2 months, so there were no data regarding his disease status.

Surgical treatment is not well established in plasmacytoma of the skull base. Most of the patients in our study who underwent surgical treatment did not have a histologic diagnosis of plasmacytoma prior to the surgery, and the final

diagnosis was reached after the surgery, with the final pathology. Adjuvant treatment was administered to 55% of the patients who had surgery with R0 resection. Although adjuvant treatment can benefit R1–2 resections, its role in young patients with small and operable solitary plasmacytoma is questionable. Our findings show that surgery alone can be sufficient for such patients and radiation treatment, and its sequel can be avoided. Wein et al recommended salvage surgery when feasible, in cases of recurrent/persistent disease, despite primary chemotherapy or radiation, especially in nasopharyngeal tumors.¹⁰

In the current analysis, the presence of multiple myeloma did not affect survival of skull base plasmacytoma, but this might be due to paucity of data. The mainstay of treatment is radiation therapy, but when total resection is feasible, endoscopic resection is a valid option.

A multivariate analysis of outcomes showed patient demographics and disease characteristics not to be associated with survival rates. This finding may be due to the small cohort.

This meta-analysis is limited due to the incomplete data presented in the studies included and due to the small number of cases that prevents reaching statistically significant results. Although data heterogeneity might better reflect overall global population trends and enable generalization of the findings, many of the included studies have relatively small populations, which subject the analysis to publication bias. This may result in an over- or underestimation of treatment effect. Randomized controlled trials are needed to further evaluate the benefit of surgical treatment in plasmacytoma of skull base.

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