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An analysis of intracranial epidermoid tumors with malignant transformation: treatment and outcomes

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ABSTRACT

Objective: While typically benign, epidermoid tumors upon rare occasion can undergo malignant transformation, which carries a poor prognosis. Here, we reviewed treatment strategies and analyzed outcomes for every case of malignant epidermoid tumor reported since its original description in 1912.
Methods: A comprehensive literature review identified all reported cases of malignant transformation of intracranial epidermoid tumor. Treatments were categorized as follows: palliative management, stereotactic radiosurgery (SRS), chemotherapy, and surgery plus multiple (2+) adjuvant therapies. Survival data of these groups were compared to treatment outcomes for patients receiving only surgical resection, as reported in our previous study.
Results: We identified 58 cases of intracranial epidermoid tumor with malignant degeneration. Average survival regardless of therapy was 11.8 months. Mean survival outcomes for groups treated with palliative management, chemotherapy, SRS, and multiple postoperative adjuvant therapies were 5.3 months, 25.7 months, 29.2 months, and 36.3 months, respectively. Outcomes for the groups including SRS, chemotherapy, and multiple post-operative adjuvant therapies were statistically significant compared to surgical resection alone.
Conclusion: While there remains a lack of consensus regarding the best approach to the management of patients with malignant epidermoid tumors, our systematic analysis characterizes and confirms the added benefit of SRS, chemotherapy, and multimodal adjuvant therapies.

1. Introduction

Epidermoid tumors represent 0.2–1.8% of all intracranial tumors [1–4] and are believed to derive from aberrant inclusions of ectodermal remnants that become trapped during neural tube formation between the third and fifth weeks of intrauterine development [1,5]. These lesions are lined with keratinized stratified squamous epithelium, and as the continual processes of desquamation and cell membrane degradation occur, cysts enlarge via keratin, water, and cholesterol build-up [1,3,6,7]. Epidermoids can be located anywhere within the cranial vault, but most are found in either the cerebellopontine angle (40–50%) or the parasellar region (30%) in an intradural and paramedian position [6,8,9]. Depending upon lesion location, extension, and mass effect, patients may present with symptoms ranging from headaches to rare fatal events. However, patients are typically asymptomatic until a mean age of 40 [6,10,11].

The first description of epidermoid tumors was provided in 1807 by an artist in a French medical school, and later documented in more complete detail by the pathologist Cruveilhier (1829) who gave them the name 'tumeurs perlees,' or 'pearly tumors.' As these lesions contain cholesterin crystals, Miller coined the term 'cholesteatom' in 1836. In 1928, Critchley and Ferguson argued that 'epidermoid cyst' was a more appropriate labeling [6,12–15]. Over the years, 'epidermoid tumor' has also become commonly used.

While these lesions are typically considered benign [16,17] and tend to have a favorable prognosis following surgical resection, they may upon rare occasion undergo malignant degeneration to squamous cell carcinoma [5,8]. In this systematic review, we aggregate and analyze details pertaining to every reported case of malignant epidermoid tumor in order to characterize its presentation and compare survival outcomes of utilized treatment modalities.

Abbreviations: C, chemotherapy; CPA, cerebellopontine angle; CSF, cerebrospinal fluid; F, female; LC, leptomeningeal carcinomatosis; M, male; MT, malignant transformation; S, surgery; SRS, stereotactic radiosurgery; UD, undetermined; XRT, radiotherapy.

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Treatment options have included palliative management, surgical resection, radiotherapy, chemotherapy, and stereotactic radiosurgery. Survival data following surgical resection (6.6 months) and radiotherapy (12.7 months) has been detailed in our previous study [18].

2. Methods

We conducted a literature review using the PubMed database, with search terms including 'intracranial,' 'epidermoid,' 'malignant,' 'transformation,' 'degeneration,' 'treatment,' 'surgery,' 'radiotherapy,' 'radiosurgery,' 'outcome,' and 'chemotherapy,' in various combinations. Data was extracted from all primary sources when possible. Studies included in our analysis consisted of patients with intracranial epidermoid tumors demonstrating malignant degeneration. Carcinomas arising from craniopharyngiomas or dermoid tumors were excluded from our study. In total, 58 cases of malignant transformation of intracranial epidermoid tumors (Table 1) have been documented under Garcia's [58] and Hamlat's [19] criteria. Any lesions which did not meet Garcia's and Hamlat's criteria were also excluded, as detailed in our discussion.

Treatment options were categorized into various groups including (1) palliative management, (2) stereotactic radiosurgery alone or in combination with other treatments, (3) chemotherapy alone or in combination with other treatments, and (4) surgery plus two or more adjuvant therapies. Patients with leptomeningeal carcinomatosis were also analyzed separately to investigate the potential benefit of adjuvant therapy. Outcome was assessed as the interval of time from the diagnosis of malignant transformation until last follow-up. Patient demographics were characterized and treatment groups were examined for differences regarding interval to malignant degeneration, sex, and age.

Data from all studies were aggregated and evaluated using the log-rank test or a *t*-test when appropriate. Survival outcomes for treatment groups were compared with survival data from intracranial malignant epidermoid patients treated with surgical resection alone, as established in our previous report [18]. Statistical significance was set as $p < 0.05$ following two-tailed analyses.

3. Results

Of the 58 total cases, 33 (56.9%) were male and 25 (43.1%) were female. Average patient age at the time of malignant degeneration was 53.6 years, ranging from 20 to 74 years. Mean interval from initial epidermoid symptom onset to diagnosis of malignancy was 6.0 years, ranging from 10 days to 33 years. Average survival regardless of therapy was 11.8 months, ranging from 1 day post-operation to 5 years. There was no detectable difference between treatment groups regarding age ($p > 0.5$), sex ($p > 0.2$), or interval to malignant degeneration ($p > 0.6$). Tumor locations included the cerebellopontine angle ($n = 26$, 44.8%), temporal lobe ($n = 7$, 12.1%), prepontine/parapontine region ($n = 6$, 10.3%), frontal lobe ($n = 5$, 8.6%), and 14 cases presented in other areas (24.1%).

3.1. Palliative management

Eleven patients (19%) were treated with palliative management, nine of which were treated before 1985. Ten patients with available data survived an average of 5.3 months, ranging from 20 days to 12 months. A statistical comparison of this group with the surgical treatment group was not conducted, as described in Section 4.

3.2. Stereotactic radiosurgery, chemotherapy, and multimodality treatments

For those treated with stereotactic radiosurgery (SRS), average patient age was 54.4 years (range of 42–67 years), with a 9.5 year average interval from initial epidermoid symptom until diagnosis of malignancy (range of 5 months to 16 years) (Table 2). In the five cases reported (8.6%), average survival from the onset of malignant degeneration was 29.2 months (log-rank test, $p < 0.025$), with marginal treatment doses ranging from 12 to 15 Gy (Fig. 1).

The use of chemotherapy for treating malignant epidermoid tumors has been documented in six cases (10.3%). Average patient age was 48.7 years (range of 38–65 years), with an average interval from initial epidermoid symptom until malignant transformation being 3.4 years (range of 5 months to 12 years). For any patient receiving chemotherapy either alone, with surgery, or with other non-surgical treatments (radiation or SRS), overall average survival was 25.7 months (range of 6 months to 5 years). This increased survival was statistically significant when compared to outcomes of patients receiving only surgery (log-rank test, $p < 0.02$).

When surgical resection was combined with two or more other treatment modalities (radiotherapy, chemotherapy, or SRS), the overall survival for these four patients (6.9%) was 36.3 months. This finding was statically significant as compared with surgery alone (log-rank test, $p < 0.02$). Within this group, average patient age was 48 years (range of 42–57), with a 6.1 year average interval from initial epidermoid symptom onset (range of 5 months to 12 years).

For patients with leptomeningeal carcinomatosis (LC) following malignant transformation of epidermoid tumors, average age was 53.7 years (range of 20–73 years), with an average interval from initial epidermoid symptom until malignant transformation being 4.8 years (range of 1 month to 17 years). Overall survival following malignant degeneration in 20 total patients with LC (34.5% of 58) was 9.2 months (range of 8 days to 25 months). Seven patients (35% of 20) treated with palliative management survived an average of 6.1 months. A statistical comparison of this group with the LC group treated surgically was not conducted, as described in Section 4.

Seven patients with LC (35% of 20) were treated with chemotherapy, radiotherapy or SRS either alone, with surgery, or in combination and had an extended average survival to 14.6 months (range of 6–25 months). When compared to those treated with only surgery (1.6 month survival) as reported in our previous study [18], this increased survival was statistically significant (log-rank test, $p < 0.001$).

4. Discussion

In accordance with our inclusion criteria, 58 cases of epidermoid tumor with malignant transformation were identified in the literature between 1912 and 2010, with a 4:3 male-to-female ratio and an average survival regardless of therapy of approximately one year. The criteria for diagnosing malignant epidermoids was established by Garcia et al. [58], with further additions contributed by Hamlat et al. [19]. The tumor must be contained within the intracranial and intradural compartments without expansion beyond the dura, cranial orifices, or extensions to the middle ear, air sinuses, or sella turcica. There must also be evidence of benign squamous cell epithelium within the malignant tumor, and both nasopharyngeal and metastatic carcinoma must be excluded [32].

4.1. Malignant degeneration

The pathogenesis of malignant degeneration is thought to be secondary to chronic inflammation due to either repeated irritation and cyst rupture or from subtotal resection (Fig. 2) [3,54].