Primary Intracranial Malignant Melanomas in Solitary Type: A Tertiary Center Experience

Yun-Cong Zheng (m7630@cgmh.org.tw)
Departments of Neurosurgery, Chang Gung Memorial Hospital, Keelung and Linkou & Chang Gung University

Yen-Min Huang
Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung

Kun-Yun Yeh
Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung

Pin-Yuan Chen
Departments of Neurosurgery, Chang Gung Memorial Hospital, Keelung and Linkou & Chang Gung University

Tsan-Yu Hsieh
Department of Pathology, Chang Gung Memorial Hospital, Keelung

Li-Sung Hsu
Institute of Biochemistry, Microbiology and Immunology, Chung Shan Medical University, Taichung

Chiao-En Wu
Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan

Research Article

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Abstract

Background

Solitary type primary intracranial malignant melanoma (PIMM) is extremely rare but fatal. The optimal treatment algorithm according to clinical relevance of symptoms and outcomes is unclear. This series emphasized the prognostic factors of solitary PIMM and established the treatment algorithm for this rare disease.

Methods

Patients with solitary PIMMs were pathologically verified and treated with neurosurgical tumor resection. All solitary PIMMs recruited at our institute received multidisciplinary team care. We analyzed the clinical findings and prognostic factors.

Results

The study cohort included 10 patients. PIMMs in solitary type impacted middle-aged populations with male predominance in Taiwan. Most patients (80%) presented a single tumor initially. Six patients had progressed to multiplicity after the initial treatment. Rates of tumor bleeding and leptomeningeal metastasis (LM) are high in solitary PIMMs. Patients who had gross-total resection (GTR) had better survival than those who had incomplete resection, with median overall survival (OS) rates of 170.4 months vs. 5.23 months (p = 0.004). Multiplicity, eloquent area involvement, initial tumor bleeding, LM, hydrocephalus, and Karnofsky Performance Score<80 at diagnosis were associated with negative outcomes in progression-free survival and OS. Adjunct radiotherapy for patients who had LM and for those who cannot undergo grossly total tumor removal resulted in a good outcome.

Conclusions

GTR demonstrated better outcomes for solitary PIMM. For recurrent tumors, aggressively repeated surgical resection remained beneficial for selected cases. Adjunct radiotherapy was a treatment option for LM following operation. We proposed a possible treatment algorithm for solitary PIMM.

Introduction

Malignant melanoma or melanocytic tumors arising in the brain are rare. These tumors arise from melanocytes of the leptomeninges, which developed from melanoblasts in the neural crest [1]. Few case reports on these tumors could be reviewed by Medline or PubMed. Most of the reviewed cases about intracranial melanoma referred to metastatic melanomas [2]. The most common primary sites were cutaneous or mucosal lesions. One article reported that among 67 central nervous system (CNS) melanoma reports, 53 cases referred to tumors from the cerebral area [3]. It is difficult to make a differential diagnosis between PIMM and metastatic intracranial malignant melanoma (MIMM). We recruited cases with only cerebral malignant melanoma without any other extracranial lesions after systemic workup, and these were considered PIMMs.

Here, we present 10 cases diagnosed as PIMM in solitary type without other primary sites. They all had higher rates of tumor apoplexy and LM, which are the special presentations of PIMMs [4]. Although the poor prognosis related to LM, multidisciplinary treatments were applied. We reviewed the clinical features, radiological, surgical, and histological findings and analyzed the possible variables influencing the prognosis.

Materials And Methods

From 1993 to 2015, 17 patients aged >18 years old at the time of diagnosis were considered to have solitary intracranial malignant melanoma after surgical resection and pathologic confirmation. Seven patients who had skin or mucosal lesions outside CNS were excluded. Ten patients were included in this study. Their pathologic and clinical data were retrospectively analyzed. Tumor size, location, surgical procedures, and adjuvant therapies were documented along with the progression-free survival (PFS) and overall survival (OS) of each patient. These patients were followed up in the outpatient clinic or through telephone interviews. The latest follow-up was in February 2020. Statistical analyses were performed using the log-rank test and Kaplan–Meier survival analysis for the categorical variables. We conducted all statistical analysis using SPSS ver. 22.0 (IBM Corp.). Statistical significance was set at p < 0.05. The data, including pathologic findings, demographic factors, and other related information were collected from the electronic medical records after Institutional Review Board Approval in Chang Gung Medical Foundation Institutional (IRB file No. 20180020380D001). Signed informed consent from the patients was not required. In order to protect the privacy of patient data, research-related data is only used for research purposes.

Results

Clinical Data at Presentation

The ages of the patients at diagnosis ranged from 22 years old to 57 years old (median, 32.8 years old). Eight patients (80%) were male. The most frequent symptoms or signs were headache, increased intracranial pressure, and limb weakness. Eight (80%) had single lesion, whereas the other two (20%) had multiple lesions initially. The tumor size ranged from 1.5 cm to 4.9 cm in diameter. Six (60%) of these lesions were located in the temporal lobe, followed by frontal, parietal, occipital, and cerebellum. Five (50%) patient had lesions over the eloquent area before neurosurgery (Fig. 1C). At the time of definite diagnosis, six (60%) had congenital melanocytic nevi over the skin, which proved to be benign according to pathological biopsy. Eight patients (80%) had combined tumor hemorrhage by pre-operative image studies (Fig. 1AB). One had cavernous sinus involvement, and two had leptomeningeal metastases according to operative findings (Fig. 1E). Only four patients (40%) carried on performing normal activities and work without special care according to Karnofsky

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performed (Fig. 1H).

Tumor bleeding and LM are two unique characteristics of solitary PIMMs that are unusual in other solid intracranial tumors. We supposed that distal LM is promoted by blood-brain barrier and blood-tumor barrier connection and is achieved by tumor bleeding [26-28]. Fragile blood-tumor barrier in solitary PIMMs contributes to tumor apoplexy. For patients with end-stage solitary PIMMs, LM-related hydrocephalus can be found, and only palliative treatments can be performed (Fig. 1H).

**Discussion**

Primary malignant melanomas of the CNS are life-threatening. They account for 1% of all cases of melanoma [5]. These tumors were derived from melanocytes and can normally be found in the leptomeninges [6]. All organs of the CNS including the spinal cord [7] could be sites of the primary malignant melanomas, although extremely rare. PIMM only comprises 0.07% among all CNS tumors [8]. All melanomas are immuno reactive for HMB-45 and S-100 protein. The PIMMs are cytologically similar to melanomas arising in other sites.

Some studies revealed the difference of primary CNS melanomas and other sites on the molecular level. GNAQ gene at codon 209 and GNA11 are a frequent event in primary melanocytic neoplasms of the CNS [9, 10]. Other mutations in BAP1 [11], SF3B1 [12] and EIF1AX [13] have also been identified. In a targeted next generation sequencing study presented by van de Nes et al. [14], primary CNS melanocytic tumors were concluded to have GNAQ or GNA11 mutations. In cutaneous melanomas, mutations such as BRAF V600 and NRAS were frequently detected [15, 16]. However, in van de Nes’s study, all the BRAF V600 and NRAS in primary CNS melanomas were wild type. These molecular differences implied the clinical deviations between PIMM and MIMM and may help achieve a definite diagnosis in the future.

In our series, we used clinical examination and image studies to exclude primary sites other than the CNS before the diagnosis was established. 18-fluoro-D-glucose positron emission tomography (18F-FDG PET) were introduced in 2010 and 3 patients diagnosed after 2010 had a negative PET finding. Solitary-type PIMMs are differentiated from the diffuse type by a nodular mass according to pathological behavior [17-19]. When diffuse PIMMs infiltrate the pia mater and subarachnoid space, which leads to an unfavorable outcome and subtotal tumor resection, solitary PIMMs can potentially be subjected to aggressive treatment that could lead to longer survival [20]. To our knowledge, this single institute experience is the first study to focus on solitary-type PIMMs.

**Tumor Bleeding and LM in Solitary PIMMs**

In a Danish review, the relative risk of hemorrhagic stroke was 1.45 in the first year after melanoma diagnosis [21]. The bleeding risk of melanoma in the brain was higher than others [22, 23]. A previous study reveals a tumor bleeding rate of 39.6% [24]. In our series, tumor apoplexy accounts for 80% in solitary PIMMs, and it contributes to recurrence and unfavorable outcomes. As tumor apoplexy leads to increased intracranial pressure or rapid deterioration in solitary PIMMs, emergent neurosurgical removal is indicated, which would make detailed stereotactic navigation or awake craniotomy impossible. Repeated tumor bleeding was not uncommon in follow-up images.

LM is a critical complication of malignant tumors and is frequently seen in solitary PIMMs. LM at 30% was present at diagnosis, and it increased to 90% in the lifetime of our patients. LM is always followed by tumor apoplexy, and it indicated the involvement of tumor cells in the cerebrospinal fluid (CSF) and leptomeninges [25]. PIMMs originate from melanocytes in the leptomeninges. Thus, it is not surprising that LM is a direct route of tumor spread. Statistically, such presentation contributes to recurrence and unfavorable outcomes.

Tumor bleeding and LM are two unique characteristics of solitary PIMMs that are unusual in other solid intracranial tumors. We supposed that distal LM is promoted by blood-brain barrier and blood-tumor barrier connection and is achieved by tumor bleeding [26-28]. Fragile blood-tumor barrier in solitary PIMMs contributes to tumor apoplexy. For patients with end-stage solitary PIMMs, LM-related hydrocephalus can be found, and only palliative treatments can be performed (Fig. 1H).
Neurosurgical Tumor Removal

In the reviews by Li et al. [29] and Aria et al. [30], gross tumor resection was most important to survival. Patients who underwent gross tumor resection had a significantly longer survival (>22 months) [30] or overall 40.8% survival in 3 years than those who did not [29]. In our study, patients who were able to receive GTR had satisfactory median survival (66 months), which was significantly better than patients without GTR (4.5 months). In advanced tumor status, the tumor was associated with local bleeding, which could be impressed by image studies or during surgical procedure. The tumor bleeding indicated a more advanced condition and shorter survival. Seven (70%) of our patients underwent a second surgical excision. Three (30%) of them underwent a third excision. One of our patients had surgical excision for 9 times and had a survival rate of 170 months. Aggressive surgical treatment, completely gross resection, and even more episodes of repeated excision were the key for longer survival regardless of tumor size or location.

Adjuvant radiotherapy following tumor resection was beneficial to survival in metastatic melanomas from systemic sites and in PIMM [29, 31]. In our series, patients with LM who are not amenable to GTR showed a trend of better outcomes after adjuvant radiotherapy. Emerging studies also supported that stereotactic radiosurgery instead of whole brain radiotherapy (WBRT) in combination with immune therapies or targeted therapy may be effective. However, this approach needs prospective studies to identify the effect of these novel regimens with radiation therapy [32]. Higher KPS at diagnosis implied lower neurological invasion and higher capability to received adjuvant surgery after neurosurgery.

Treatment algorithm

Most of recent case reviews of PIMMs were mixed cases of leptomeningeal carcinomatosis and solitary cases [29, 30, 33, 34]. In our presentation, we focused on solitary-type PIMMs. The solitary tumor for surgical attempt was first considered after initial workup. We proposed a treatment algorithm for solid brain melanoma according to both current evidence and our findings (Table 3). When the patient presented with solid brain melanoma, systemic workup included the following: dermatologist consultation, confirmatory biopsy examinations, and PET study. When solitary PIMMs were confirmed, surgical total resection was performed by neurosurgeons when the eloquent area was not involved. If complete resection was not executed, focal radiotherapy as adjuvant therapy was scheduled to deal with the residual tumor and LM. Intensity-modulated radiation therapy was the major treatment option in our team's work, and it avoided neurologic decline and preserved better neurological function (Figure 1D, 3).

When tumor recurrence was observed by viewing the follow-up MRI images, GTR was still the first treatment choice if possible. Diffuse LM occurred, and focal radiotherapy was not applicable. Thus, WBRT could be considered only if patient and the family understood the consequent injury to neurological function caused by radiation. However, terminal stage was indicated when hydrocephalus was present in the images. Thus, the disease was refractory to the whole procedure. Cerebrospinal fluid (CSF) cytology could be considered to identify diffuse leptomeningeal spread [35]. The presence of CSF involvement indicated carcinomatosis and hospice care. When metastasis was confirmed, palliative treatments would include ventriculo-peritoneal shunt, supportive care, or immunotherapy. In patients with hydrocephalus, the prognosis is dismal (range from 0.7 to 8.1 months in our study). Multidisciplinary team care in our institute all followed this treatment algorithm. Multimodality management following surgical resection was discussed in combined meetings before it was put in practice.

Prospective Therapy

Dacarbazine (DTIC)-based chemotherapies were used for other melanomas. Li et al. concluded that chemotherapy was beneficial for PIMMs [29]. DTIC has an effectiveness of 16% to 20%. However, in uveal melanoma, DTIC-based chemotherapies are ineffective [36]. In a review of blood–brain and blood–tumor barriers, melanoma cells displayed a vessel co-option phenotype [27], which was different from that of lung cancer. The systemic therapies need to overcome barriers of the neurovascular unit. In our study, adjuvant chemotherapy showed no survival benefit.

BRAF kinase inhibitors, including vemurafenib, showed efficacy on BRAF V600 mutation-positive melanoma even when combined with MEK inhibitors [37]. Dabrafenib plus trametinib had a good but short response to BRAFV600-mutant melanoma with brain metastases [38]. However, the incidence of BRAF V600 mutation was low in a previous study [14]. The checkpoint inhibition with an anti-programmed cell death 1 (PD-1) antibody (pembrolizumab, nivolumab) in combination with the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab had good efficacy on metastatic melanomas [39]. The nivolumab concentrations ranged from 35 ng/ml to 150 ng/ml with a CSF/serum ratio of 0.88%–1.9% [40]. Two phase II studies with the combination nivolumab and ipilimumab revealed clinically meaningful intracranial efficacy on metastatic melanoma [41, 42]. A systemic review suggested that ipilimumab and nivolumab are active in melanoma brain metastases [43]. However, their efficacies on primary brain melanoma remained unclear. More randomized trials would be very desirable.

Conclusion

We revealed 10 cases of solitary PIMMs in our institute. Tumor apoplexy and LM were the unique characteristics of these entities. Gross-total resection and single tumor were associated with better survival. Although the prognosis remained poor, aggressive surgical resection with adjuvant radiotherapy was the most promising treatment.

Limitations

We could analyze only 10 cases in our hospital from the previous 20 years of experience. Considering this small number of cases, multivariate analysis with Cox regression model was not applicable. We need more randomized clinical trials or meta-analysis to achieve better evidence in the future.

List Of Abbreviations
CNS: central nervous system
CSF: cerebrospinal fluid
CT: chemotherapy
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
DTIC: Dacarbazine
GTR: gross-total resection
IR: incomplete resection
KPS: Karnofsky performance status
LM: leptomeningeal metastasis
MIMM: metastatic intracranial malignant melanoma
MRI: magnetic resonance imaging
OS: overall survival
PET: positron emission tomography
PFS: progression-free survival
PIMM: primary intracranial malignant melanoma
RT: radiotherapy
VP shunt: ventriculoperitoneal shunt
WBRT: whole brain radiotherapy

**Declarations**

**Ethics approval and consent to participate:** The "Chang Gung Medical Foundation Institutional Review Board" reviewed and determined that it is expedited review according to case research or cases treated or diagnosed by clinical routines. However, this does not include HIV positive cases. The study has been granted ethics committee approval prior to our commencing. The need for consent to participate was waived by above committee. The IRB is organized and operates in accordance with Good Clinical Practice and the applicable laws and regulations. Thus, our study was followed by the BMC guidelines of retrospective ethics approval. ([IRB file No.201800203B0D001], see the uploaded related file)

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

**Competing interests:** None

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**Authors’ contributions:**
YCZ, YMH, KYY, PYC, TYH, LSH, CEW contributed to the data collection and analysis. YCZ, YMH, KYY, PYC contributed to the conception and design of the study. YCZ, YMH contributed to drafting the text and preparing the figures. All authors reviewed the manuscript

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**References**

1. Dupin E, Le Douarin NM: Development of melanocyte precursors from the vertebrate neural crest. *Oncogene* 2003, 22(20):3016-3023.
2. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE: Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004, 22(14):2865-2872.
3. Liubinas SV, Maartens N, Drummond KJ: Primary melanocytic neoplasms of the central nervous system. *J Clin Neurosci* 2010, 17(10):1227-1232.
4. Harstad L, Hess KR, Groves MD: Prognostic factors and outcomes in patients with leptomeningeal melanomatosis. *Neuro Oncol* 2008, 10(6):1010-1018.

5. Greco Crasto S, Soffietti R, Bradac GB, Boldorini R: Primitive cerebral melanoma: case report and review of the literature. *Surg Neurol* 2001, 55(3):163-168; discussion 168.

6. Brut DJ, Giannini C, Scheithauer BW, Burger PC: Primary melanocytic neoplasms of the central nervous systems. *Am J Surg Pathol* 1999, 23(7):745-754.

7. Zheng YC, Jung SM, Chang JWC, Huang YC: Primary intracranial melanoma: A case report and review of literature. *Chirurgia (Turin)* 2013, 26:411-414.

8. Byun J, Park ES, Hong SH, Cho YH, Kim YH, Kim CJ, Kim JH, Lee S: Clinical outcomes of primary intracranial malignant melanoma and metastatic intracranial malignant melanoma. *Clin Neurol Neurosurg* 2018, 164:32-38.

9. Kusters-Vandevelde HV, Klaasen A, Kusters B, Groenen PJ, van Engen-van Grunsven IA, van Dijk MR, Reifenberger G, Wesseling P, Blokx WA: Activating mutations of the GNAQ gene: a frequent event in primary melanocytic neoplasms of the central nervous system. *Acta Neuropathol* 2010, 119(3):317-323.

10. Habour JW, Onken MD, Roberson ED, Duan S, Cao L, Worley LA, Council ML, Matalall KA, Helms C, Bowcock AM: Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science* 2010, 330(6009):1410-1413.

11. Kusters-Vandevelde HV, Kusters B, van Engen-van Grunsven AC, Groenen PJ, van Dijk MR, Reifenberger G, Wesseling P, Blokx WA: Primary melanocytic tumors of the central nervous system: a review with focus on molecular aspects. *Brain Pathol* 2015, 25(2):209-226.

12. Kusters-Vandevelde HV, Kusters B, van Engen-van Grunsven AC, Groenen PJ, Wesseling P, Blokx WA: Primary melanocytic tumors of the central nervous system: a review with focus on molecular aspects. *Brain Pathol* 2015, 25(2):209-226.
37. Eroglu Z, Ribas A: Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. Ther Adv Med Oncol 2016, 8(1):48-56.

38. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, Chiarion-Sileni V, Thomas L, Lesimple T, Mortier L et al: Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multcohort, open-label, phase 2 trial. Lancet Oncol 2017, 18(7):863-873.

39. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P et al: Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015, 373(1):23-34.

40. Pluim D, Ros W, van Bussel MTJ, Brandsma D, Beijnen JH, Schellens JHM: Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid. J Pharm Biomed Anal 2019, 164:128-134.

41. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, Khushalani NI, Lewis K, Lao CD, Postow MA et al: Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med 2018, 379(8):722-730.

42. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, Wilmott JS, Edwards J, Gonzalez M, Scolyer RA et al: Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018, 19(5):672-681.

43. van Bussel MTJ, Beijnen JH, Brandsma D: Intracranial antitumor responses of nivolumab and ipilimumab: a pharmacodynamic and pharmacokinetic perspective, a scoping systematic review. BMC Cancer 2019, 19(1):519.

Tables

Table 1. Demographic characteristics and clinical demonstrations of patients from our institutional case series

| Case No. | Age (yrs) | Sex | Multiplicity | Tumor Size (cm) | Tumor Localization | Eloquent Area | Congenital Melanocytic Nevus | Tumor Bleeding | LM | Hydrocephalus | KPS at D’x | Surgical Resection | Recurrence Interval (mos) |
|----------|-----------|-----|--------------|-----------------|-------------------|---------------|-----------------------------|---------------|----|--------------|-----------|---------------------|--------------------------|
| 1        | 27.3      | M   | S-> Mu       | 2.8             | R; F-T            | N              | Right face; chest           | Y             | N->Y | N->Y         | 90        | GTR                 | 41.47                    |
| 2        | 56.7      | M   | S-> Mu       | 2.5             | R; F              | N              | N                           | Y             | N->Y | N->Y         | 40        | IR                  | 5.70                     |
| 3        | 33.8      | M   | S-> Mu       | 1.8             | R; T              | N              | Right eyelid; right buccal mucosa | Y             | N->Y | N            | 90        | GTR                 | 71.17                    |
| 4        | 31.8      | M   | S            | 2.4             | L; O-P            | Y              | Neck                        | Y             | N->Y | N->Y         | 20        | IR                  | 10.93                    |
| 5        | 39.5      | F   | S-> Mu       | 5.8             | L; F-P            | Y              | N                           | Y             | Y    | N->Y         | 30        | IR                  | 4.50                     |
| 6        | 57.7      | M   | S-> Mu       | 2.5             | L; C              | N              | Left face; conjunctiva      | N             | N->Y | N            | 90        | GTR                 | 27.63                    |
| 7        | 24.0      | M   | S-> Mu       | 3.1             | L; T              | Y              | N                           | Y             | Y    | N->Y         | 70        | IR                  | 5.37                     |
| 8        | 23.6      | M   | Mu           | 2.0             | L; T; R; F       | Y              | Sacral skin                 | Y             | Y    | Y            | 30        | biopsy              | 1.15                     |
| 9        | 35.8      | M   | Mu           | 4.5             | L; T-P; BG       | Y              | Chest; left knee            | Y             | Y    | N->Y         | 10        | IR                  | 1.87                     |
| 10       | 22.4      | F   | S            | 4.2             | L; T              | N              | N                           | N             | N    | N            | 90        | GTR                 | 48.43a                   |

M= male; F= female; S= single; Mu= multiple; R= right; L= left; F= frontal; T= temporal; O= occipital; P= parietal; C= cerebellum; BG= basal ganglion; KPS= Karnofsky performance status; D’x= diagnosis; GTR= grossly total resection; IR= incomplete resection; OP= operation; LM= leptomeningeal metastases; RT= radiotherapy; CT= chemotherapy

a no evidence of recurrence in MRI follow-up in 2020/02

b patient still alive at last follow-up in 2020/02

Table 2. Primary characteristics and univariate analyses of unfavorable factors in the solitary type of PIMM
| Variable of Interest                  | No. | Median Progression-free Survival Time (mons) | Log-rank Test (p value) | Median Survival Time (mons) | Log-rank Test (p value) | 1-year Survival Rate (%) | 3-year Survival Rate (%) |
|--------------------------------------|-----|---------------------------------------------|-------------------------|-----------------------------|-------------------------|--------------------------|--------------------------|
| Age at Diagnosis (yrs)               |     |                                             |                         |                             |                         |                          |                          |
| < 40                                 | 8   | 5.37                                        | 0.820                   | 14.93                       | 0.556                   | 62.5                     | 37.5                     |
| ≥ 40                                 | 2   | 5.70                                        |                         | 11.73                       |                         | 50                       | 50                       |
| Gender                               |     |                                             |                         |                             |                         |                          |                          |
| Female                               | 2   | 4.50                                        | 0.510                   | 5.23                        | 0.851                   | 50                       | 50                       |
| Male                                 | 8   | 5.70                                        |                         | 14.93                       |                         | 62.5                     | 37.5                     |
| Multiplicity (initial)               |     |                                             | 0.001*                  |                             | 0.001*                  |                          |                          |
| Single                               | 8   | 10.93                                       |                         | 19.20                       |                         | 83.3                     | 66.7                     |
| Multiple                             | 2   | 1.15                                        |                         | 1.15                        |                         | 0                        | 0                        |
| Tumor Diameter (cm)                  |     |                                             | 0.509                   |                             | 0.400                   |                          |                          |
| < 3                                  | 6   | 10.93                                       |                         | 19.20                       |                         | 66.7                     | 50                       |
| ≥ 3                                  | 4   | 4.50                                        |                         | 5.23                        |                         | 25                       | 25                       |
| Initail Tumor Sites                  |     |                                             |                         |                             |                         |                          |                          |
| Infratentorium                       | 1   | 27.63                                       | 0.920                   |                             | 0.224                   | 100                      | 100                      |
| Supratentorium                       | 9   | 5.70                                        |                         | 14.93                       |                         | 55.5                     | 33.3                     |
| Right                                | 3   | 41.47                                       | 0.272                   | 96.56                       | 0.508                   | 66.7                     | 66.7                     |
| Left                                 | 7   | 5.37                                        |                         | 14.93                       |                         | 57.1                     | 28.6                     |
| Eloquent Area Involved               |     |                                             | 0.006*                  |                             | 0.013*                  |                          |                          |
| No                                   | 5   | 41.47                                       |                         | 170.40                      |                         | 80.0                     | 80.0                     |
| Yes                                  | 5   | 4.50                                        |                         | 5.23                        |                         | 40.0                     | 0                        |
| Congenital Melanocytic Nevus         |     |                                             | 0.934                   |                             | 0.553                   |                          |                          |
| Yes                                  | 6   | 10.93                                       |                         | 19.20                       |                         | 66.6                     | 50.0                     |
| No                                   | 4   | 5.37                                        |                         | 11.73                       |                         | 50.0                     | 25.0                     |
| Tumor Bleeding (initial)             |     |                                             | 0.001*                  |                             | 0.001*                  |                          |                          |
| No                                   | 2   | 10.93                                       |                         | 19.20                       |                         | 100                      | 100                      |
| Yes                                  | 8   | 1.15                                        |                         | 1.15                        |                         | 37.5                     | 25                       |
| Leptomeningeal Metastasis (initial)  |     |                                             | 0.001*                  |                             | 0.001*                  |                          |                          |
| No                                   | 7   | 27.63                                       |                         | 19.20                       |                         | 85.7                     | 57.1                     |
| Yes                                  | 3   | 1.87                                        |                         | 1.15                        |                         | 0                        | 0                        |
| Hydrocephalus (initial)              |     |                                             | 0.003*                  |                             | 0.003*                  |                          |                          |
| No                                   | 9   | 10.93                                       |                         | 19.20                       |                         | 66.7                     | 44.4                     |
| Yes                                  | 1   | 1.15                                        |                         | 1.15                        |                         | 0                        | 0                        |
| KPS at Diagnosis                     |     |                                             | 0.004*                  |                             | 0.004*                  |                          |                          |
| ≥ 80                                 | 4   | 41.47                                       |                         | 170.40                      |                         | 100                      | 100                      |
| < 70                                 | 6   | 4.50                                        |                         | 5.23                        |                         | 33.3                     | 0                        |
| Neurosurgery                         |     |                                             | 0.004*                  |                             | 0.004*                  |                          |                          |
| GTR                                  | 4   | 71.17                                       |                         | 170.40                      |                         | 100                      | 100                      |
| No GTR                               | 6   | 4.50                                        |                         | 5.23                        |                         | 33.3                     | 0                        |
| Adjuvant Radiotherapy                |     |                                             | 0.302                   |                             | 0.765                   |                          |                          |
| Yes                                  | 6   | 5.37                                        |                         | 14.93                       |                         | 66.7                     | 50                       |
|                | 4 | 5.70 | 11.73 | 50  | 25  |
|----------------|---|------|-------|-----|-----|
| Adjuvant Chemotherapy | 0.149 | 0.253 |
| Yes            | 2 | 41.47| 96.56 | 100 | 100 |
| No             | 8 | 5.37 | 11.73 | 50  | 25  |

* Log rank test analysis reaches significance

Due to technical limitations, table 3 is only available as a download in the Supplemental Files section.