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

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## Abstract

# Purpose

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. Adjuvant 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. Adjuvant 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 (Dupin and Le Douarin 2003). 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 (Barnholtz-Sloan et al. 2004). 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 (Liubinas et al. 2010). 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 (Harstad et al. 2008). 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.

## Patients 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. 201800203B0D001). 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). Two patients had leptomeningeal metastases including one had cavernous sinus involvement according to operative findings (Fig. 1E). Only four patients (40%) carried on performing normal activities and work without special care according to Karnofsky performance status (KPS) at diagnosis. A summary of the patients' characteristics is listed in Table 1. Diagnosis was made by regular hematoxylin and eosin stain. Immunohistochemical studies confirmed positive human melanoma black-45 and S100 (Fig. 1I-L).

### *Treatment*

Gross total resection (GTR) was achieved in most patients (60%). Three (30%) had incomplete resection and one (10%) had biopsy, only because the disease was at the terminal stage with diffuse leptomeningeal metastasis and hydrocephalus (Fig. 1FG). Six (60%) had received post-operative radiotherapy with 60 Gy in 30 fractions. Adjuvant chemotherapy was performed after gross total tumor removal in cases 1 and 3. The adjuvant therapy was arranged according to surgeon's determination. Seven patients (70%) had repeated surgical excision due to recurrence. One patient had 9 episodes of surgical excision between February 1993 and March 2007 for repeated tumor bleeding.

### *PFS and OS*

Nine (90%) recurrence events occurred in their clinical course and eight (80%) deaths were recorded in last follow-up. The mean PFS was 21.82months (range, 1.15–71.17 months; median, 8.32 months). The mean OS was 51.83 months (range, 1.15–146.83 months; median, 17.07 months) (Fig. 1M). The 1 and 3 year OS rates were 60% and 40%, respectively. At the last follow-up in February 2020, two survivors underwent GTR initially.

### *Survival Analyses*

The analyses for variables of interest to PFS and OS are listed in Table 2. According to log-rank test, the factors including initial multiplicity ($p$ = 0.001), eloquent area involvement ($p$ = 0.013), initial tumor bleeding ($p$ = 0.001), initial leptomeningeal metastasis ($p$ = 0.001), initial hydrocephalus ($p$ = 0.003), Karnofsky performance status< 80 ($p$ = 0.004) at diagnosis, and no GTR ($p$ = 0.004) negatively influenced the prognosis of PIMM in solitary type with statistical significance (Fig. 2A-G). Tumor bleeding occurred before or at the time of leptomeningeal metastases. As patients had developed leptomeningeal metastases according to image or operation findings, the median survival time was 17.5 months (range, 2.2–144.3 months). Hydrocephalus following the leptomeningeal metastases contributed to dismal outcomes. After developing of hydrocephalus, the median survival time was only 5.02 months (range, 0.7–8.1 months). For the patient with leptomeningeal metastases who could not undergo gross total tumor removal, adjuvant radiotherapy after the operation led to longer survival but did not reach statistical significance ($p$ = 0.338, Fig. 2H).

## Discussion

Primary malignant melanomas of the CNS are life-threatening. They account for 1% of all cases of melanoma (Greco Crasto et al. 2001). These tumors were derived from melanocytes and can normally be found in the leptomeninges (Brat et al. 1999). All organs of the CNS including the spinal cord (Zheng et al. 2013) could be sites of the primary malignant melanomas, although extremely rare. PIMM only comprises 0.07% among all CNS tumors (Byun et al. 2018). 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 (Kusters-Vandevelde et al. 2010; Kusters-Vandevelde et al. 2015). Other mutations in *BAP1*(Harbour et al. 2010), *SF3B1*(Harbour et al. 2013) and *EIF1AX* (Martin et al. 2013) have also been identified. In a targeted next generation sequencing study presented by van de Nes et al. (van de Nes et al. 2016), 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 (Hodis et al. 2012; Krauthammer et al. 2012). 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 ($^{18}$F-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 (Ma et al. 2015; Allcutt et al. 1993; Gibson et al. 1957). 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 (Rodriguez y Baena et al. 1992). 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 (Andersen and Olsen 2018). The bleeding risk of melanoma in the brain was higher than others (Licata and Turazzi 2003; Kondziolka et al. 1987). A previous study reveals a tumor bleeding rate of 39.6% (Wronski and Arbit 2000). 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 (Pan et al. 2018). 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 (Keep et al. 2014; Arvanitis et al. 2020; Assi et al. 2015). 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. (Li et al. 2019) and Aria et al. (Arai et al. 2018), gross tumor resection was most important to survival. Patients who underwent gross tumor resection had a significantly longer survival ( >22 months) (Arai et al. 2018) or overall 40.8% survival in 3 years than those who did not (Li et al. 2019). 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 (Li et al. 2019; Primoz 2010). 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 (Goyal et al. 2015). 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 (Li et al. 2019; Hung et al. 2019; Puyana et al. 2019; Arai et al. 2018). 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 neurologic 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 (Corbin and Nagpal 2016). 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 (Li et al. 2019). DTIC has an effectiveness of 16% to 20%. However, in uveal melanoma, DTIC-based chemotherapies are ineffective (Bedikian et al. 1995). In a review of blood–brain and blood–tumor barriers, melanoma cells displayed a vessel co-option phenotype (Arvanitis et al. 2020), 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 (Eroglu and Ribas 2016). Dabrafenib plus trametinib had a good but short response to BRAFV600-mutant melanoma with brain metastases (Davies et al. 2017). However, the incidence of BRAF V600 mutation was low in a previous study (van de Nes et al. 2016). 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 (Larkin et al. 2015). The nivolumab concentrations ranged from 35 ng/ml to 150 ng/ml with a CSF/serum ratio of 0.88%–1.9% (Pluim et al. 2019). Two phase II studies with the combination nivolumab and ipilimumab revealed clinically meaningful intracranial efficacy on metastatic melanoma (Tawbi et al. 2018; Long et al. 2018). A systemic review suggested that ipilimumab and nivolumab are active in melanoma brain metastases (van Bussel et al. 2019). 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.

## Limitation

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.

## Declarations

**Funding:** The study has received no financial support

**Conflicts of interest/Competing interests:** All the authors have no conflict of interest to declare.

**Availability of data and material:** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

**Code availability:** *The code that support the findings of this study are available from the corresponding author, upon reasonable request*

**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

**Ethics approval:** The"C**hang 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.

**Consent to participate:** 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

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## Abbreviations

CNS: entral 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

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## Tables

| 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) | OP Times | Adjuvant RT | Adjuvant CT | Survival (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 | 9 | Y | Y | 170.40 |
| 2 | 56.7 | M | S-> Mu | 2.5 | R; F | N | N | Y | N-> Y | N-> Y | 40 | IR | 5.70 | 2 | N | N | 11.73 |
| 3 | 33.8 | M | S-> Mu | 1.8 | R; T | N | Right eyelid; right buccal mucosa | Y | N-> Y | N | 90 | GTR | 71.17 | 3 | Y | Y | 96.56 |
| 4 | 31.8 | M | S | 2.4 | L; O-P | Y | Neck | Y | N-> Y | N-> Y | 20 | IR | 10.93 | 3 | N | N | 19.20 |
| 5 | 39.5 | F | S-> Mu | 5.8 | L; F-P | Y | N | Y | Y | N-> Y | 30 | IR | 4.50 | 2 | Y | N | 5.23 |
| 6 | 57.7 | M | S-> Mu | 2.5 | L; C | N | Left face; conjuntiva | N | N-> Y | N | 90 | GTR | 27.63 | 1 | N | N | 146.83[b] |
| 7 | 24.0 | M | S-> Mu | 3.1 | L; T | Y | N | Y | N-> Y | N | 70 | IR | 5.37 | 2 | Y | N | 14.93 |
| 8 | 23.6 | M | Mu | 2.0 | L; T, R; F | Y | Sacral skin | Y | Y | Y | 30 | biopsy | 1.15 | 1 | N | N | 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 | 2 | Y | N | 3.81 |
| 10 | 22.4 | F | S | 4.2 | L; T | N | N | N | N | N | 90 | GTR | 48.43[a] | 1 | Y | N | 48.43[b] |

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

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 urivariate analyses of unfavorable factors in the solitary type of PIMM

| Variable of Interest | | | | | | | |
|---|---|---|---|---|---|---|---|
| Covariate | No. | Median Progression-free Surival 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) | | | 0.820 | | 0.556 | | |
| < 40 | 8 | 5.37 | | 14.93 | | 62.5 | 37.5 |
| ≧40 | 2 | 5.70 | | 11.73 | | 50 | 50 |
| Gender | | | 0.510 | | 0.851 | | |
| Female | 2 | 4.50 | | 5.23 | | 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 |
| No | 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

**Table 3 is available as a download in the supplementary files section.**

## Figures

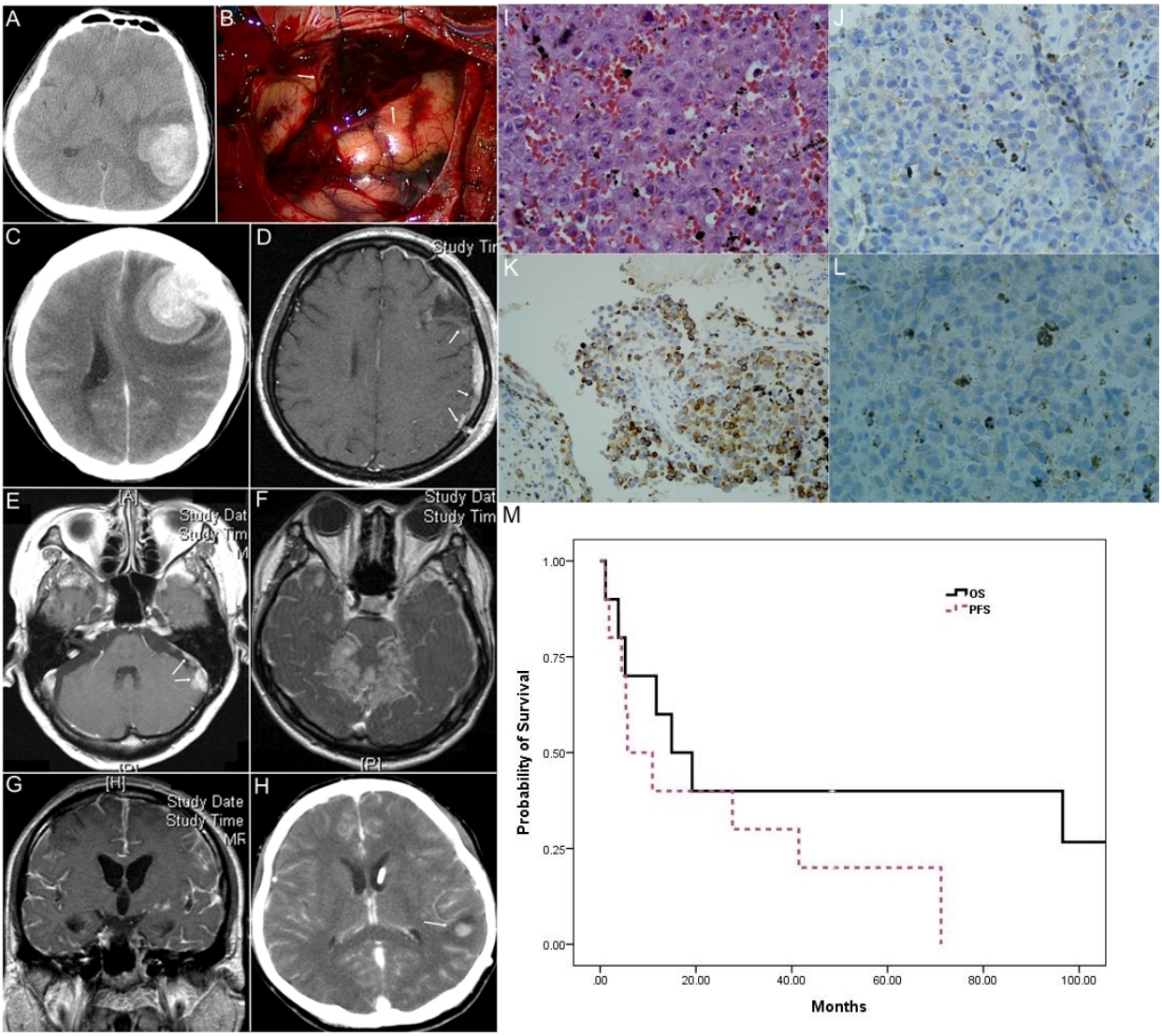


**Figure 1**

Radiological and clinical features of solitary PIMM. (A) Tumor hemorrhage in the brain CT was a special presentation of solitary PIMM that led to rapidly conscious disturbance and neurosurgical emergency in case 9. (B) Melanin deposits in surrounding meninges were noticed in case 9. White arrows showed the mixture of hematoma and melanoma. (C) Tumor was adjacent to eloquent area and major vessels, preventing case 5 from undergoing total tumor removal. (D) Intensity modulated radiation therapy was delivered with the help of CT to residual tumor area with adequate margins. Normal brain tissue was spared as much as possible. T1-weighted brain MRI with contrast highlighted the residual tumor with leptomeningeal metastasis in case 5 after the treatment (white arrows). (E) The solitary PIMM spread to the other parts of the brain by leptomeningeal metastasis. Infratentorial meninges were compromised from supratentorial PIMM in case 3. White arrows showed leptomeningeal tumor seeding at left tentorium. (F) End-stage leptomeningeal metastasis caused diffuse metastatic melanoma in cerebellum (white arrows) in case 8. (G) Diffuse leptomeningeal metastasis also led to CSF disturbance and hydrocephalus in case 8. (H) After VP shunt insertion for palliative treatment, the hydrocephalus temporally improved. However, another tumor bleeding (white arrows) was noted during follow-up in case 8. Histopathologic examinations for the solitary-type PIMM. (I) Routine hematoxylin and eosinstain showed neoplastic epithelioid cells with prominent nucleoli and pigmentation in blood clots. (J) S100 expression increased. (K) Anti-melanin antibody (HMB45) stain showed positive result. (L) Epithelial membrane antigen stain shows negative that indicates meningiomas or adenocarcinomas are less likely. (M) Kaplan-Meier survival curve for progression-free survival and overall survival of patients with solitary type PIMM.

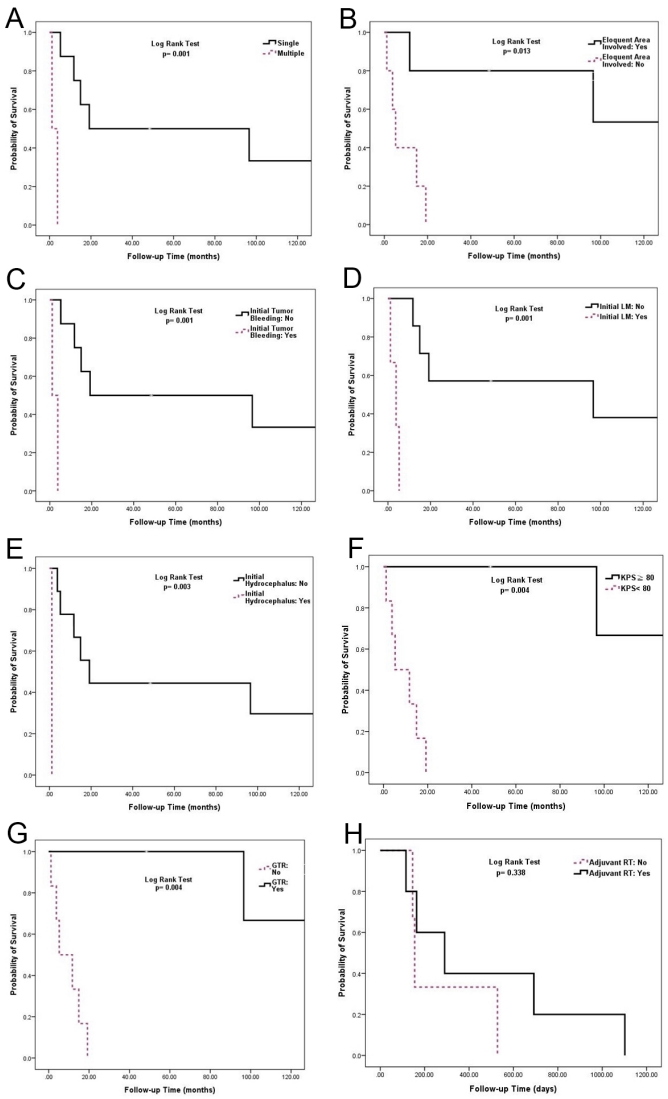


Figure 2

Kaplan-Meier survival rate by (A) initial multiplicity, (B) initial eloquent area involved, (C) initial tumor bleeding, (D) initial LM, (E) initial hydrocephalus, (F) KPS at diagnosis, and (G) GTR. (H) Kaplan-Meier survival rate for adjuvant RT to patients died of LMs.

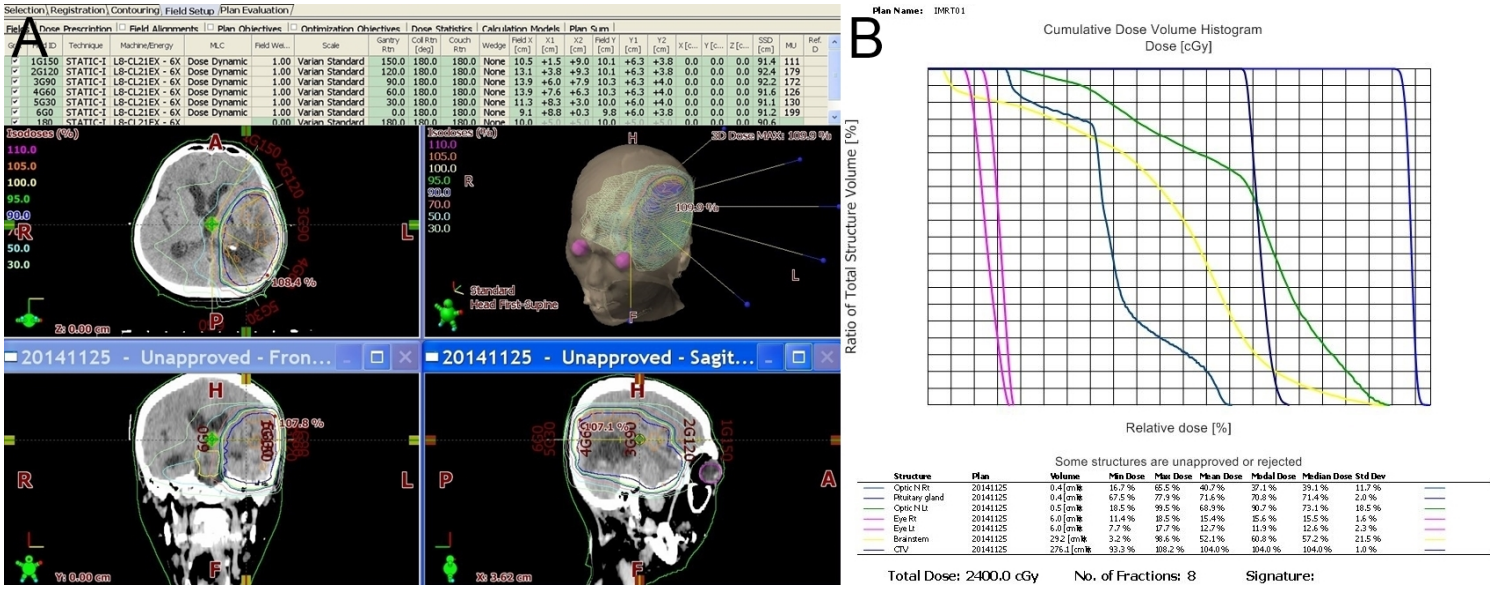


Figure 3

Intensity-modulated radiation therapy for case 9 who was unable to received total tumor resection due to eloquent cortex involvement. (A) Adjuvant radiotherapy plan for control of recurrent tumor and leptomeningeal metastases. (B)The radiation intensity of each beam is modulated to protect the eloquent area and to decrease the spectrum of vital tissue toxicities.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table3JCRCO.pdf
- SpringerNatureTransferDesk.docx