Primary Intracranial Malignant Melanomas: Retrospective Analysis of Management in a Single Chinese Institution and literature Review

Lifeng Chen  
The first medical center of the Chinese PLA General Hospital

Yang Yang  
The second medical center of the Chinese PLA General Hospital

Dongmei Li  
The second medical center of the Chinese PLA General Hospital

Bo Bu  
The first medical center of the Chinese PLA General Hospital

xiaodong ma (✉️ maxiaodong301@126.com)  
The first medical center of the Chinese PLA General Hospital  https://orcid.org/0000-0002-5404-6480

Research

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Abstract

**Background:** Primary intracranial malignant melanoma (PIMM) is a rare malignant tumor. The authors retrospectively reviewed and discussed the clinical features, treatment modalities, and clinical outcomes of patients with histologically proven PIMM.

**Methods:** The data of 15 patients with PIMM in our hospital within 14 years (from January 2005 to January 2019) were collected. The clinical and imaging presentations, pathology, surgical strategies, adjuvant treatment and the prognosis were analyzed in this study.

**Results:** Eleven men and 4 women with mean age 37.9 years (19-61 years) were observed over an average follow-up period of 22.6 months (range, 6–36 months). CT showed iso or high density in 12 cases (80%). MRI scans indicated that 14 tumors were mainly hyperintensity on T1 weighted images, hypointensity on T2 weighted images, and had no or mild enhancement. The treatment modalities included total resection followed by conventional radiotherapy (RT) (n=12), and subtotal resection followed by stereotactic radiosurgery (SRS) (n=3). Fifteen cases had recurrence or metastasis at the average 14.7 months (6-23 months): local recurrence (8 cases), distant metastasis (5 cases), both of them (2 cases). Fourteen cases (93.3%) died and the mean overall survival was 22 months (6-36 months). The median survival period was 23 months. The overall survival rates at 1, 2 and 3 years were 80%, 47%, and 13%, respectively. Radical resection with RT was associated with longer overall survival (log-rank, p<0.05).

**Conclusions:** PIMM is an extremely rare tumor with poor prognosis, which is difficult to get correct preoperative diagnosis. Improvement of the recognition of MRI features of melanoma can increase the preoperative diagnosis rate, and radical resection with RT may provide longer overall survival rate. Targeted and immunotherapy therapies may provide promise as treatment options for PIMM.

**Background**

Primary intracranial malignant melanoma (PIMM) is a rare tumor, representing 0.07% of all intracranial tumors (1). It accounts for about 1% of all melanoma cases (2). Because of the rarity of PIMMs and the lack of randomized study, there are the high chance of misdiagnosis and limited knowledge regarding therapy. Resection or biopsy combination with adjuvant treatment, including whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), chemotherapy, and/or immunotherapy are recommended (3). Gross total resection can improve the outcomes of PIMMs (3). But the benefit of radiation therapy, chemotherapy and immunotherapy is still controversy, and the prognosis of the disease is poor. In the present study, we retrospectively reviewed the therapeutic strategies and follow-up combined with literature reviewing to better understand the clinical characteristics and the therapeutic schedule.

**Material And Methods**
Patients

During a 14-year period from January 2005 to January 2019, there were 15 consecutive patients with pathologically confirmed PIMM were treated in the Department of Neurosurgery of our hospital including 11 men and 4 women with mean age 37.9 years (19-61 years).

The study was approved by the Ethics Board of the Chinese People's Liberation Army (PLA) General Hospital. Patients with a postoperative pathological diagnosis of malignant melanoma were included based on the following criteria outlined by Willis

Patient Evaluation

CT imaging was performed in 12 patients. Magnetic resonance imaging (MRI) was performed for all 15 patients before and after surgical treatment. Tumor size was defined as the greatest tumor diameter on MRI. Gross total resection (GTR) was defined as 100% gross resection of the tumor. There was no residual tumor on MRI within 3 months after operation. Subtotal resection (STR) is close to total resection, but the purpose is incomplete resection. The postoperative MRI showed tumors that increased in size were considered as tumors recurrence or regrowth. All 15 patients were followed up by neuroimaging and neurological examination. Neurological and imaging examinations were carried out preoperatively, at 3 months postoperatively, and at 1 year to 3 years intervals after surgery. The Karnofsky Performance Status (KPS) score was also determined for each patient based on clinical evaluation.

Surgical tumor specimens were fixed in formaldehyde and embedded in parain. It underwent microscopic and immunohistology-chemical analysis. Two senior neuropathologists independently verified the histological examinations.

Statistical Methods

The characteristics of patients were described in descriptive statics. Kaplan–Meier method was used to analyze overall survival (OS); P-values are considered significant if less than 0.05. All statistical analyses were performed using SPSS, version 19.0 (SPSS, Chicago, IL, USA).

Results

Preoperative characteristics
The duration of preoperative symptoms was 6 days to 2 years, with an average of 6.3 months. The demographics and presenting symptoms of 15 patients are described in detail in Table 1. Twelve CT scans and 15 MRI scans were performed. CT showed iso or high density in 12 cases (80%) (Figure 1a, Figure 2a, Figure 3a, Figure 4a). MRI showed short T1 and slightly short T2 in 14 cases (93.3%) (Figure 1b, c, Figure 2b, c, Figure 3c, d, Figure 4b, c). The tumors showed mild or no enhancement on enhanced MRI (Figure 3e). The maximum diameter of tumor was 2.5–8.0 cm, with an average of 4.6 cm. 14 patients had solitary tumors (93.3%). One patient had two tumors located in the supratentorial region. Peritumoral brain edema was observed in 3 cases (20%). Based on the preoperative MRI, three patients (20%) were accurately diagnosed with melanoma. Other patients were misdiagnosed as glioma, metastasis, schwannomas or meningiomas.

Table 1

Summary of 15 patient’s characteristics with primary malignant intracranial melanomas.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Mean age, years</td>
<td>37.9 (range 19-61)</td>
</tr>
<tr>
<td>Males: Females</td>
<td>11:4</td>
</tr>
<tr>
<td>Major symptoms and signs</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Vomit</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Weakness of left limb</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Tinnitus and deafness</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Numbness of left face</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Mean symptom duration, months</td>
<td>6.3 (range 6 days-2 years)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Cerebral</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>CPA</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Foramen magnum</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Middle fossa</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Mean size, cm</td>
<td>4.6 (range 2.5-8.0)</td>
</tr>
<tr>
<td>Median pre-operative KPS</td>
<td>80 (range 70-90)</td>
</tr>
</tbody>
</table>

**Surgical characteristics**

The tumors were removed through the different approaches according to the location of tumor. During the operation, the dura mater or the surrounding brain tissue were found to be black in 6 cases, the tumor was black (Figure 1e, Figures 2e, f) in 14 cases and tan appearance in 1 case. Tumors were soft and mild or moderate vascularized. Two cases of supratentorial tumor had hemorrhage. Intraoperatively, the involved the section of the dura involved with the tumors was coagulated or removed. GTR was achieved
in 12 cases (80%) (Figures 1d, g, Figure 2d, Figure 3f, Figure 4d). STR was achieved in 3 cases (20%) because of their close relationship with pyramidal tract.

There was no perioperative mortality. Facial paralysis was observed in one patient. He recovered after three months. One patient had postoperative intracranial infection. He was successfully treated with continuous drainage of cerebrospinal fluid for 5 days. At time of discharge, the preoperative neurological function was maintained or improved in 14 patients (93.3 %). The KPS scores ranged from 70 to 100 (Table 2).

Table 2
Outcome of treatment in 15 patients with primary malignant intracranial melanomas.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade of resection</td>
<td></td>
</tr>
<tr>
<td>Total resection</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>3</td>
</tr>
<tr>
<td>Recurrence after first treatment</td>
<td></td>
</tr>
<tr>
<td>local recurrence alone</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Metastasis alone</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Both</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Location of metastasis</td>
<td></td>
</tr>
<tr>
<td>Cerebellar</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Multiple cerebral metastases</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Time to local recurrence(n=10) Mean, months</td>
<td>13.6 (range, 6–20)</td>
</tr>
<tr>
<td>Time to metastasis(n=7) Mean, months</td>
<td>16.5 (range, 12–23)</td>
</tr>
<tr>
<td>to extraneural metastasis(n=5) Mean, months</td>
<td></td>
</tr>
<tr>
<td>Time to overall death(n=14)</td>
<td></td>
</tr>
<tr>
<td>Mean, months</td>
<td>22 (range, 6–36)</td>
</tr>
<tr>
<td>Mean follow-up duration, months</td>
<td>22.6 (range, 6–36)</td>
</tr>
<tr>
<td>Median post-operative KPS</td>
<td>90 (70–100)</td>
</tr>
</tbody>
</table>

Postoperative course and follow-up
Adjuvant treatments included conventional radiotherapy (RT) and stereotactic radiosurgery (SRS). No patients received adjuvant chemotherapy. All 12 patients with GTR underwent postoperative conventional RT with a mean dose of 50 Gy (range, 45–54 Gy) in 1.8–2 Gy fractions. Three patients with STR received Cyber Knife radiosurgery (CKRS; Accuray, Sunnydale, CA, USA). The average follow-up was 22.6 months (range, 6–36 months). All 15 patients were independent at 1 month postoperatively. Fifteen cases had recurrence or metastasis (Figure 1h) at the average 14.7 months (6-23 months): local recurrence (8 cases), distant metastasis (5 cases), both of them (2 cases). Of the 15 patients, 4 patients received second surgery, 1 patient received radiosurgery. The average progression free survival time was 16 and 8 months in the GTR combined with RT and STR combined with CKRS groups, respectively (a difference of 8 months, p=0.001; Figure 5). The mean overall survival was 22 months (6-36 months) (Figure 6). The median survival period was 23 months (Table 1). Fourteen patients died due to the tumor. The overall survival rates at 1, 2 and 3 years were 80%, 47%, and 13%, respectively. The average survival time was 25 and 9 months in the GTR combined with RT and STR combined with CKRS groups, respectively (a difference of 16 months, p=0.000; Figure 7).

Pathological examination

The senior neuropathologist verified the histological examinations. Microscopic examination showed the typical histological diagnosis of malignant melanoma (Figure 1f, Figure 2g). The most tumor cells contained rich melanin and large nuclei. The giant polygonal or spindle-shaped cells could be seen, and mitosis was usually noted. Immunohistochemical analysis demonstrated the positive rates of S-100 protein, antimelanoma antibody (HMB-45) and Vimentin (VIM) were 14 cases (93.3%), 13 cases (86.7%) and 13 cases (86.7%) respectively. The marker of proliferation Ki-67 labeling index in all the tumors ranged from 10% to 30%.

Discussion

Epidemiology and clinical features

Primary intracranial melanoma is a rare tumor in the central nervous system (CNS), which was first described by Virchow in 1859 (5). The estimated incidence is 0.5 cases per 10,000,000 person-years in the literature (6). Malignant intracranial melanomas can be divided into two types including primary and secondary subtypes. The diagnosis of PIMMs should be consistent with that outlined by Willis (4). In this report, perioperative examination demonstrated all patients had no melanoma or non-brain melanoma surgical history in the other parts of body, and all of 15 patients were diagnosed with PIMM. While the reports of sex predominance in literature are inconsistent, and some studies showed male predominance (5,6). There was male predominance (male: female=11:4) in our series, which is consistent with the literature (7). The mean age of onset was 37.9 years (19-61 years), which is younger than that in the literature (1).
PIMMs were divided into diffuse meningeal tumors and solitary melanomas by Gibson in 1957 (3).
Although PIMMs can occur throughout the central nervous system, they are more likely to develop in the posterior cranial fossa, Meckel cave, and spinal cord, and often present with mass effect (5). In this study, 5 cases located Infratentorial, and 1 case located in middle and posterior cranial fossa. The clinical symptoms of PIMM are nonspecific and consistent with those of other malignant brain tumors. The most common clinical symptoms were intracranial hypertension and hydrocephalus (43.2%) in the literature (5), and the diffuse type has a higher possibility of intracranial hypertension and hydrocephalus than the solitary type (3). While the 14 cases were the solitary type tumors in this report. Symptoms at presentation include headache, vomiting, and focal neurological deficits. The most common clinical symptoms were headache, vomiting due to intracranial hypertension. The mean duration of symptoms was 6.3 months, longer than common intracranial malignant tumors.

Radiology

CT and MRI are very important for preoperative differential diagnosis of PIMMs. Typical PIMMs may show high density in CT scan, which needs to be differentiated from hemorrhage (Figure1a, Figure2a, Figure3a, Figure4a). But some PIMMs also display equal or low density in CT scan, and generally lack specificity. MRI is still the gold imaging diagnosis standard of PIMMs. MRI scans can reveal typical features of most PIMMs, which are high signal on T1 weighted images and low signal on T2 weighted images. It is different from that of other common intracranial tumors including meningioma, schwannoma, metastasis, and glioma. There is a bipolar dipole interaction between the unpaired electrons of the stable melanin organic radicals and the aquaporin, resulting in the shortening of T1 and T2 relaxation time and the generation of typical MRI features. The decrease of relaxation time is directly proportional to the content of melanin in melanoma (8).

Most of tumors with hyperintensity on T1 weighted images indicate hemorrhage, fat, or melanin. Furthermore, hypointensity on T2 weighted images may be a clue to distinguish lipoma from melanoma. Typical T1 and T2 weighted signals may provide clues for diagnosis of PIMMs. In this study, 14 tumors were mainly hyperintensity on T1 weighted images, hypointensity on T2 weighted images, and had no or mild enhancement. But only three patients were accurately diagnosed with melanoma before surgery. The definite diagnosis was not made until a typical black tumor was found during the operation. Intratumor hemorrhage which leads to MRI signal confusion and the rarity of melanoma make the correct initial diagnosis very difficult. However, the enhancement of the recognition to MRI features of melanoma can improve the preoperative diagnosis rate.

Histopathology and differential diagnosis

Pathological examination is standard protocol for diagnosis. Malignant melanomas can be diagnosed by routine H&E and immunohistochemically staining techniques. The cells of malignant melanomas are
densely pleomorphic, spindle-shaped cells with mitosis and abundant cytoplasm with melanin deposits \(^4\). In this report, the tumor tissue rich in melanin (Figure 1f), heteromorphous large cells with obvious nucleoli (Figure 2g) and giant tumor cells can be seen under a light microscope.

Immunohistochemically staining can differentiate malignant melanomas from other tumors. S-100 is highly sensitive (95\%) to malignant melanomas, and HMB-45 is another highly sensitive and specific pathological marker for diagnosing malignant melanomas \(^5, 9\). Vimentin (VIM) is a mesenchymal tumor marker, which can provide a complementary effect in the diagnosis and the differential diagnosis of PIMMs combined with other markers \(^5, 9\). In this report, the positive rates of S-100, HMB-45 and vimentin were 93.3\%, 86.7\% and 86.7\%, respectively, which were consistent with the literature.

**Treatments and outcomes**

Most authors \(^1, 5, 7, 10, 11\) agree gross total resection is the most important treatment for melanoma of the central nervous system. The incomplete removal increases the risk of recurrence and poor prognoses. The prognoses of the patients that received total resection are better than those of the patients who received incomplete resection \(^3, 11\). Total resection combined with postoperative radiotherapy seems to be the preferred treatment for eliminating mass effect, improving preoperative symptoms, and achieving a histological diagnosis \(^3\). Rodriguez \(^7\) reported the mean survival in patients who received total removal of their tumor (19.6 months) was significantly longer than that in patients who underwent partial resection or biopsy (9.3 months). Man \(^6\) reported complete surgical resection could increase the survival rate, while the age of less than 19 years and intracranial tumor were independent factors of poor prognosis. Subtotal resection or biopsy plus radiotherapy (chemotherapy) cannot change the survival of patients \(^5, 9, 12\). Our current study further validates the results. GTR with RT appeared to extend progression free survival. The average overall survival time of the GTR group was significantly higher than that in the STR group (25 versus 9 months, \(p=0.000\)). Surgical resection is based on the patients’ symptoms, the location, size and number of the lesion. Total resection should be attempted with microsurgical techniques on the basis of protecting nerve function. But it is difficult to achieve total resection because of the occult onset of the tumor, the abundant blood supply of the tumor and the close relationship between the tumor and the important neurological structure. In this group, GTR was achieved in 80\% cases, and STR was achieved in 20\% cases because the tumors had very close relationship with pyramidal tract.

Yamane \(^13\) reported the mean survival in patients with solitary tumors was 20.7 months. Man \(^6\) reported that the 1-year, 2-year, 3-year and 5-year survival rates of primary CNS melanoma were 89.3\%, 75.6\%, 65.2\%, 37.7\% respectively, and the median survival rate was 15 months. The median survival time was 23 months in this group. The treatment effect is basically the same as that reported in the literature, but due to the small number of cases, it is necessary to further increase the number of cases to analyze the treatment results.
Although many scholars reported that melanoma is not sensitive to the commonly used doses radiotherapy, some studies also showed that the addition of adjuvant radiotherapy to surgery significantly reduces the local recurrence risk compared with resection alone\(^{(11,14-17)}\). The combined application of WBRT and SRS is more effective than that of WBRT and SRS alone\(^{(11,15)}\). The prognosis of patients undergoing microsurgery combined with SRS and / or WBRT is better than that of patients undergoing microsurgery or WBRT\(^{(11,15)}\). In this study, 12 patients with GTR received adjuvant RT postoperatively, and other 3 patients with STR received CKRS. The average overall survival time of the GTR combined with RT group was significantly higher than that of STR combined with CKRS group.

The role of adjuvant chemotherapy for PIMMs is controversial. There is little evidence that chemotherapy carries significant effect for PIMMs. Chemotherapy drugs have not efficacy because they cannot penetrate the blood-brain barrier\(^{(11)}\). some authors reported when the tumors grow within the brain parenchyma, the blood-brain barrier is damaged in structure and function, increasing the permeability\(^{(11)}\). Adjuvant chemotherapy has shown limited effect in the management of metastatic melanoma\(^{(11)}\). There was no patient received postoperative chemotherapy in our series. Some authors\(^{(11,18-22)}\) reported that immunotherapy could prolong the overall survival of metastatic melanoma patients. Some clinical investigators\(^{(11,23,24)}\) were also exploring the effect of gene therapy (targeted therapy) on PIMMs. Gene therapy (targeted therapy) combined with immunotherapy could improve the prognosis of metastatic melanoma better than immunotherapy combined with radiotherapy\(^{(25)}\). These results also need further evaluation.

**Limitation**

A Solitary tumor with leptomeningeal enhancement could be have in a manner similar to diffuse leptomeningeal melanosis, which is considered be a benign feature, but with a very poor prognosis and a mean survival of 6.7 months\(^{(1)}\). In this series we excluded the patients with diffuse leptomeningeal enhancement who had no surgical indication. More patients and studies are required to confirm the role and efficacy of surgery and adjuvant therapy for PIMM. The incidence rate of this tumor is low, most of which are reported in the form of case report in literature. It is difficult to compare our report with other series in the literature.

**Conclusions**

PIMM is an extremely rare tumor with poor prognosis, which is difficult to get correct preoperative diagnosis. Improvement of the recognition of MRI features of melanoma can increase the preoperative diagnosis rate, and radical resection with RT may provide longer overall survival rate. Targeted and immunotherapy therapies may provide promise as treatment options for PIMM.

**Abbreviations**
Declarations

Acknowledgements

Not applicable.

Authors’ contributions

LC, YY, and XM contributed to the conception, design, and data analysis and drafted and revised the manuscript. DL and YY collected and analyzed the data. BB reviewed the manuscript. LC drew the simulated diagram of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital.

Consent for publication

The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.
Competing interests

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author details

1Department of Neurosurgery, The first medical center of the Chinese PLA General Hospital, No.28 Road Fuxing, Haidian District, Beijing, China.

2Department of Neurology, The second medical center of the Chinese PLA General Hospital, No.28 Road Fuxing, Haidian District, Beijing, China.

References


**Figures**
Preoperative, intraoperative and postoperative imaging and pathological examination of a 29-year-old female patient with left petrous apex melanoma. a) Preoperative axial CT showed a high-density lesion (red arrow). b) Preoperative axial T1WI showed an irregular high signal lobulated lesion (red arrow). c) Preoperative axial T2WI showed an irregular low signal lobulated lesion (red arrow). d) Axial CT at 1 day after surgery showed total tumor resection (red arrow). e) Intraoperative imaging showed melanoma (green arrow) with clear boundary. f) Postoperative Hematoxylin and eosin (H&E) staining at×100 showed the tumor tissue rich in melanin. g) Axial T1-weighted contrast-enhanced MRI at 12 months after surgery showed total tumor resection (white arrow). h) Axial T1-weighted contrast-enhanced MRI at 22 months after surgery showed melanoma metastasis (red arrow) of tentorial.
Figure 2

Preoperative and postoperative imaging, specimens and pathological examination of a 28-year-old male patient with right cerebellopontine angle melanoma. a) Preoperative axial CT showed a high-density round lesion (red arrow). b) Preoperative axial T1WI showed a high signal round lesion (red arrow). c) Preoperative axial T2WI showed a low signal round lesion (red arrow). d) Postoperative axial T2WI showed total tumor resection (red arrow). e) Intraoperative imaging showed black melanoma (asterisk). f) Melanoma specimen. g) Postoperative Hematoxylin and eosin (H&E) staining at×400 showed heteromorphous large cells with obvious nucleoli.
Figure 3

Preoperative and postoperative imaging of a 43-year-old male patient with foramen magnum melanoma. a) Preoperative axial CT showed a high-density round lesion (red arrow). b) Preoperative sagittal CT showed a high-density round lesion (red arrow). c) Preoperative axial T1WI showed a high signal round lesion (red arrow). d) Preoperative axial T2WI showed a low signal round lesion (red arrow). e) Preoperative sagittal T1-weighted contrast-enhanced MRI showed mild enhancement lesion (red arrow). f) Axial CT at 1 day after surgery showed total tumor resection (red arrow).
Figure 4

Preoperative and postoperative imaging of a 34-year-old male patient with left cerebellopontine angle melanoma. a) Preoperative axial CT showed a high-density round lesion (red arrow). b) Preoperative axial T1WI showed a high signal round lesion (red arrow). c) Preoperative axial T2WI showed a low signal round lesion (red arrow). d) Axial CT at 1 day after surgery showed total tumor resection (red arrow).
Figure 5

The Kaplan-Meier curves of extended progression free survival of patients were treated with gross total resection (GTR) with radiotherapy (RT).
Figure 6

The Kaplan-Meier curve of overall survival of the 15 patients.
Figure 7

The Kaplan-Meier curves of extended overall survival of patients were treated with gross total resection (GTR) with radiotherapy (RT).