Primary Pineal Malignant Melanoma - Illustrated Review

ABSTRACT

AIM: Primary pineal melanoma is a rare tumor. We herein review the histogenesis, pathology, radiology and therapeutic options of this rare tumor.

MATERIAL and METHODS: We conducted a PUBMED search using a combination of keywords such as “primary pineal melanoma”, “CNS melanoma”, and “pineal tumor” and identified 16 cases of primary pineal melanoma. Clinical features, pathologic characteristics and treatment details of these patients were noted from respective case reports. We also describe a case of a 45-year-old Indian woman with primary pineal melanoma treated with a combination of surgery and post-op radiation.

RESULTS: The median age at presentation is 50 years. Median duration of symptoms is 6 weeks. Common symptoms at presentation include headache (58.8%), personality changes (41.2%), gait disturbance (35.3%) and Parinaud’s syndrome (29.4%). Surgery, radiotherapy and chemotherapy have been used in 29.4%, 47.1% and 23.5% of patients respectively. Median overall survival is 56 weeks. Leptomeningeal dissemination and ventricular ependymal spread were noted in 70.6% and 35.3% patients, respectively.

CONCLUSION: Combined modality treatment comprising maximal safe surgery and post-operative radiation should be preferred in patients with localized pineal melanoma without leptomeningeal dissemination. Taking a cue from other subsites of melanoma, chemotherapy can perhaps be deferred until recurrence.

KEYWORDS: Primary, Pineal, Melanoma, Tumor

ÖZ

AMAÇ: Primer pineal melanom nadir bir tümördür. Burada, bu nadir tümörün histogenezi, patolojisi, radyolojisi ve terapötik seçeneklerini gözden geçirdik.


BULGULAR: Medyan başvuru yaş 50 idi. Medyan belirti süresi 6 haftaydı. Başvuruda sık görülen belirtiler arasında baş ağrısı (%58,8), kişilik değişiklikleri (%41,2), yürüme bozukluğu (%35,3) ve Parinaud sendromu (%29,4) vardı. Hastaların sırasıyla %29,4, %47,1 ve %23,5’inde cerrahi, radyoterapi ve kemoterapi yapılmıştı. Medyan genel sağkalım 56 haftaydı. Leptomeningeal yayılım ve ventriküler ependimal yayılım hastaların sırasıyla %70,6 ve %35,3’ünde görülmüştü.

SONUÇ: Leptomeningeal yayılım olmadan, lokalize pineal melanomlu hastalarda maksimum güvenliklen cerrahi ve postoperatif radyasyon içeren kombin kombin modalite tedavisi tercih edilmelidir. Diğer melanom bölgeleri dikkate alınarak, kemoterapi nüks zamanına kadar gecektirilebilir.

ANAHTAR SÖZÇÜKLER: Primer, Pineal, Melanom, Tümör

INTRODUCTION

Primary pineal gland tumors represent 0.4-1% of intracranial tumors in adults and 3-8% of intracranial tumors in children (7, 12). Tumors of pineal region are of varied histology: germinoma (50%), teratoma (15%), choriocarcinoma (5%), pineal parenchymal tumor (15%) and others like glioma, meningioma, mesenchymal tumors and metastatic tumors (12, 15). Melanocytic tumor is the rarest of the pineal region tumors. Intracranial melanocytic tumors are commonly metastatic, accounting for the third largest group of central nervous system (CNS) metastases in adults (1). Primary central nervous system melanoma accounts for only 0.07% of all intracranial neoplasms (16). Primary central nervous system melanoma of pineal region is an exquisite rarity with only sixteen cases reported till date in available literature. We herein discuss the clinico-pathological features, radiology and treatment options of this enigmatic tumor citing a case of primary pineal melanoma treated with surgery followed by post-operative radiation.

REVIEW of LITERATURE

Incidence

Intracranial melanocytic tumors can be broadly divided into primary CNS melanoma, metastatic melanoma to CNS and melanocytic variant of other CNS tumors (14). Primary pineal melanoma is a rarity and constitutes 3.6% of all primary intracranial melanomas (15). Primary pineal malignant melanoma was first reported by Ogle in 1899, but even a century later only 17 such cases have been documented worldwide (1, 19).

Symptomatology

Pineal region tumors commonly present with features of raised intracranial tension like headache, vomiting and seizure. Symptoms may also be due to midbrain compression-cerebellar or sensorimotor disturbance; obstructive hydrocephalus due to compression of the aqueduct of Sylvius; hormonal imbalance due to hypothalamic involvement or perturbation of melatonin secretion- precocious puberty or hypogonadism. Patients may also present with Parinaud’s syndrome characterized by a triad of deficient upgaze, convergence retraction nystagmus and pupillary light reflex near dissociation due to compression of tectal plate by tumor (12).

Histogenesis

Primary intracranial melanoma may arise from melanoblasts accompanying the pial sheaths of vascular bundles or from neuroectodermal congenital rests (14, 20). Meninges separating the lobes of the pineal gland normally contain several melanocytes that may give rise to melanoma after malignant transformation (13, 25).

Pathology

Gross pathology usually shows diffuse pineal involvement and in some instances even complete replacement of the gland by a dark, encapsulated tumor. Foci of hemorrhage and necrosis are common. Leptomeningeal, ventricular and intraparenchymal invasion are frequently associated with high-grade lesion (11, 13, 19). Primary pineal malignant melanoma however remains confined to the CNS and there has been no report of extracranial dissemination till date.

Definitive diagnosis relies on histological appearance (presence of intracellular melanin), immunohistochemistry profile and ultrastructural features of the tumor. On microscopy, large pigmented cells growing in loose nests or sheets with varying degrees of pigmentation- dense to amelanotic, highly variable cytological atypia, mitotic activity and necrosis, increased MIB-1 labeling index (>3%) and invasion of surrounding CNS tissue are usually discerned. Electron microscopy reveals neoplastic cells with irregular nuclei and a variety of melanotic granules, ranging from premelanosomes to Type IV melanosomes (21). Immunohistochemical positivity to HMB 45, S-100 and Melan A are noted in majority of the tumors (1). The differential diagnosis includes other melanotic tumors of this region- meningeal melanocytoma, pineal anlage tumor, melanotic neuroectodermal tumor, melanotic ganglioglioma (5). CSF cytopathology showing atypical cells with pleomorphic nuclei and strongly eosinophilic cytoplasm may be suggestive of malignant melanoma. This may be confirmed by immunohistochemistry panel of HMB 45 and Melan A (4, 24). There might be occasional cases when pineal biopsy report is noninformative but CSF cytology shows atypical cells immunopositive for HMB45 & Melan A, aiding in diagnosis (4).

Radiology

Melanocytic neoplasms appear iso- to hyperdense with homogenous contrast enhancement with or without abnormal calcification on CT scan of brain. Pre-operative MRI helps in diagnosis, assessment of extent of lesion and classification of intracranial melanomas into melanotic and amelanotic types. The melanotic type contains more than 10% of melanin containing cells. The paramagnetic property of melanin is responsible for shortened T1 relaxation time rendering this group hyperintense on T1-weighted images, hypointense on T2-weighted images and isointense or hyperintense on proton density weighted MR images. Amelanotic type contains less than 10% melanin containing cells and is hypointense on T1- and hyperintense on T2- weighted MR images (1, 9). In a study of 42 patients with intracranial metastatic melanoma by Isiklar et al, 24 patients had a melanotic pattern, 38% had an amelanotic pattern and others (38%) had variable T1 and T2 signals due to intratumor hemorrhage (17). The author attributed the image findings to the melanin content based on correlation studies with histopathology. However, in a study involving 13 patients of intracranial melanoma, Woodruff et al attributed the imaging findings principally to hemorrhage with minor contribution from free radicals in melanin (27). MRI of the complete neuroaxis is recommended in all cases of CNS melanomas.
**Treatment**

Given the rarity of this tumor, treatment of choice is unclear but a combined modality treatment comprising surgery, radiation therapy and chemotherapy should be preferred (1, 18). The initial 5 patients reported till early 1970s did not receive any treatment and the tumor was mostly diagnosed at autopsy. Meningeal dissemination was noted uniformly in this cohort of 5 patients. Interestingly, one of these 5 patients underwent exploratory craniotomy but the primary lesion was not found (11).

Surgery is technically challenging in primary pineal melanoma due to complexity of the anatomical location of the tumor and frequent leptomeningeal dissemination. Also, it is difficult to obtain a pre-operative diagnosis of this rare tumor solely on the basis of radiology. Whenever feasible, maximal safe surgery should be attempted. Radiation therapy is an important component of the treatment arsenal and can be considered in a radical, post-operative or palliative setting. Chemotherapy also has been tried in this rare tumor with temozolomide being the most attractive option due to its proven efficacy in malignant melanoma, favorable toxicity profile and ease of administration.

**Pattern of Recurrence**

Primary pineal melanoma recurs intracranially. Leptomeningeal dissemination and ventricular ependymal spread are frequent causes of treatment failure in this group of tumor (15, 18).

**Treatment Outcome and Prognostic Issues**

As with metastatic intracranial melanoma, primary CNS melanoma carries a dismal prognosis. With aggressive intervention, patients with primary CNS melanoma survive on average 5 months. In case of primary pineal melanoma, overall survival varies from 4 to 280 weeks with 7 out of 17 patients surviving 1 year and beyond (Table I). The important determinants of long-term survival are degree of differentiation of tumor and leptomeningeal dissemination (4 &18).

**RESULT ANALYSIS**

Table I present a summary of the previous case reports of primary pineal malignant melanoma including our patient (1-4, 6, 8, 11, 13, 18, 19, 21-23, 26, 28). Table II highlights the therapeutic options and clinical outcome in this rare tumor.

The median age at presentation in patients with primary pineal melanoma is 50 years (range 20 -77 years). There is no sex predilection (male: female= 8:9). Median duration of symptoms before diagnosis is 6 weeks (range 1-40 weeks). Common symptoms include headache (58.8%), personality changes (41.2%), gait disturbance (35.3%), Parinaud's syndrome (29.4%), vomiting (23.5%), and motor impairment (11.8%).

Out of 17 patients of primary pineal melanoma, CT scan and MRI of brain were done in 9 and 10 patients respectively. CT brain uniformly showed a hyperdense pineal mass with calcification and post-contrast enhancement in 3 patients each. MRI brain showed a melanotic pattern in a large majority of patients (9/10). Post-contrast enhancement and leptomeningeal involvement (at presentation) were noted in 9 and 3 patients respectively.

Since 1990s, out of 9 patients with primary pineal melanoma, results of CSF cytology are available in 6 patients out of whom 4 show the presence of atypical cells (1, 18).

Only 5 out of 17 patients (29.4%) underwent surgery. Radiation therapy was given in 8 out of 17 patients (47.1%). Radical radiation was used in 4 patients (2-4, 18) and post-operative radiation was used in another 4 (1,21, 22). Systemic chemotherapy has been used in only 4 out of 17 (23.5%) patients of primary pineal melanoma with mixed response.

Leptomeningeal dissemination and ventricular ependymal spread were noted in 12 (70.6%) and 6 (35.3%) patients respectively. 4 out of 17 patients (23.5%) had features of tectal invasion by tumor. In case of primary pineal melanoma, median overall survival is 56 weeks with 7 out of 17 patients surviving 1 year and beyond (Figure 1).

**CLINICAL REPORT**

**History:** A 45-year-old woman presented with complaints of headache, recurrent vomiting, altered sensorium and blurring of vision for the last 2 weeks. Her headache increased in severity at night and early in the morning and was not relieved by non-steroidal anti-inflammatory drugs.

**Examination:** On neurological examination, altered sensorium, superior gaze palsy and positive cerebellar signs were noted. There was no sensorimotor deficit and sphincter control was normal. A detailed skin and ophthalmic examination did not reveal any cutaneous or ocular melanotic lesion. CSF cytology did not reveal any atypical cell.

**Figure 1:** Overall survival.
<table>
<thead>
<tr>
<th>Series [Year] (Ref)</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Time to diagnosis (wks)</th>
<th>Symptoms</th>
<th>CT</th>
<th>MRI</th>
<th>Treatment</th>
<th>Metastasis/ tumor extension</th>
<th>Survival (wks)</th>
</tr>
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<tbody>
<tr>
<td>Ogle [1899] (19)</td>
<td>32</td>
<td>F</td>
<td>3</td>
<td>Headache, paralysis, aphasia</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Pia-arachnoid</td>
<td>13</td>
</tr>
<tr>
<td>Stoerk et al. [1904] (23)</td>
<td>31</td>
<td>M</td>
<td>8</td>
<td>Parinaud's, headache, diplopia</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Meninges</td>
<td>12</td>
</tr>
<tr>
<td>Foot &amp; Zeek [1931] (11)</td>
<td>49</td>
<td>M</td>
<td>2</td>
<td>Headache</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Pia-arachnoid, third &amp; lateral ventricle</td>
<td>4</td>
</tr>
<tr>
<td>Gibson et al. [1957] (13)</td>
<td>68</td>
<td>F</td>
<td>8</td>
<td>Headache, vomiting, coma</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Pia-arachnoid, ependyma &amp; ventricle</td>
<td>8</td>
</tr>
<tr>
<td>Enriquez et al. [1973] (8)</td>
<td>43</td>
<td>M</td>
<td>32</td>
<td>Left sided weakness, changes in character</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Meninges</td>
<td>37</td>
</tr>
<tr>
<td>Arlant et al. [1977] (2)</td>
<td>56</td>
<td>M</td>
<td>40</td>
<td>Parinaud's, gait disturbance, memory impairment</td>
<td>None</td>
<td>None</td>
<td>Radiation</td>
<td>Meninges-ventricles</td>
<td>56</td>
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<td>Carlson et al. [1987] (6)</td>
<td>77</td>
<td>F</td>
<td>1</td>
<td>Gait disturbance, poor memory</td>
<td>None</td>
<td>None</td>
<td>VP shunt, Evacuation of hematoma, Biopsy</td>
<td>Meninges, tectal invasion, ventricles</td>
<td>5</td>
</tr>
<tr>
<td>Weindling et al. [1988] (26)</td>
<td>59</td>
<td>M</td>
<td>2</td>
<td>Headache, vomiting, papilledema</td>
<td>Small, noncalcified, heterogenously enhancing lesion posterior to third ventricle</td>
<td>Biopsy</td>
<td>Tectal invasion</td>
<td>NA</td>
<td></td>
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<tr>
<td>Author(s)</td>
<td>Age</td>
<td>Gender</td>
<td>Duration</td>
<td>Symptoms</td>
<td>Imaging Findings</td>
<td>Treatment</td>
<td></td>
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<tr>
<td>Yamane et al. [1994] (28)</td>
<td>53</td>
<td>F</td>
<td>2</td>
<td>Headache, Parinaud’s</td>
<td>Well-demarcated heterogeneous high-density mass with homogeneous enhancement</td>
<td>Resection Chemotherapy None &gt;280</td>
<td></td>
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<td>Mitchell et al. [1998]</td>
<td>49</td>
<td>M</td>
<td>12</td>
<td>Symptoms of raised intracranial tension, dysarthria, left homonymous quadrantanopsia</td>
<td>Pineal mass hyperintense on T1 with post contrast enhancement, diffuse leptomeningeal involvement</td>
<td>Biopsy Leptomeninges Not stated</td>
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<td>Suzuki et al. [2001] (22)</td>
<td>50</td>
<td>F</td>
<td>16</td>
<td>Poor memory</td>
<td>High-density mass in the pineal region with homogeneous enhancement</td>
<td>Resection Radiation Right hippocampus, ependyma, ventricles, bilateral frontal lobes, subarachnoid space. 88</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bookland et al. [2007] (4)</td>
<td>20</td>
<td>F</td>
<td>3</td>
<td>Headache cervical pain</td>
<td>Hyperdense mass in the pineal region extending into the posterior 3rd ventricle with calcification</td>
<td>Biopsy VP shunt Radiation Chemotherapy Subarachnoid dissemination involving the cerebellar folia &gt;37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barron Jane et al. [2007] (3)</td>
<td>73</td>
<td>F</td>
<td>Not stated</td>
<td>Headache, gait unsteadiness, diplopia, memory change</td>
<td>Mass lesion in the pineal region involving the tectum, heterogenous, predominantly high signal density</td>
<td>Radiation Tectal invasion Leptomeninges 69</td>
<td></td>
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</table>
Gadolinium-enhanced MRI of brain showed a 2x1.6x1.7 cm well demarcated lesion in pineal region- hyper intense on T1W images and hypointense on T2W images with intense post contrast enhancement causing obstructive hydrocephalus (Figure 2A-C).

Surgery: She underwent suboccipital craniotomy and tumor decompression by infratentorial, supracerebellar approach with VP shunt placement. Intraoperative findings included a well-defined, blackish, moderately vascular, firm, nonsuckable tumor in the pineal region with nice plane of cleavage. The postoperative course was uneventful.

Histopathology: Postoperative histopathology revealed an infiltrative neoplasm arranged in irregular nests of closely packed malignant cells with prominent nucleoli, some of which contained intracytoplasmic melanin pigment and frequent mitotic figures. Immunohistochemistry showed the tumor cells to be positive for HMB-45 and S-100 and negative for EMA, GFAP and chromogranin. Based on the morphological and immunohistochemical features, a diagnosis of primary pineal melanoma was suggested (Figure 3A-D).

Postoperative treatment: In view of the malignant histology, she was referred for adjuvant radiotherapy. Radiation therapy 59.4 Gy / 33 fractions / 6½ weeks (at 1.8 Gy per fraction) was delivered to the tumor bed by 3 dimensional conformal technique (3D-CRT) by 3 fields [left anterior oblique, right anterior oblique and superior vertex] with six MV photons. She tolerated radiotherapy well with no unplanned treatment break.

Follow-up: 2 months after completion of radiation therapy, the patient was asymptomatic. MRI brain showed no evidence of residuum or recurrence (Figure 2D). At last follow-up, the patient is disease free 40 weeks after diagnosis.

DISCUSSION

Primary pineal malignant melanoma is a rarity and the our patient is the first reported case from the Indian subcontinent. Considering the rarity of this tumor, there is no established protocol for its management. Previously published case reports suggest that this group of tumor can be managed by a judicious combination of surgery, radiotherapy and chemotherapy.

Surgical Policy

Surgery is technically challenging in primary pineal melanoma due to intricate tumor topography and frequent leptomeningeal dissemination. Only 5 out of 17 patients (29.4%) underwent surgery (1, 21, 22, 28). All of these 5 patients underwent subtotal resection. Proximity of the tumor to great cerebral vein of Galen precluded a complete resection in majority of cases. Whenever feasible, maximal safe resection should be attempted. A shunt should be placed beforehand in case of hydrocephalus.

Radiotherapy Policy

Radiation therapy is an important component of the
Figure 2: Preoperative MRI brain with A) T1-weighted axial image showing hyperintense lesion in the region of pineal gland with obstructive hydrocephalus and intense post-contrast enhancement, B) T2-weighted axial image showing hypointense lesion in the region of pineal gland with obstructive hydrocephalus, C) T1-weighted sagittal image showing hyperintense mass in the region of pineal gland compressing the tectum. Follow-up MRI brain with D) T2-weighted sagittal image showing no evidence of residual lesion or recurrence.

Figure 3: A,B) High-power (x400) histologic section (hematoxylin-eosin stain) shows an infiltrative neoplasm arranged in irregular nests of closely packed malignant cells, some of which contain intracytoplasmic melanin pigment (arrows) and frequent mitotic figures, C) High-power view (x400) shows strong immunoreactivity (brown-appearing areas) with the antibody HMB-45, which is the most specific marker for melanoma. These cells are melanocytes. D) The S–100 marker also shows marked positive staining of the tumor cells (nuclear staining).
therapeutic armamentarium in this rare tumor. Radiotherapy was delivered in 8 out of 17 patients (47.1%). Radiotherapy target volume encompasses the entire neuraxis in craniospinal irradiation, whole brain in whole brain radiation, and the tumor bed (pineal region) in local radiation. Rampant leptomeningeal dissemination often mandates whole brain radiation but local radiation to pineal region may be considered in localized tumor without meningeal spread. Tumor control dose varies from 50-60 Gray (Gy) in this rare tumor.

Radical radiation alone (60 Gy / 30 fractions / 6 weeks - 18 MV photons) resulted in prolonged survival of 56 weeks in a 73-year-old lady with primary pineal melanoma (3). Bookland et al. used gamma knife radiosurgery for stereotactic radiation to the pineal tumor followed by whole brain radiation and adjuvant temozolomide in a 20-year-old lady with primary pineal melanoma with leptomeningeal dissemination leading to clinical and radiological disease stabilization for 37 weeks (4). Martin-Blondel et al. used whole brain radiation in a 44-year-old gentleman with primary pineal melanoma with leptomeningeal dissemination in the face of disease progression after 3 cycles of temozolomide leading to overall survival of 52 weeks (18). Post-operative whole brain radiation has been used in most patients undergoing resection (21, 22). Arantes and associates have used post-operative craniospinal irradiation (36 Gy / 20 fractions / 4 weeks to neuraxis followed by pineal boost 14 Gy / 7 fractions / 1.5 weeks) and adjuvant temozolomide in a 54-year-old lady leading to impressive overall survival of 80 weeks (1). Our patient received post-operative radiation 59.4 Gy / 33 fractions / 6 ½ weeks by the 3DCRT technique after tumor decompression and is disease free 40 weeks after diagnosis. We refrained from using whole brain radiation in the illustrative case due to localized nature of the tumor without any evidence of leptomeningeal dissemination.

Chemotherapy Policy

Systemic chemotherapy has been used in only 4 out of 17 (23.5%) patients of primary pineal melanoma with variable response. The most commonly used chemotherapy regimen is single agent temozolomide – 2 in the adjuvant setting (1, 4) and 1 in the neoadjuvant setting (18). Three cycles of monthly regimen of single agent temozolomide in the neoadjuvant setting led to clinical and radiological disease progression in a 44-year-old gentleman as reported by Martin-Blondel et al (18). In a report from Japan, Yamane et al used multiagent chemotherapy regimen containing dacarbazine, nimustine (ACNU), vincristine and interferon leading to dramatic tumor shrinkage and recurrence-free survival in excess of 4 years (28). There may be a potential benefit of intrathecal recombinant interleukin-2 (rIL-2) in patients of CNS melanoma with leptomeningeal involvement (10). Given the rarity of the tumor and the limited use of chemotherapy in this tumor, the role of chemotherapy in primary management is unclear. Taking a cue from other sites of melanoma, chemotherapy perhaps can be deferred until recurrence. Prognosis in this group of tumor is however far from encouraging with leptomeningeal dissemination being the most important determinant of treatment outcome.

CONCLUSION

Primary pineal melanoma is an exceedingly rare tumor with only 16 cases reported in available literature. We have reported the first case of this rare tumor from the Indian subcontinent. Given the rarity of the tumor and heterogeneity of management in the available reports, treatment of choice is largely undefined. Combined modality therapy comprising maximal safe surgery and post-operative radiation should be preferred in patients with localized lesion without leptomeningeal dissemination. Taking a cue from other subsites of melanoma, chemotherapy perhaps can be deferred until recurrence. Prognosis in this group of tumor is however far from encouraging with leptomeningeal dissemination being the most important determinant of treatment outcome.

REFERENCES


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<th>Table II: Therapeutic Options &amp; Outcome</th>
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<tbody>
<tr>
<td>Treatment modality</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Biopsy ± shunt</td>
</tr>
<tr>
<td>Resection + radiation</td>
</tr>
<tr>
<td>Resection + chemotherapy</td>
</tr>
<tr>
<td>Resection + radiation + chemotherapy</td>
</tr>
<tr>
<td>Radical radiation</td>
</tr>
<tr>
<td>Radiation + chemotherapy</td>
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</tbody>
</table>
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