Management of pineal region tumours in children

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Received: November 1, 2011 Accepted: February 15, 2012 Published: April 1, 2012 DOI: 10.5430/jst.v2n2p15 URL: http://dx.doi.org/10.5430/jst.v2n2p15

Abstract
Pineal region tumors in children are rare. A wide diversity of lesion arises from the pineal gland or the surrounding tissues. Among them, germinomas, nongerminomatous germ cell tumors and pineoblastoma are the most common. These tumors do not have pathognomonic imaging findings. However, tumor markers evaluation may narrow the differential diagnosis. Symptoms are usually related to tumor size and location. Treatment depends on tumor type but still the standard management remains unclear.

Key words
Pineal tumor, children, Germinoma, Nongerminomatous germ cell tumors, Pineocytoma, Pineoblastoma, Surgery, Chemotherapy, Radiotherapy

Introduction
The pineal region is comprised of the pineal gland, posterior third ventricle, tela choroidea and velum interpositum. A wide diversity of lesion arises from the pineal gland or the surrounding tissues. The primary pineal tumors are pineoblastoma and pineocytoma. Extrapineal tumors are usually germ cell tumors, tumors of glial cell origin, meningiomas, metastases, pineal cysts or vascular malformations [1, 2].

Symptomatology of the pineal region tumors is directly related to the surrounding structures and tumor histology. Hydrocephalus is a common manifestation as a result of obstruction of the cerebrospinal fluid (CSF) pathway at the level of the aqueduct of Sylvius. Consequently, patients may present with symptom and signs of hydrocephalus. Additionally, compression of efferent pathways or the cerebellar peduncles can produce gait abnormalities. It is also not uncommon for pineal region tumors to produce endocrinological deficits [1]. Furthermore, initial clinical manifestations, are frequently ocular in nature. One of the most common symptoms (50%-70% of patients suffering from pineal region tumors) is Parinaud’s syndrome which is characterized by typical ocular movement disorder including paralysis of upward gaze, convergence or retraction nystagmus and light-near dissociation [3, 4].

MRI has a pivotal role in the detection of pineal region tumors. However, an accurate diagnosis, other than pineal cysts, is difficult, since the majority of tumors share similar radiological findings. Germ cell tumors, non-germ cell tumors and astrocytomas usually are hypo or isointense on T1, hyperintense on T2-weighted MRI and enhance after contrast administration. CT might be useful for determining the extent of calcification [5]. Alternatively, biochemical markers in
serum or CSF may be very helpful in establishing the final diagnosis. A-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are the most important. In germinomas, AFP is negative [6]. In nongerminomatous germ cell tumors AFP and β-HCG are usually elevated in serum and CSF. β-HCG is elevated in choriocarcinoma and some mixed germ cell tumors. AFP is markedly elevated in endodermal sinus tumors and elevated to a lesser degree in embryonal cell carcinomas. Usually teratomas do not secrete AFP, whereas the less differentiated immature teratomas can produce detectable amounts [3, 6, 7]. When both AFP and β-HCG are elevated, neuro-oncologists and neurosurgeons tend to advocate an open biopsy to distinguish malignant teratomas from undifferentiated germ cell tumors. These markers are dependable parameters for following response to therapy and failure of markers to normalize demonstrate incomplete response to therapy. Patients with elevated tumor markers appear to have a poorer survival (60% vs. 78%, 5 year overall survival) independent to tumor histology. Patients with elevated markers have a higher risk of death than those with normal markers. Patients with elevated AFP are associated with an even worse prognosis than patients with elevated β-HCG [8]. In the current study we reviewed the available treatment modalities for pineal region tumors in children.

**Surgery**

Patients with pineal tumors will develop hydrocephalus in about 90% of cases and they will require CSF diversion. Ventriculo-peritoneal (V-P) shunt placement is a viable option with low morbidity and mortality rate. However, shunt malfunction in this population is as high as 20% [9, 10]. In addition, tumor metastasis through a CSF shunt has been reported [11]. Endoscopic third ventriculostomy (ETVC) is an alternative option, which also permits a biopsy of the tumor in the same procedure. Ahn et al reported that biopsy samples, obtained in the lateral ventricle or pineal region, were more favorable toward a successful diagnosis than those in the thalamus or tectal region [12]. Neuroendoscopic biopsy procedures have been proven safe with low complication rate. In a recent multicenter study neuroendoscopy provided a diagnosis in 90% of patients [13]. Furthermore, endoscopic-assisted open tumor surgery shows promise [14]. In all cases, CSF samples for the assessment of AFP and bHCG levels can be obtained during ventricle puncture and are important for tumor characterization. Stereotactic biopsy has also been used for diagnosis. Nevertheless, stereotactic biopsy has several risks since pineal region has numerous large vessels that can also be displaced from their normal position in case of tumor [15-18]. Apart from that, certain tumors such as pineoblastomas or choriocarcinomas are highly vascular, whereas histological heterogenic tumors such as mixed malignant tumors may pose a problem for an accurate diagnosis [19]. In experienced centers, stereotactic biopsy has been reported to be safe with no mortality and permanent morbidity and only 6% transient morbidity rates. Tissue diagnosis accuracy has been reported to be as high as 99% [20].

Benign pineal tumors can be cured with surgery alone. Nevertheless, malignant tumors, apart from aggressive resection, should be treated with radiotherapy and chemotherapy. Surgical approach to the pineal region constitutes a challenge given the complexity and the nearby several neurovascular structures. The venous anatomy is one of the most complex in the central nervous system. The main venous structures exposed during surgery are the vein of Galen with its tributaries [21]. Preservation of these deep veins is mandatory and frequently pose a limitation for the radical removal of the tumors in the pineal region [22]. The main goal of open surgery on pineal region lesions is the complete tumor removal with minimal morbidity, whenever possible. However, even if gross total excision cannot be achieved, establishment of an accurate diagnosis, maximal cytoreduction and restoration of CSF pathways may be achieved [23].

The latest CT and MRI-based neuronavigation systems allow a more targeted approach, providing a more accurate intraoperative guidance. Thus, reduction of surgery duration and of the mortality and morbidity rates have been achieved. Furthermore, neuronavigation systems provide a better representation of the spatial relationship between cerebral veins and surrounding structures and allow for the identification of variants that will be encountered on the trajectory to reach the lesion [24].

Because of the central location of the pineal region in the cranial cavity, the surgical approach depends on tumor’s size and extension, the tumor’s relationship to the deep venous system and the splenium of the corpus callosum [25]. Among the various operative approaches, the major are:

1) The infratentorial supracerebellar approach can be used for medium or small sized tumors and when the main bulk of tumor is located below the tentorium [26]. This approach has been considered safe and effective since the midline trajectory of the approach avoids damage to the deep venous structures. However, if the lesion extends lateral or involves the corpus callosum then another approach may be required [27]. The median or paramedian suboccipital infratentorial supracerebellar approach may also be used. The later provides better visualization and preserves the deep venous system [22].

2) The occipital transtentorial approach is usually indicated when the tumor is growing through the tentorial hiatus with a supracerebellar-infratentorial extension and the majority of the tumor is located above the tentorium [22, 26]. Konovalov et al reported that this approach proved effective and safe [28].

3) The posterior transcallosal approach is used for tumors that are located superior to the venous complex and expand anteriorly into the third ventricle, as well as for those tumors extending upward into the corpus callosum [29].

4) The transventricular approach is used only rarely for very large eccentric lesions that extent into the lateral ventricle [30, 31].

Treatment

Pineocytoma
Pineocytomas are exceedingly rare. Gross total resection is the most appropriate treatment and should be attempted whenever possible. Clark et al. after performing a systematic review of the literature reported that the 1 and 5 year progression free survival (PFS) rates for patients that underwent resection versus the biopsy group were 97% and 90%, and 89% and 75% respectively. The 1 and 5 year PFS rates for the gross total resection group versus the group undergoing subtotal resection combined with radiation therapy were 100% and 94%, and 100% and 84% respectively. The authors concluded that gross total resection should be the goal of treatment [32]. Radiotherapy administration to subtotally resected tumor is not associated with an increase in either tumor control or survival [33]. Stereotactically guided iodine-125 seed implantation has been proposed as a potential alternative to microsurgery in de novo diagnosed pineocytomas, since it was proven efficient and safe [34].

Pineoblastoma
Pineoblastoma together with germ cell tumors are the most common pineal tumors in children. Pineoblastoma has an unpredictable clinical behavior and is usually aggressive, displaying rapid recurrence and cerebrospinal dissemination. Gross total resection has been associated with improved survival, similar to treatment with craniospinal irradiation and multi-agent chemotherapy [35]. Children under the age of 36 months with this malignant tumor, should be treated with multi-agent chemotherapy for 12 to 24 months with the goal of delaying radiation past the age of 36 months. Craniospinal irradiation before this age of 3 has been associated with significant cognitive and neuroendocrine sequelae. Tate et al. summarized the existing literature on patients with pineoblastoma and found that children under 5 years of age and subtotal tumor resection markedly worsened patient survival [36]. According to Children's Oncology Group trials, these tumors require craniospinal irradiation (with local tumor doses of at least 50 Gy) and adjuvant chemotherapy [37]. When carboplatin and vincristine were administered during craniospinal irradiation followed by 6 months of non-intensive
non-cisplatin containing adjuvant chemotherapy, an 84% 2-years progression free survival was reported in pineoblastomas without evidence of dissemination at presentation \cite{38}.

Germ cell tumors

Germinoma

Germinomas are the most common type of the primary CNS germ cell tumors and have a superior prognosis. They are usually solitary and located predominately in the pineal region followed by suprasellar region and basal ganglia \cite{39}. Multifocal or disseminated lesions are associated with poorer prognosis. Germinomas usually have a predilection to spread along ventricles, supra and intrasellar areas and CSF pathways. These tumors are highly radiosensitive and historically they were treated by radiotherapy alone \cite{40}. In children, there is an attempt to reduce the toxicity of radiation therapy by using chemotherapy in combination with reduced dose radiation to decrease the volume of normal tissue irradiated by stereotactic radiotherapy/radiosurgery \cite{41}. Tseng et al. treated 16 children with cisplatin-based and etoposide-based chemotherapy, and 2340 cGy of radiotherapy and reported a favorable outcome \cite{42}. In this study, there was no treatment failure during a median follow-up period of 45 months. There was complete response to chemotherapy, monitored by brain MRI, when the initial tumor size was smaller or equal to 2.5cm. The authors concluded that the lower radiation dose in the combined treatment modality may reduce the neuropsychological deficits in these children \cite{42}.

The value of chemotherapy alone has also been investigated. However, progression-free survival was shorter in patients treated with chemotherapy alone \cite{43}. In multifocal and disseminated disease, whole ventricle and whole central nervous system irradiation appeared to be sufficient \cite{44}. Germinomas usually present with negative tumor markers. The prognosis of patients with βHCG secreting germinoma has been suggested to be worse than that of patients with pure germinoma \cite{45}. However, a recent study found that βHCG elevations in biopsy proven germinomas did not alter the patient's prognosis \cite{46}.

Nongerminomatous germ cell tumors

Nongerminomatous germ cell tumors (NGGCTs) include embryonal carcinoma, choriocarcinoma, teratoma (mature, immature or with malignant transformation), yolk sac tumors and mixed germ cell tumors. NGGCTs constitute approximately 30% of the germ cell tumors and have a poor prognosis compared to germinomas. These tumors are also less radiosensitive than germinomas. Resection has been associated with favorable results \cite{47-49}. However, attempt for gross total resection might be associated with high morbidity \cite{50}. Furthermore, apart from mature teratoma, in which total resection is often curative; the importance of radical resection in the remaining tumors is unclear \cite{51}. Chemotherapy has also been proven useful, resulting in complete response in one third of patients; whereas salvage therapy with irradiation is a feasible option in recurrent disease \cite{52}. Patients with NGGCTs, in whom the lesions on MR imaging disappeared after combination therapies consisting of resection, radiation therapy, and chemotherapy, had favorable prognosis \cite{43}. Recently, Nakamura et al reported that neoadjuvant therapy consisting of combined chemotherapy and radiotherapy followed by complete resection of the residual tumor resulted in 93% survival rate \cite{53}.

Gliomas

Gliomas located in the pineal region are rare. They can either arise from astrocytes in the pineal gland or more commonly they grow into the pineal region arising from adjacent brain parenchyma of the quadrigeminal plate and posterior third ventricle. Low grade and high grade tumors have been reported \cite{53-55}. In a series of 150 pediatric patients that were treated surgically for pineal region tumors, there were 14 astrocytomas and 3 glioblastomas \cite{56}. Glioblastomas in this location are associated with high rate of leptomeningeal and ependymal metastatic disease \cite{57}. The role of aggressive surgical resection in the management of pineal glioblastomas is not clear. After surgical excision, radiotherapy and chemotherapy survival usually does not exceed one year \cite{57, 58}. Two patients who underwent a surgical resection only died 2 months after the diagnosis \cite{59, 60}.
Meningiomas

Meningiomas in children are rare and constitute 2.2% of all brain tumors [61]. Meningiomas in the pineal region are exceedingly rare, constituting nearly 0.3% of all intracranial meningiomas [62]. These tumors originate from velum interpositum, the double layer of pia mater that forms the roof of the third ventricle [63]. Complete resection has been associated with good results [64]. All subtypes of meningiomas have been reported in this position [62-64].

Metastases

Metastatic tumors in the pineal region in pediatric population are exceedingly rare. In adults, Lassman et al. reported ten cases, in which the primary cancer was clinically silent [65]. The most common site of origin is the lung, followed by the breast, and other organs [66]. Surgical excision is a viable treatment option. Stereotactic radiosurgery has also been employed with good results.

Pineal cysts

Pineal cysts are of benign nature. Al-Holou et al. after evaluating 106 patients reported that 98/106 remained unchanged after a 3-year mean follow-up period. Younger age was associated with cyst change or growth on follow-up imaging. The gender, initial cyst’s size and MR imaging characteristics were not significant predictors of growth or change in imaging appearance at follow-up [67].

Conclusion

Pineal region tumors in children are rare. A wide diversity of lesions arise from the pineal gland or the surrounding tissues. Among them, germinomas, NGGCTs and pineoblastoma are the most common. These tumors do not have pathognomonic imaging findings. However, tumor marker evaluation may narrow the differential diagnosis. Symptoms are usually related to tumor size and location. Treatment depends on tumor type but still the standard management remains unclear.

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