Results of the treatment of pineal tumors in children: The Lyon experience

Alexandru Szathmari
Hospices Civils de Lyon
Pierre-Aurélien Beuriat
Hospices Civils de Lyon
Alexandre Vasiljevic
GHE, Hospices Civils de Lyon
Pierre Leblond
Institut d'Hématologie et d'Oncologie Pédiatrique
Cécile Faure-Conter
Institut d'Hématologie et d'Oncologie Pédiatrique
Line Claude
Centre Léon Bérard
Federico Di Rocco
Hospices Civils de Lyon
carmine mottolese (carmine.mottolese@chu-lyon.fr)
Hôpital Femme Mère Enfant

Research Article

Keywords: pediatric pineal tumors, pineal surgery, chemotherapy, radiotherapy

Posted Date: May 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1555588/v1

Abstract

Pineal tumors are rare and their incidence is of 1% among all pediatric tumors of the central nervous system. The survival depends on the histology, the extension of the surgical removal, the efficacy of the complementary treatment (chemotherapy and cranio-spinal irradiation) in relation with the age of the children.

We report our experience in Lyon concerning 151 patients treated from 1997 to 2021. All patients were recorded in the French Register of Pineal tumors which is centralized in Lyon since 2010.

The analysis shows that benign tumors have a good survival rate and a total surgical removal is manadatory. Concerning true pineal tumors, pinealoblastomas have a bad prognostic especially in children aged inferior to three years old. The new pathological classification allows a better stratification with different groups identified and also the identification of a DICER 1 syndrome in family of patients with a pinealoblastoma that need medical investigations. Results of Germ Cell Tumors are more favorable with a global survival rate of 87 % and a rate of survival for pure germinomas of almost 97%. Results for gliomas of the pineal gland, that are tectal plate gliomas, are good for pilocytic astrocytomas while for other gliomas the prognosis is related to the grade of malignancy and the efficacy of complementary treatment. Papillary tumors need a complete removal for the best chance of survival. Finally, AT/TR still have a bad prognosis.

Our results show that many progresses have to be accomplished for pineal region tumors and that these pathologies need a multidisciplinary approach to choose the best treatment to improve the survival rate and the patients' quality of life.

Introduction

Treatment of pineal tumors is complex because of the multiplicity of histological lesions that are found in this deep region and a multidisciplinary approach is necessary to define the best strategy for each patient.[1, 2].

Each case needs a multidisciplinary discussion that has to take into acount the clinical manifestations, the radiological characteristic of the tumor and its extension, the results of markers studies in the blood and the CSF, the presence or not of hydrocephaly.

Hydrocephaly can need an emergency treatment to decrease the risk of an evolving intracranial hypertension and to prevent ophthalmological and neuropsychological sequels. [3, 4] .

We report the results of pineal tumors treatment in children in Lyon from January 1997 to December 2020 in the Neurosurgical Pediatric Department of Lyon (Hopital Femme Mere Enfant).

All the cases belong to the French Register of Pineal Tumors in which are registered until now 891 patients, adults and children, treated in twenty six neurosurgical centers in France [5].

Out 891 tumors 316 patients (33%) are children: 165 of the 316 patients (54%) have been treated in different French centers and 151(46%) have been treated in Lyon and are considered for this report.

Results of the French register were already published in a previous paper.[6]

Materials And Methods

All pediatric patients that have been treated from January 1997 to December 2020 in Lyon in the Department of Pediatric Neurosurgery have been considered. All these patients are recorded in the French Register of Pineal Tumors.

151 patients were eligible for the study with an age between one years to eighteen years old. The sex ratio was of 1.2 males /Girl.

The symptomatology was characterized in 54% by signs of intracranial hypertension with headaches and vomiting. Ophthalmological troubles were present in 21% of patients, endocrinological problems were associated in 5% of cases, while in others 18% of patients the clinical manifestations were characterized by more insidious manifestations as asthenia, tiredness and gradual lowering of scholar performances.

All patients were studied with a cerebro-spinal MRI with and without Gadolinium with angio-MRI sequences to study arterial feeders and the venous structures. The CT-scan was realized in some patients performed in peripheral hospitals. We never realized angiography by the Seldinger technique for the surgical procedure.

All patients were studied with blood and CSF markers when a surgical procedure for hydrocephaly was necessary or with a lumbar puncture when the MRI didn't show severe signs of intracranial hypertension. When clinical signs of intracranial hypertension impeded the realization of a lumbar puncture for the study of markers in the CSF a decision for the therapeutical strategy was taken after a discussion with the interregional oncological committee to realize a biopsy. The choice of the surgical technique for the biopsy was decided by the surgical team.

Out 151 patients collected in the Lyonnais series true pineal tumors (PPT) represented 15% of cases, germ cells tumors (GCT) 39% of cases, low grade gliomas 10% of cases, pineal cysts 26% of cases, papillary tumors of the pineal region (PTPR) represented 3,4% of cases, Atypical teratoid/ rabdoid tumors (AT/RT) 2,6% of cases. Others non-definite tumors represented 4% of cases.

In the French Register out 316 pediatric cases patients PPT represented 23% of cases, Germ cells tumors (GCT) 41%, Pineal gliomas 13%, Pineal cysts 13%, Atypical teratoid/rabdoid tumors (ATRT) 2%, PTPR 3,4%, others 4,6%.

Hydrocephaly was present in 58% of patients and in 38% of cases was realized an ETV and in the same time a biopsy.

The true pineal tumors in the Lyonnais series represented 24 patients (15,8%). Eighteen patients were pinealoblastomas, five cases were pineal parenchymal tumors of intermediary differentiation, of grade II two cases, of grade II- III two cases and grade III one case and one patient a pinealocytoma.

60% of cases were of feminine sex and 40% males. The distribution of age varied from eighteen months old to eighteen years old, the median age was of 8,8 years.

Concerning the group of intermediate differentiation pineal parenchymal tumors the feminine sex was predominant while the only pinealocytoma was of masculine sex.

In two patients the disease was metastatic at beginning.

The surgical removal was total in 67% of cases and subtotal in the 27% of case. A stereotactic biopsy was realized in a patient with a metastatic disease in a poor clinical condition and for him it was decided to start a chemotherapic program rapidly.

Germ Cell Tumors represented 39% of pineal tumors. Out of 59 patients 36 were germinomas, ten were mature teratomas, two patients immature teratomas,11 patients were mixes teratomas. 12 patients presented a bifocal tumor with an extension to the anterior portion of the third ventricle with infiltration of the pituitary stalk or of the anterior portion of the floor of the third ventricle visualized on the MRI.

87% of patients were of masculine sex and 13% were females. The median age was of 10,8 years old.

A biopsy was realized in sixteen patients with an endoscopic technique and in the same procedure was also realized a third ventriculostomy. For all cases biopsied the histological diagnosis was established.

In five patients the biopsy was done with an open approach and in three case the biopsy was realized with a stereotactic approach. In a case the biopsy was realized with the neuronavigation system. For the others patients the study of markers in the blood and the CSF permitted the diagnosis. Two patients were treated for hydrocephaly with a VP shunt after the ETV.

Out of the forty-four patients with a pineal location that could be revised for this study, twenty-one were pure germinomas, two immature teratomas, 11 mixes teratomas and ten patients a mature teratoma.

Five patients, two immature teratomas and three mixed teratomas were treated with a surgical approach after chemotherapy while the ten patients with a mature teratomas were operated after an endoscopic biopsy in two cases and a direct approach at the diagnosis in the others eight cases.

Pineal gland gliomas in our series concern 16 patients while in the French Register were censored 37 pediatric cases. Pilocytic astrocytomas represented the most frequent histological type in our series.

Other gliomas operated were gangliogliomas (two patients), oligodendrogliomas (5 patients).

Three patients were operated for a pineal ependymoma.

Four patients were operated for an atypical teratoid rabdoid tumor: one patient was operated after an intratumoral hemorrhage responsible of a severe aggravation with clinical signs of cerebral engagement. The other three patients were treated with a massive chemotherapy in two cases associated with a cranio-spinal radiotherapy in one case.

Forty patients of the Lyonnais series presented pineal cyst and 11 patients have been operated ten with a direct approach and one patient with the endoscopic technique. All patients are alive.

Results

The rate of survival of pinealoblastomas was of 22%: nine patients (50%) of the eighteen patients with pinealoblastomas died after a surgical removal and a complementary treatment with chemotherapy in five patients in age younger than 5 years old and associated with cranio-spinal irradiation in patients older than four years old, two patients were lost to the follow-up and all the others died. (Fig. 1)

Out of the five patients with pineal parenchymal of intermediate differentiation tumors four were still alive after a complete removal and radiotherapy, one is still in remission after a salvage chemotherapy and one died for a recurrence with metastatic disease. The only patient operated for a pinealocytoma was alive.

Thirty-six patients treated for a Germ Cell Tumor located in the pineal region were alive with a median survival of 68,7 months (5,7 years). All these patients were treated with different protocols according the SFOP society and a cranial irradiation with a boost on the lesion.

In the group of the patients with bifocal location two died and one patient was lost to the follow-up. The overall survival for patients in the group of Germ Cells pineal tumors was of 89% of cases (Fig. 2).

Patients with Germ cell tumors belonging to the French Register represented 130 patients 14% died, 79% were alive and 7%were lost to the follow-up (Fig. 3).

Mature teratoma concerned 11 patients with an increased volume for eight patients and their treatment was based essentially on a complete surgical removal: in this group, eight patients are alive, two patients dead and one patient was lost to the follow-up.

Immature teratomas had more severe evolution because of 16 patients only seven patients were alive, five patients dead and four patients were lost to the follow-up.

Out of the four patients treated for an AT/RT one operated in severe neurological condition died two days after the surgical procedure for a cardiac arrest while the other three patients deceased after a massive chemotherapy in two cases and after a cranio-spinal irradiation after chemotherapy in one case.

Of the two patients with a gangioglioma both are still alive, while of the five patients with oligodendrogliomas four are alive and one patient is lost to the follow-up.

All patients operated for a pineal cyst are alive.

We considered 75 alive patients alive avec a complete follow-up and at December 2021.

85% of the patients were able to live normally while 15 of patients presented minor sequels as mild motors deficits without impeding the walk, mild cerebellar troubles or visual troubles documented by the ophthalmological routine control.

We focused the scholar performances as an important factor of quality of live.

Out of 75 patients in scholar age, 63% were able to follow a normal program without problems; 15% presented mild difficulties with fair troubles in memory and concentration activities but able to follow a normal program and 12% of patients needed an adapted school program.

Complication of surgical treatment

The surgical treatment of pineal tumor is associated with complications. We focused on the rate of complications observed in our series that was not statistically different from that observed in the French Register [5].

In the Lyonnais series the rate of mortality was of 1.5% related to an embolic complication the days after the surgical procedure without a precise explanation. The rate of post- surgical hemorrhage was of 3,3%: three patients presented a subdural hematoma and two patients an extradural hematoma. The subdural hematoma was evacuated surgically and drained forty-eight hours, while the extradural hematoma observed in two patients, in a case it was well tolerated while the other case needed a surgical evacuation.

Infectious complications were observed in five patients (3,3%): a sepsis in one patient, an abscess of the operative field in a patients and a meningitis in three patients.

Two patients presented an infection of the skin flap that needed a new surgical procedure for the sacrifice of the bone flap an antibiotic treatment for six months according the protocol suggested by the Infectious Committee of our hospital. (CLIN)

The rate of Parinaud syndrome was of 7,3% in the post-operative period and decreased progressively to a rate of 0,7% during the follow-up at least six months after the surgical procedure.

Four patients (2,6%) presented a diminished visual acuity. Seizures occurred in 7,5% of cases in the post-operative period and treated in all patients with anti-epileptic drugs that, after their disappearance, and with an EEG normal, could be weaned after six months or one year according the advice of our pediatric neurologists.

In 5% of patients operated we observed a pinealoprive syndrome but its incidence could not be established in other centers affiliated to the Register. This syndrome Claustra exists in children and can be treated with the administration of melatonin.

Discussion

Pineal tumors are rare and only limited series concerning pediatric patients can be compared in literature. This is true mainly for true pineal tumors in pediatric age considering that the Children Oncology Group enrolled only 34 patients [7], in age superior to three years old, 41 patients the Saint Jude Hospital[8], while a cooperative SIOP E study reported 131 patients trying to compeer clinical evolution, neuro-oncological treatment and bio-molecular and genetic difference [9]

All our cases were enrolled in the French Register for pineal region tumors [6] that concerned 891 patients recordered until the end of December 2021 : 316 cases (35%) were in pediatric age and 151 pediatric cases (16%) were treated in Lyon representing 47% of all pediatric cases.

This Register was created in Lyon at beginning with the first 22 cases, reported in the thesis of Science of the prof. Anne Jouvet+,that became a specialist of pineal tumors, and analyzed with electronic microscopy of [10].

It collected all national patients treated in all the twenty-six neurosurgical centers of France since the years 2000 and was declared to the CNIL in the year 2008 and definitively located in Lyon since 2010.

Our experience confirmed, according literature, that surgical mortality and morbidity for pineal tumor treatment was reduced in the last twenty years and surgical mortality was of only 1,8% in the French Register and of 1,5% in our experience [6].

The progress of microsurgical and anesthesiological techniques have permitted also to region tumor reduce the rate of post-operative sequels [11–13].

The surgical approaches have to be tailored in function of the volume of the lesion and the axis of the growth of the tumor also if surgeons choose the avenue with which they are more familiar. Our deep conviction is that each surgeon, that take in care pineal region tumors, should be familiar with different approaches to offer the best surgical alternative to each patient.

The endoscopic third ventriculostomy has permitted to manage hydrocephaly reducing the rate of complications related to the shunts, favoring also a histological diagnosis because, with the experience, pathologists became more performant to establish a precise diagnosis also in presence of small samples [6, 14, 15].

Used at the end of microsurgical removal, endoscopy can facilitate the visualization of residual piece of tumor in the blind corners improving the rate of total resection. In the pineal region many histological types are present and many of them need a neuro-oncological treatment and the complete removal represent a good prognostic factor.

We don’t think that the exclusive use of endoscopy have a large place for surgery of pineal region tumors for the potential risks of hemorrhagic complications specially when the dissection of the lesions is done

at level of the venous structures represented by the veins of the Galen, the basilar veins and the cerebral internal veins. The exclusive use of endoscopic technique can be reserved to particular cases [16];

True pineal tumors concern 30% of cases pinealoblastomas, 52% are PPT-ID and 18% are pinealocytomas of grade I [10] while in our series pinealoblastomas represent 75% of cases, pineal parenchymal tumors with intermediary differentiation represent 24% and pynealocytomas only 1% of cases.

Looking at this histological repartition we can underlie that pinealocytomas are very rare in children and it is more frequent in young adults and only 6 cases were censored in the French Register, confirming their rarity. [17]

For benign lesions the surgical complete removal could guarantee the definitive cure and consequently, if the post-operative MRI showed a residual nodule, a new surgical procedure was indicated for us and there was no indication for a complementary chemotherapy or radiotherapy except particular situations [18]. The role of radiotherapy could be different in adults patients in which a redo surgery can be correlated with high surgical risks[19] .

Generally, for malignant tumors a total removal should be the goal but, in case of residual nodule, surgery should be discussed at the light of the possible surgical risks and at the light of efficacy of complementary treatments.

The prognosis of pinealoblastomas remains severe with an high rate of mortality as observed in our series of 18 pediatric cases treated in the last twenty years and specially in very young children confirming that age inferior to three years old represent a bad prognostic factor also in case of complete removal [20, 21].

The histological and bio-molecular knowledge have permitted to definite five sub group for pinealoblastomas with a different biological evolution considering the stratification of patients according age because patients younger of 3 years old represent 24% of cases while 59% of patients are aged between > 3 years and < 18 years old [17].

Patients with PB MYC/FOX R2 and PBRB1 were younger children and had a dismal prognosis. The group with PB-miRNA1 or PB-miRNA2 was found in older children or young adolescents with a more favorable prognosis [22] The genetic studies of our cases confirm the indications of the Tumor Consortium Study.

The stratification of patients in different subgroup has permitted to establish criteria of gravity of the disease and consequently the possibility to adapt therapeutical protocols to different degree of gravity of the disease with the hope that new drugs could improve clinical results specially for very young patients.

Germ-line mutations predispose to pinealoblastoma and De Kock *et al* have reported that DICER1 is an important susceptibility gene for pinealoblastoma and PB can be the expression of a germ-line mutation [23]

The genetic studies demonstrated that the extension of surgery was not always a significant factor for survival in patients with a localized disease and non-metastatic disease [8, 9, 24].

Tomita underlined the importance of a radical surgery for long term survival and also if we agree with him, other reports showed no significant relationship between the total resection and the overall survival [25, 26].

Complete surgical removal of pinealoblastomas needs experimented surgeons because these tumors are hemorrhagic and it is important to avoid in very young patient severe sequels in the early post-operative period.

Our series of pinealoblastomas showed an overall survival in 27% of cases but all patients in an age inferior to 5 years old had a very dismal prognosis because all were dead. The median survival of our series was of 3,9 years with a range between 17 and 1 years.

Progression free survival reported in the recent literature in a series 25 patients varied from 47,1%, 12,5% and 0% in patients treated with cranio-spinal radiotherapy, all brain therapy and focal RT [27].

The analysis of 135 children reported in the SIOP-E and the US Head Start pooled data showed that in patients younger than 4 years chemotherapy without RT was ineffective to obtain remission in treatment of pinealoblastomas [9].

The high rate of mortality makes necessary to discover new drugs to improve the clinical results avoiding the risk of the brain irradiation if possible in very young patients.

A better stratification of patients should allow tailored treatments, especially for young children, and could represent the evolution of therapeutical strategies in a next future as preconized in literature. [17]

The PPT –ID are more frequent in adolescents and young adults patients in age of 33 years old and except for grade II with a total removal they need a complementary treatment to improve the survival [6, 21].

For Germ Cells tumors it is necessary to establish at beginning a precise diagnosis, or with the study of tumoral markers in the CSF and in the blood or with the help of a biopsy [28] [29]. It is important to consider the presence of a diabete insipidus that facilitates the discovery of a bifocal location. This situation was found in twelve patients (20%) of our series. A diabete insipidus in the exclusive pineal location is extremely rare [6].

In case of Germ Cell tumors surgery can be necessary or to treat hydrocephaly or, in cases in which, tumoral markers remain elevated in the blood and in the CSF after a treatment with chemotherapy, to remove non germinomatous components before radiotherapy [30].

In case of hydrocephaly consequence of the compression of the aqueduct of Silvius, ETV permits to cure hydrocephaly and also to realize a biopsy [1]. The rate of success diagnosis with the endoscopic

technique is now of 87,9% [31] and of 95% for Schulz [1]. Kinoshita has preconized the necessity of samples from different region of the tumor to improve the precision of the diagnosis in cases of Germ Cell Tumor to discover non germinomatous components and to ensure adapted treatments [15].

We think that the endoscopic biopsy need sufficient material but we have to avoid multiple samples of material from different region of the tumor to avoid risks of severe hemorrhagic complications possible also with the use of a flexible endoscope [15].

In our series two patients needed a shunt after the failure of the ETV showing that the ETV alone was not always able to treat hydrocephaly.

Germ cells tumors has been treated with different protocols of chemotherapies following the indication of the French Society of Oncological Pediatry (SFOP) or of the International Pediatric Oncology Society (SIOP) associated with radiotherapy on the ventricular system with a boost on the tumor location.

The results of treatment for embryonal carcinomas, yolk stalk tumors and chorioncarcinomas depended by the effectiveness of chemotherapic program to reduce their volume but still now we had limited results because the rate of mortality remained still elevated [32].

The surgical treatment of these tumors was proposed after chemotherapy or radiotherapy to reduce the volume of the lesion but it was demonstrated that radiotherapy, producing a reaction of fibrosis, increased the surgical difficulties for a complete removal and also the rate of morbidity [33].

For Germ Cells tumors The French Society of Pediatric Oncology and the European SIOP CNS GCT-96 and the Japanese Cooperative Group studies [34] adopted a strategy with an upfront chemotherapy (Platinum based) followed by involved field irradiation to 40 Gy. With a front line chemotherapy and the extended field of radiotherapy including the ventricles a 100% survival and a 89% of progressive free survival was reported by Khatua [35].

For mature teratomas surgery is the only treatment with a rate of survival that varied between 80 and 100% as reported in literature [14, 36, 37].

All our cases treated with a complete removal with a sub-occipital trans-tentorial approach were alive with a median survival of 5,7 years with a range varying from 1 year to 17 years [6].

Immature teratomas have on the contrary a rate of survival less important and the five years survival reported in literature varies between 35 and 40% [32].

Surgical treatment of glioma of the pineal gland is associated in our experience with good results [6]. In our opinion pineal gliomas represent essentially tectal plate gliomas and we think that all exophytic gliomas have to be operated with a direct surgical approach. Surgery is certainly debated but can play an important role for their treatment [6].

The limits of resection have to respect the plane of the aqueduct anteriorly, the plane delimited by the encroachment of the fourth nerves inferiorly and the colliculi or at least to respect one of the two colliculi if invaded by the tumor and if one is removed. The per operative recording of the auditory evoked potential is mandatory to reduce sequels and to favorite a large removal. The sixteen exophytic astrocytomas operated during the period of this study are all alive while the prognosis of more aggressive glioma is related to their malignancy instead of the complementary treatment as already reported [6].

Papillary tumors of the pineal region have been described in Lyon [10]. These tumors are not true pineal tumor but they belong to the pineal region. They origin from the sub-commissural organ of the third ventricle and their treatment need a total surgical removal to increase the chance of cure [10, 38] They are rare in children and we have censored in our experience only two cases that are alive, one needed an another program of chemotherapy following a total removal for a recurrence and now still in remission.

In literature only thirty cases were reported and consequently it is difficult to have a precise idea of the survival in children but it seems that total surgical removal represent a good prognostic factor to increase the survival and also to avoid sequels due to radiotherapy on an evolving brain but their incidence is rather in adolescent age and our patients were aged of ten years and thirteen years old [39].

Patients with a complete removal had a rate of survival in 63% of cases while patients with a partial removal or a biopsy had a worse evolution with a survival rate of only 26% of cases also after a complementary treatment with chemo and radiotherapy [6]

These results were reported by Févre-Montange while Poulgrain stressed the role of chemotherapy and radioptherapy on the rate of survival at five and ten years [40, 41].

The treatment of pineal ATRT tumors is very dismal because no patient of the four treated during the period from 1997 to 2020 were alive.

Pineal cyst represent benign lesions and their surgical treatment is necessary in children when an increased volume is responsible of a clinical picture, or when an intracystic hemorrhage is observed or when preoperative radiological diagnosis can orientate through a diagnosis of pinealocytoma [6]

The high number of pineal cysts operated in our series is related to an effect of recruitment consecutive to the expertise developed on the topic of tumors of the pineal region [6].

Of incidental discover pineal cysts are generally asymptomatic. Their diagnosis is increased with the advent of MRI studies and they have a benign evolution but in some cases, they can present an acute increase in volume and also an intra lesional hemorrhage responsible of a clinical aggravation and need a surgical treatment.

Their surgical treatment can be realized with a microsurgical technic or with an endoscopic approach and the presence of hydrocephaly, in adults as in children can justify the use of endoscopic removal [42, 43].

We know that pynealocytomas are very rare in children and the better knowledges of MRI permit us to establish a correct diagnosis and in consequence we limited the surgical indication and reserved surgery only in case with an important increase in volume or in case of acute intracystic hemorrhage.

The surgical approaches used are the infra tentorial supracerebellar, the sub occipital trans tentorial, the trans callosal trans fornical approach and many others [4, 42, 44–46].

The mini invasive techniques consist in a stereotactic aspiration, endoscopic marsupialization, endoscopic infra tentorial approach [47–49].

The use of ETV seems easier in presence of hydrocephaly while the direct approach is indicated in all cases with small ventricles. The use of neuronavigation can be useful with both techniques.

The endoscopic technique permits to treat in the same time the hydrocephalus and to realize the marsupialization of cysts or its complete removal through the ventricular system also if a complete removal can be risky for the hemorrhagic complications as reported by OI [43, 50].

It is always important the histo-pathological examination to confirm the diagnosis because in case of diagnosis of tumor, the complete surgical removal can be useful, if necessary, before the decision of an oncological treatment, if necessary, to give the best chances for a definitive cure.

Out of eleven cases operated in our series the sub-occipital trans –tentorial approach was used in ten ceses and the endoscopic removal in one case.

As already reported [3, 4] we prefer the sub-occipital transtentorial approach for the advantages to expose and to work in this region under the venous arch represented by the basilar veins and the Galen veins. The benignity of the pathology explains the high rate of survival observed in our experience [6].

After the surgical treatment, it is also important to recognize the post pinealectomized syndrome that was studied and described in Lyon by Claustra and Chazot [51]. This syndrome is characterized by headaches, fatigability, behavioral troubles and anomalies of the circadian rhythm with sleep disturbances. This syndrome is diagnosed in 10% of patients operated for a pineal tumor [6] and it is observed also in children that complain of irritability and tiredness mainly in school activity also if its incidence is lessen frequent than in adult patients because observed in only five % of our cases. The treatment of this syndrome is represented by the administration of melatonin.

Conclusions

Surgical treatment of pineal lesions is possible in experimented hands with a low rate of sequels as demonstrated by the quality of life of patients operated also if, sometimes it can be difficult to separate the sequels related to the disease, the surgical treatment, the oncological program with chemotherapy and radiotherapy

We have to emphasize that the treatment of pineal tumors, in children, ask a multidisciplinary approach to adopt the best strategy for their cure and to obtain a satisfactory quality of life for patients considering the diversity of histology of these tumors.

It is important to establish, at beginning, the precise diagnosis to establish the right program for each patient: we have to avoid surgery in case of Germ Cell Tumors or in some case of neoplasms that can be treated with chemotherapy and to use surgery for benign lesions with attention to reduce the risks of post-surgical morbidity.

The decisional tree has to take in care the age of patients because some tumors are found in particular age: in very young patients we have to think to PNET or pinealoblastomas or teratomas or ATRT tumors. In adolescent or young adult, Pineal parenchymal tumors with intermediate differentiation or pinealocytomas or gliomas.

It is imperative to realize the complete program of investigations before to establish the strategy of treatment.

Pynealocytoma are very rare in children while pinealoblastoma are more frequent also if they represent less than 1% of childhood brain tumors.

Their treatment needs surgery, chemotherapy and radiotherapy but the age less than three years remain a bad prognostic factor.

For germ cells pineal tumors in presence of elevated markers chemotherapy and radiotherapy will be the treatment. In case of non-elevated markers and in absence of ventricular dilatation a biopsy with a direct approach or in stereotactic condition should be performed [14].

In case of non-elevated markers with a ventricular dilatation an ETV associated to a biopsy can be considered [52].

The genetic studies are essential to establish new protocols of treatment with tailored chemotherapies and adapted cranio-spinal radiotherapy for pineal ATRT, pineal PNET and pinealoblastomas and papillary pineal region tumors.

Surgery has an important place for treatment of benign lesions and the approach of the pineal region has adapted to the axis of development and growth of the tumor.

It is essential for each pineal tumor to have a multidisciplinary discussion to establish the right program to improve the survival rate, to decrease the long-term side effects ensuring satisfactory survival curves.

Declarations

Ethics approval and consent to participate : Study was approved by the local ethic committee. No patients opposed to participate in the study

Consent for publication : all authors consent for publication of the manuscript

Availability of data and materials : data and materials are available upon request to the corresponding author

Competing interests : All authors report no disclosures relevant to this manuscript

Funding : No funding

Authors' contribution :

- AS, PAB collected data, designed and performed research, analyzed and interpreted the data, wrote the paper, and performed the statistical analysis

- CM designed and performed research, analyzed and interpreted the data, wrote the paper and supervised the study

- All others authors perform research and revised the manuscript

References

1. Schulz M, Afshar-Bakshloo M, Koch A, et al (2021) Management of pineal region tumors in a pediatric case series. Neurosurg Rev 44:1417–1427. https://doi.org/10.1007/s10143-020-01323-1
2. Pettorini BL, Al-Mahfoud R, Jenkinson MD, et al (2013) Surgical pathway and management of pineal region tumours in children. Childs Nerv Syst 29:433–439. https://doi.org/10.1007/s00381-012-1954-y
3. Mottolese C, Szathmari A, Ricci-Franchi AC, et al (2015) Supracerebellar infratentorial approach for pineal region tumors: Our surgical and technical considerations. Neurochirurgie 61:176–183. https://doi.org/10.1016/j.neuchi.2014.02.004
4. Mottolese C, Szathmari A, Ricci-Franchi AC, et al (2015) The sub-occipital transtentorial approach revisited base on our own experience. Neurochirurgie 61:168–175. https://doi.org/10.1016/j.neuchi.2013.12.005
5. Mottolese C (2015) Report 2013: Tumors of the pineal region. Neurochirurgie 61:60. https://doi.org/10.1016/j.neuchi.2013.03.004
6. Mottolese C, Beuriat PA, Szathmari A (2015) Pineal tumours: Experience of the French National Register and the Lyon School, results and considerations. Neurochirurgie 61:223–235. https://doi.org/10.1016/j.neuchi.2014.02.006
7. Jaju A, Hwang EI, Kool M, et al (2019) MRI Features of Histologically Diagnosed Supratentorial Primitive Neuroectodermal Tumors and Pineoblastomas in Correlation with Molecular Diagnoses and Outcomes: A Report from the Children's Oncology Group ACNS0332 Trial. AJNR Am J Neuroradiol 40:1796–1803. https://doi.org/10.3174/ajnr.A6253

8. Parikh KA, Venable GT, Orr BA, et al (2017) Pineoblastoma-The Experience at St. Jude Children's Research Hospital. Neurosurgery 81:120–128. https://doi.org/10.1093/neuros/nyx005
9. Mynarek M, Pizer B, Dufour C, et al (2017) Evaluation of age-dependent treatment strategies for children and young adults with pineoblastoma: analysis of pooled European Society for Paediatric Oncology (SIOP-E) and US Head Start data. Neuro Oncol 19:576–585. https://doi.org/10.1093/neuonc/now234
10. Jouvet A, Fauchon F, Liberski P, et al (2003) Papillary tumor of the pineal region. Am J Surg Pathol 27:505–512
11. Dallier F, Di Roio C (2015) Sitting position for pineal surgery: Some anaesthetic considerations. Neurochirurgie 61:164–167. https://doi.org/10.1016/j.neuchi.2014.10.110
12. Lindroos A-C, Niiya T, Randell T, et al (2010) Sitting position for removal of pineal region lesions: the Helsinki experience. World Neurosurg 74:505–513. https://doi.org/10.1016/j.wneu.2010.09.026
13. Hernesniemi J, Romani R, Albayrak BS, et al (2008) Microsurgical management of pineal region lesions: personal experience with 119 patients. Surg Neurol 70:576–583. https://doi.org/10.1016/j.surneu.2008.07.019
14. Tanrıkulu B, Özek MM (2020) Management of mature pineal region teratomas in pediatric age group. Childs Nerv Syst 36:153–163. https://doi.org/10.1007/s00381-019-04204-1
15. Kinoshita Y, Yamasaki F, Tominaga A, et al (2017) Pitfalls of Neuroendoscopic Biopsy of Intraventricular Germ Cell Tumors. World Neurosurg 106:430–434. https://doi.org/10.1016/j.wneu.2017.07.013
16. Tanikawa M, Yamada H, Sakata T, et al (2019) Exclusive Endoscopic Occipital Transtentorial Approach for Pineal Region Tumors. World neurosurgery 131:. https://doi.org/10.1016/j.wneu.2019.08.038
17. Li BK, Vasiljevic A, Dufour C, et al (2020) Pineoblastoma segregates into molecular sub-groups with distinct clinico-pathologic features: a Rare Brain Tumor Consortium registry study. Acta Neuropathol 139:223–241. https://doi.org/10.1007/s00401-019-02111-y
18. Deshmukh VR, Smith KA, Rekate HL, et al (2004) Diagnosis and management of pineocytomas. Neurosurgery 55:349–355; discussion 355–357
19. Kumar N, Srinivasa GY, Madan R, Salunke P (2018) Role of radiotherapy in residual pineal parenchymal tumors. Clin Neurol Neurosurg 166:91–98. https://doi.org/10.1016/j.clineuro.2018.01.027
20. Tian Y, Liu R, Qin J, et al (2018) Retrospective Analysis of the Clinical Characteristics, Therapeutic Aspects, and Prognostic Factors of 18 Cases of Childhood Pineoblastoma. World Neurosurg 116:e162–e168. https://doi.org/10.1016/j.wneu.2018.04.135
21. Görgün Ö, Koç B, Kebudi R, et al (2021) Clinical characteristics, late effects and outcomes in pineoblastomas in children: a single center experience. Turk J Pediatr 63:955–961. https://doi.org/10.24953/turkjped.2021.06.002

22. Vasiljevic A, Szathmari A, Champier J, et al (2015) Histopathology of pineal germ cell tumors. Neurochirurgie 61:130–137. https://doi.org/10.1016/j.neuchi.2013.06.006
23. de Kock L, Sabbaghian N, Druker H, et al (2014) Germ-line and somatic DICER1 mutations in pineoblastoma. Acta Neuropathol 128:583–595. https://doi.org/10.1007/s00401-014-1318-7
24. Gilheeney SW, Saad A, Chi S, et al (2008) Outcome of pediatric pineoblastoma after surgery, radiation and chemotherapy. J Neurooncol 89:89–95. https://doi.org/10.1007/s11060-008-9589-2
25. Tomita T (1998) Neurosurgical perspectives in pediatric neurooncology. Childs Nerv Syst 14:94–96. https://doi.org/10.1007/s003810050185
26. Huo X-L, Wang B, Zhang G-J, et al (2020) Adverse Factors of Treatment Response and Overall Survival in Pediatric and Adult Patients with Pineoblastoma. Cancer Manag Res 12:7343–7351. https://doi.org/10.2147/CMAR.S258476
27. Abdelbaki MS, Abu-Arja MH, Davidson TB, et al (2020) Pineoblastoma in children less than six years of age: The Head Start I, II, and III experience. Pediatr Blood Cancer 67:e28252. https://doi.org/10.1002/pbc.28252
28. Regis J, Bouillot P, Rouby-Volot F, et al (1996) Pineal region tumors and the role of stereotactic biopsy: review of the mortality, morbidity, and diagnostic rates in 370 cases. Neurosurgery 39:907–912; discussion 912–914
29. Faure-Conter C (2015) Tumoral markers in tumors of the pineal region. Neurochirurgie 61:143–145. https://doi.org/10.1016/j.neuchi.2013.12.006
30. Takami H, Graffeo CS, Perry A, et al (2021) The Third Eye Sees Double: Cohort Study of Clinical Presentation, Histology, Surgical Approaches, and Ophthalmic Outcomes in Pineal Region Germ Cell Tumors. World Neurosurg 150:e482–e490. https://doi.org/10.1016/j.wneu.2021.03.030
31. Somji M, Badhiwala J, McLellan A, Kulkarni AV (2016) Diagnostic Yield, Morbidity, and Mortality of Intraventricular Neuroendoscopic Biopsy: Systematic Review and Meta-Analysis. World Neurosurg 85:315–324.e2. https://doi.org/10.1016/j.wneu.2015.09.011
32. Matsutani M, Sano K, Takakura K, et al (1997) Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg 86:446–455. https://doi.org/10.3171/jns.1997.86.3.0446
33. Lapras C, Patet JD, Mottolese C, Lapras C (1987) Direct surgery for pineal tumors: occipital-transtentorial approach. Prog Exp Tumor Res 30:268–280
34. Calaminus G, Frappaz D, Kortmann RD, et al (2017) Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial. Neuro Oncol 19:1661–1672. https://doi.org/10.1093/neuonc/nox122
35. Khatua S, Dhall G, O'Neil S, et al (2010) Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. Pediatr Blood Cancer 55:42–46. https://doi.org/10.1002/pbc.22468
36. Noudel R, Vinchon M, Dhellemmes P, et al (2008) Intracranial teratomas in children: the role and timing of surgical removal. J Neurosurg Pediatr 2:331–338.

https://doi.org/10.3171/PED.2008.2.11.331

37. Ostrom QT, de Blank PM, Kruchko C, et al (2015) Alex's Lemonade Stand Foundation Infant and Childhood Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. Neuro Oncol 16 Suppl 10:x1–x36. https://doi.org/10.1093/neuonc/nou327
38. Jouvet A, Fèvre-Montange M, Besançon R, et al (1994) Structural and ultrastructural characteristics of human pineal gland, and pineal parenchymal tumors. Acta Neuropathol 88:334–348
39. Mathkour M, Hanna J, Ibrahim N, et al (2021) Papillary tumor of the pineal region in pediatric populations: An additional case and systematic review of a rare tumor entity. Clin Neurol Neurosurg 201:106404. https://doi.org/10.1016/j.clineuro.2020.106404
40. Fèvre-Montange M, Hasselblatt M, Figarella-Branger D, et al (2006) Prognosis and histopathologic features in papillary tumors of the pineal region: a retrospective multicenter study of 31 cases. J Neuropathol Exp Neurol 65:1004–1011. https://doi.org/10.1097/01.jnen.0000240462.80263.13
41. Poulgrain K, Gurgo R, Winter C, et al (2011) Papillary tumour of the pineal region. J Clin Neurosci 18:1007–1017. https://doi.org/10.1016/j.jocn.2010.12.027
42. Berhouma M, Ni H, Delabar V, et al (2015) Update on the management of pineal cysts: Case series and a review of the literature. Neurochirurgie 61:201–207. https://doi.org/10.1016/j.neuchi.2013.08.010
43. Chaussemy D, Cebulla H, Coca A, et al (2015) Interest and limits of endoscopic approaches for pineal region tumours. Neurochirurgie 61:160–163. https://doi.org/10.1016/j.neuchi.2015.03.001
44. Kodera T, Bozinov O, Sürücü O, et al (2011) Neurosurgical venous considerations for tumors of the pineal region resected using the infratentorial supracerebellar approach. J Clin Neurosci 18:1481–1485. https://doi.org/10.1016/j.jocn.2011.02.035
45. Lazar ML, Clark K (1974) Direct surgical management of masses in the region of the vein of Galen. Surg Neurol 2:17–21
46. Stern J, Ross D (1993) Stereotactic management of benign pineal region cysts: report of two cases. Neurosurgery. https://doi.org/10.1097/00006123-199302000-00024
47. Mottolese C, Szathamari A, Beuriat PA, et al (2015) Neuroendoscopy and pineal tumors: A review of the literature and our considerations regarding its utility. Neurochirurgie 61:155–159. https://doi.org/10.1016/j.neuchi.2013.12.008
48. Turtz AR, Hughes WB, Goldman HW (1995) Endoscopic treatment of a symptomatic pineal cyst: technical case report. Neurosurgery 37:1013–1014; discussion 1014–1015. https://doi.org/10.1227/00006123-199511000-00025
49. Cardia A, Caroli M, Pluderi M, et al (2006) Endoscope-assisted infratentorial-supracerebellar approach to the third ventricle: an anatomical study. J Neurosurg 104:409–414. https://doi.org/10.3171/ped.2006.104.6.409
50. Oi S, Kamio M, Joki T, Abe T (2001) Neuroendoscopic anatomy and surgery in pineal region tumors: role of neuroendoscopic procedure in the "minimally-invasive preferential" management. J Neurooncol 54:277–286

51. Claustrat B, Brun J, Chazot G (2005) The basic physiology and pathophysiology of melatonin. Sleep Med Rev 9:11–24. https://doi.org/10.1016/j.smrv.2004.08.001
52. Zaazoue MA, Goumnerova LC (2016) Pineal region tumors: a simplified management scheme. Childs Nerv Syst 32:2041–2045. https://doi.org/10.1007/s00381-016-3157-4

Figures

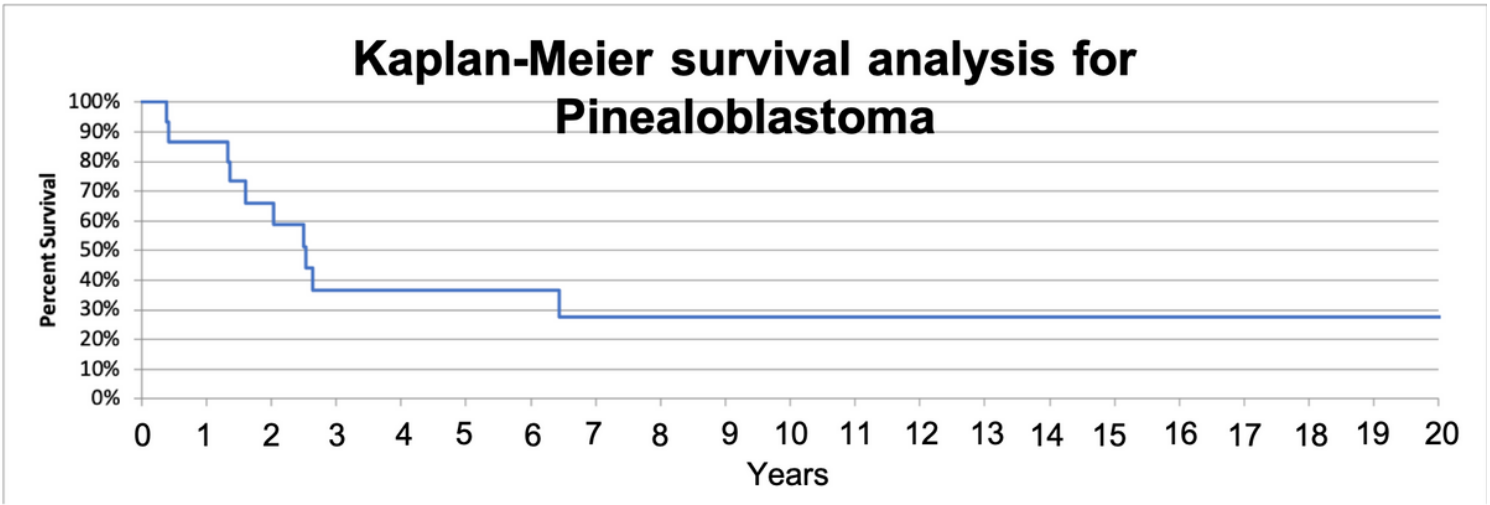

Figure 1

Kaplan-Meier Survival curve for pinealoblastoma

Figure 2

Kaplan-Meier Survival curve for germ cell tumor

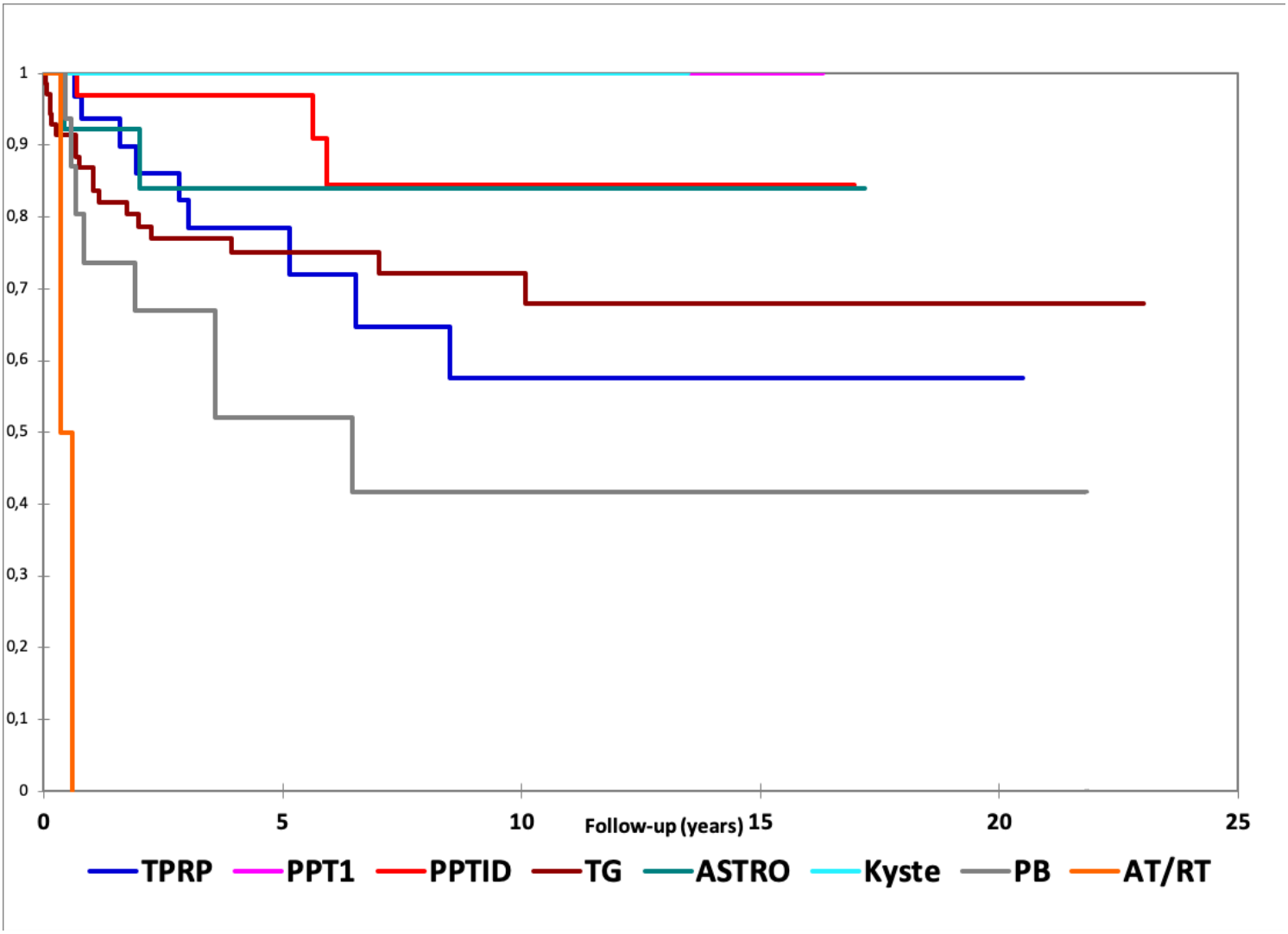

Figure 3

Kaplan-Meier Survival curve for germ cell tumor of the National French Register of Pineal Region Tumors