MINISTRY OF EDUCATION AND TRAINING MINISTRY OF HEALTH

HA NOI MEDICAL UNIVERSITY

HOC TRAN VAN

STUDY OF CLINICAL FEATURES, HISTOPATHOLOGY, ASSESSMENT OF TREATMENT OUTCOMES OF CEREBELLAR TUMORS IN CHILDREN AT THE VIETNAM NATIONAL HOSPITAL OF PEADIATRICS

Speciality : Pediatrics

Code : 62720135

SUMMARY OF THESIS OF DOCTOR OF PHILOSOPHY IN MEDICINE

HA NOI - 2016

THE WORK HAS BEEN COMPLETED AT

HA NOI MEDICAL UNIVERSITY

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INTRODUCTION

1. Research Questions

Brain tumors make up approximately 20% of all cancers in children under the age of 15. Childhood brain tumors are commonly found in the posterior fossa, in which the incidence and mortality rate of cerebellar tumors rank the highest. Cerebellar tumors compose of neoplasm originating from the vermis, cerebellar hemisphere and fourth ventricle. Histopathologically, cerebellar tumors embody medulloblastoma, astrocytoma, ependymoma and some other rare types. Medulloblastoma is a common cancer, making up about 15-20%, the second most prevalent malignant tumor is Astrocytoma (10-12%), but this type mostly has the lowest malignancy rate, the ependymoma makes up solely 10% of central nervous system tumors. The roots of cerebellar tumors generally remains obscure, however some cases relate to hereditary factors. In children, the age of onset of brain tumors in the cerebellum is normally under 10 years old, except some patients suffering from it right in first months after birth.

Nowadays, thanks to the development of early diagnosis and cooperation of distinct interventions like surgery, chemo and radiotherapy, more than 60% of children with brain tumors in the cerebellum have survived for more than 5 years, children with low grade astrocytoma have a chance to live up to 10 years.

The National Hospital of Pediatrics, from 2008 until now, has improved diagnosis and treatment of this disease. Histopathological techniques, cancer surgery, radio and chemotherapy have been better than those in the past. For these reasons, we decided to research a topic: **"Study of clinical features, histopathology and assessment of the outcomes of treatment for childhood cerebellar tumors at the National Hospital of Pediatrics**" with two objectives:

1. ***Describing several clinical features and histopathology of childhood cerebellar tumor.***
2. ***Assessment of the outcomes of treatment for childhood cerebellar tumors at the National Hospital of Pediatrics.***

1. Scientific and practical meaning of the project.

Determining notable signs of clinical symptoms and pathological lesions on diagnosis images, histopathological features of Vietnamese children, the results of therapy applications following medication at the National Hospital of Pediatrics and the causes and factors that affect survival or death rates.

Determining average incidence rate of cerebellar tumors as well as histopathological tumors in different ages; important clinical symptoms and lesion image specific for distinct cerebellar histopathological tumor sorts.

The malignant stages of histopathological neoplasm.

Survival and death outcomes of therapy combinations like surgery, radio and chemotherapy based on hospital's medication.

2. Project 's new role

Until recently, there have not been any projects studying in clinical detail the histopathology and brain tumors in the cerebellum treatment results in children, hence this research plays new roles:

Determining the incidence rate of cerebellar tumors and histological forms according to different age groups of children.

Determining clinical symptoms and significant pathologic lesions of cerebellar tumors, specifically many tumors type in histological manner.

Assessing mortality and survival rate after 5 years of being treated with distinct therapies like surgery, radio and chemotherapy.

The cause and factors impinge on treatment results.

Some necessary recommendations for diagnosis, treatment, caring and supplemental studies that aim to extend the life and living standards of Vietnamese children with cancer.

3. The composition of thesis.

The thesis composes of 142 pages including: 3 pages of research questions, 45 pages of literature review, 21 pages of research subjects and methods, 31 pages of results, 38 pages of discussions, 2 pages for the conclusion, 1 page for recommendations, and 1 page for limitations of the project.

The thesis has 31 tables, 8 charts, and 11 figures.

References: 117 references, which includes 102 and 15 articles written in English and Vietnamese respectively.

Chapter 1: LITERATURE REVIEW

1.1. Definitions

A Cerebellar tumor is neoplasm stemming from the cerebellum and IV ventricle in the posterior fossa. Histopathologically, there are two main categories of cerebellar tumor, which are medulloblastoma and astrocytoma. Ependymoma that traces in ventricular membrane of IV ventricle connecting with cerebellum can invade cerebellum, clinically

expressed as medulloblastoma and astrocytoma so it is categorized in cerebellum tumors. There are also some rare cancer types.

1.2. Some epidemiological features and cerebellar neoplasm researches.

1.2.1. Incidence rate

In the world, the incidence of central nervous system cancer takes 30% of total tumor prevalence in children under the age of 15. In the USA, there are approximately 3700 pediatric cancer patients each year. The incidence proportion of under 20 year-old-children is 45/100000 individuals/year, and reaches the highest rate in age under five (about 52/100000 juveniles/year). In Canada, statistics from 2003 to 2007 showed that 1039 children were susceptible to central nervous system cancer, in which 16% of childhood cancer with 44% astrocytoma, 20% were tumors originating in the skull and spinal cord and the percentage of ependymoma was 10%. The incidence rate of under age 5 and age 10 children was 30% and 75% respectively. The lodgment of cancer is found commonly in the posterior fossa.

Ten to twenty percent of all total tumors arising in children is astrocytoma, commonly found in posterior fossa and makes up one third to one fourth of all total posterior fossa neoplasm types. Prevalent astrocytomas have low malignancy level.

Medulloblastoma is the most cancerous, which makes up 15-20% of all brain tumors and 30-40% of posterior fossa tumors. Common age of onset is 3-4 years old, boys are likely to suffer more often than girls (ratio: 1.5/1). Medulloblastoma apparently tends to invade by following the cerebrospinal fluid path and triggering cord tumor in 11-43% of diagnosed cases.

Ependymoma stems from the ventricular membrane. In children, prevalent lodgment is in IV ventricle, the incidence proportion in both genders is similar, average diagnosed age is 5 years old, 25-40% of children with cancer is under 2 years old.

Akay K.M evaluates 27 brain tumors in the cerebellumcases cytologicaly classified, and observes the percentages of pilocytic astrocytoma, medulloblastoma, ependymoma, anaplastic astrocytoma, cystic oligodendroglioma and hemangioblastoma 48.2%, 22.2%, 18.5%, 3.75%, 3.7%, 3.7% respectively.

Eventhough intervention has improved in recent decades, yet childhood tumors are severe diseases with high medical expenses, survival rate for living more than 5 years of all brain cancers is 64%.

In Vietnam, there have not been any researchs reporting the incidence rate of cerebellar tumors and symptoms in histological manner.

1.2.2. Causes and risk factors.

The roots of cerecellar neoplasm now remains elusive. The genetic problems of brain neoplasms are paid more attention in recent decades, however, it is still in the experimental stages. People see that this disease can arise in the first months after birth and have high proportion in first decade of childhood. Several related factors like impacts of radio, toxin, tobaco and some viruses can relate to the increased risk of cancer epidemy, particularly cerebellar tumors.

1.3. Brain and cerabellar tumor classification

The first time brain tumors were histologically categorised was in 1926 by Perci Bailey and Harvey Cushing. World Health Organization (WHO) modifed and supplemented, in turn in 1979, 1993, 2007.

The classification are widely used now belong to WHO 2007.

1.3.1. Prevalent brain tumors in children: cancer lodgmentand histopathological origin.

Posterior fossa tumors:

- Medulloblastoma 43-63% brain tumor types
- Low-grade astrocytoma 20-25% ……
- Ependymoma 12-18%.....
- Glioma 4-8%.....
- Other cancer types 2-5% ……

1.3.2. Classification of malignant grade regarding to WHO 2007.

The World Health Organization "grades" on scale from I to IV.

Grade I: Tumor develops slowly, surgery gives good pronogtic results

Giant cell astrocytoma beneath ventricular membrane, pilocytic astrocytoma, rare ependymoma, and myxopapillary ependymoma.

Grade II: Cancer cells spreading growth, high recurrence rate, surviving for more than 5 years

Myxoid astrocytoma, diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma.

Grade III: Irregular border and invasive neoplasm, having abnormal nucleus

Anaplastic Astrocytoma, anaplastic oligodendroglioma, and anaplastic ependymoma.

Grade IV: Diffused, irregular border tumor, variable cell types and having many abnormal nucleuses

Medulloblastoma and glioblastoma.

1.4. Pathological features of cerebellar tumor regarding to localization.

1.4.1. Clinical presentations of cerebellar regarding to brain localization

Intracranial hypertension syndrome

Intracranial hypertension syndrome can either occur suddenly or may gradually happen over time.

Headaches are the most common symptom (76-85%). Vomiting associated with headache, but vomiting, perhaps, don't occur together with headaches. Vomiting is recurring and tends to occur in the morning. Papilloedema is also a common sign. Small baby patients: Intracranial hypertension syndrome can be seen as big head, fontanel is bulged outward, bony plates spread apart.

Cerebellar syndrome

Motor ataxia, limb tremor, ataxic gait, hypotonia, nystagmus, and language impairments. Basic movement disorders like dysmetria and hypermetria. Complex motion impairments: asynergy.

1.4.2. The roles of diagnostic imaging in brain and cerebellar tumor diagnosis.

Diagnostic magnetic resonance and CT imaging is vital tests in detecting the locations and morphological characteristics of cerebellar cancer. Spectroscopy assists in diagnosing the malignancy level of cancer. Histopathological diagnosis helps classifying sorts of cancer type which are important basement for apply therapies.

1.5. Pathological characteristics according to histopathology

1.5.1. Medulloblastoma

In histopathology, these are small, round blue cells originating from the posterior fossa. In recent WHO classification, medulloblastoma is sub-divided into many groups composing of medulloblastoma with small nodules, medulloblastoma with extensive nodules anaplastic medulloblastoma, and medulloblastoma multiforms.

The most common symptoms of cerebellar cancers were unspecific symptoms of raised intracranial pressure and no local paralysis. Papilloedema, headaches, vomiting and ataxia make up 90% of cases, diplopia secondly arises because of the fourth cranial nerve palsy. In addition, raised tendon reflex leading to ventricular dilatation is a prevalent symptom.

1.5.2. Cerebellar astrocystoma

According to WHO 2007, astrocystoma has 4 grades:

Grade 1: Pilocytic Astrocytoma is tumor growing at similar rates as normal cells and is a less invasive neoplasm. In MRI and CT

imaging, this type presents as cystic component with cancer has cysts with enhancing mural nodule.

Grade II: Diffuse Astrocytoma grows quite slowly, when modified signs appear, it is considered as having potential to transform into cancer and begin moving to benign tissue.

Grade III: An anaplastic astrocytoma, neoplasms lack of structure and function of normal cell, grow rapidly and invade nearby brain tissues.

Grade IV: Glioblastoma, abnormal cells growing steadily and invade aggressively.

Clinical presentations are headache in early morning, vomiting. There can be papilloedema, motor ataxia, ataxic gait, one or both lateral apraxia, cranial nervous lesions like nystagmus, I nervous palsy.

1.5.3. Ependymoma

Ependymoma is cancer stemming from ependyma composing of oval nucleus and have alteration in areas of high fibrillation cells. The neoplasms can form long or round structure like ventricular zone of embryonic neural tube, spread in the blood vessel canals and form a rose like shape surrounding blood vessel.

Clinical presentations are not different from other posterior fossa tumors. Some types can damage brain stems and palsy cranial nerves prior to signs of raised intracranial pressure. Ependymoma spreads in cerebellar sphere will be the root for lateral nerve VI,VII,VIII palsy and appears early. Stiff neck and head are common signs.

1.5.4. Some other rare cerebellar cancers.

Hemangioblastoma, germinoma, sarcoma, melanoma, choroid plexus tumors and phrenic nerve tumors.

1.6. Treatment

1.6.1. General principles of treatment

Basic therapies are surgery, chemo and radio therapy, rehabilitation, psychotherapy and palliative care.

Surgery

Complete removal of the tumor is the best option, but practically almost all tumor borders are so irregular that it is extremely difficult to totally remove nodules. Sometimes, surgery removes only part of the cancer and cooperate with needle biopsy.

Radiotherapy

The purposes of this therapy are killing cancer cells while causing as little harm as possible to surrounding normal cells. Patients can be treated with radiotherapy alone or in combination with other methods. The dose requiring for completely kill cancer is 50-55 Gy, each divided dose is 1.8-2 Gy and 1 divided dose/day.

Chemotherapy

Chemotherapy plays a vital role in the combination of variable treatment therapies. Chemotherapy in children under age 3 helps delay the initiation of radiotherapy; avoiding severe complications of radiotherapy in very young children.This therapy is given in rounds, after each round, there will be break to allow the patient's body time to recover.

1.7.2. Treatment of some tumor types

1.7.2.1. Treatment of medulloblastoma

Surgery removing cancer is followed by radiation to the entire craniospinal axis (for 6 years old children and above). Treatment is followed the standard 3600 cGy for intracranial and spinal cord radiation, total radiation dose is 5580 cGy. The administration of chemo, in turn, is performed. The surgery for children under age 6 is followed by chemo regarding to protocol, if they live more than 6 years, radiation can be additionally given.

1.7.2.2. Cerebellar astrocystoma treatment

Surgery is used to remove as much of the tumor as possible. The removal of cancer will reduce intracranial pressure, improve symptoms, if the entire tumor is not removed, the rest will be treated by radiation. Chemo is used in some certain situations.

1.7.2.3. Ependymoma treatment

Surgery to remove completely cancer is the best option; combine with radiotherapy (for children above age 6). The treatment of high-grade ependymoma is similar to the one of medulloblastoma but the prognosis is worse.

1.7.2.4. Treatment of other cancers.

There are some protocols might be suitable for each specific tumor types .

1.7.3. Consequences, complications of treatment methods.

Acute reactions: Diapedesis, raised sensitivity, defensive shock, vomiting and nausea. *Some early advert effects*: mucositis, alopecia, diarrhea, constipation, altered nutrition, aplastic anemia.

1.7.4.Rehabilitation and palliative care.

Including physiotherapy, language practice, work-related exercises, temporarily relieving disease, psychological care and palliative care.

1.7.5. Prognosis of cerebellar cancers.

Prognosis depends on the tumor location, histopathological characteristics, age and how patients respond to treatment… Early and quick treatment and credible protocol is the most important for prognosis.

Chapter 2: Subject and research methods

2.1. Research subject

124 pediatric patients who are diagnosed with brain tumors in the cerebellum were admitted to the National Hospital of Pediatrics. They were operated and histologically categorized from 1/1/2009 to 31/12/2013. Observations were kept on until 31/12/2014.

2.2. Research methods

2.2.1. Research methods:

Prospective descriptive study observes a series of medical cases.

2.2.2.Sample size

Sample size is chosen according to the convenience sampling method. In 5 years, 124 patients with cerebellar cancers will be operated and histologically categorized.

2.2.3. Study organization

Patients that admitted were diagnosed and treated in Neurology Department. Consultation was hold to decide surgery. They were treated in SICU after surgery. After 14 days, head MRI was performed to check. Chemotherapy, radiation or combination plans or periodic observation plan were set up and evaluate each therapies. Radiotherapy was given to patients at Radio Medical and Oncology Center. Observation was perform in durations: once every three months in the first year, once every 6 months in second year and once every year in the following years.

2.2.4. Sampling method

Having sufficient standards for cerebellar diagnosis.

Being uniform in clinical, sub clinical examination, treatment and observation procedures. Recording in medical reports.

Fellow and neurologist periodically re-checked

2.2.5. Study content and assessment methods:

2.2.5.1. First aim: Description of some clinical and histological features of pediatric cerebellar cancer.

Some epidemiological clinical characteristics: Age and gender, location, incidence in month and year, distribution according to histopathology (medulloblastoma, astrocytoma, ependymoma and other types), common characteristics of histological tumor in age and gender.

Clinical features: Primary symptoms of disease, time from appearance of symptoms to hospitalization, clinical signs at admission time and clinical traits according to histopathology.

Characteristics of Magnetic resonance imaging: Estimate tumor image as: location, margin, size, density, cysts, drug penetration level, invasive level, local cerebral edema, ventricular dilatation, cord metastasis.

Histological features and classification: Histological diagnosis was performed in the anapathological department of the National Hospital of Pediatrics, based on WHO 2007 classification.

2.2.5.2. Second aim: Assessment of childhood cerebellar treatment outcome

- Treatment protocol at the National Hospital of Pediatrics:

+ Surgery: given for all types of cancer, performed right after diagnosis and if the patient's condition allows. The removal of cancer cell mass is performed one time or after placing a shunt between the brain ventricles and abdominal cavity.

+ Radiotherapy at Radio Medical and Oncology Center, Bach Mai Hospital for patients with medulloblastoma, ependymoma, astrocytoma. Subsequently: for children 6 years and above: combine with chemo including vincristine, cisplatin and cyclophosphamid in 6 rounds (except low-grade astrocytoma).

+ Chemotherapy: for children under age 6: cannot take radiation therapy or are given radiotherapy after surgery: 4 rounds, first week: vincristine and cyclophosphamid, week 3 and week 5: vincristine and methotrexate, seventh week: vincristine and etoposide. Resting for two weeks and repeat 2 rounds like above. Low grade astrocytoma does not need chemo and radiotherapy.

- General outcomes of cerebellar treatment

+ Survival and mortality conditions of children in each years of research period. Lapland-Meier graph estimate surviving patients.

+ Assessment of treatment results in merely surgery and cooperating with radiotherapy, chemotherapy or both types of therapy.

-Treatment outcomes following medical protocol and histopathology

*Medulloblastoma:*Results show the number of surviving children in tumor removal surgery, complete and partial removal, assessment results of adjuvant therapies.

Astrocytoma: Outcomes of patients taking solely surgery for low grade astrocytoma.

Ependymoma: The survival and death rate after applying distinct therapies.

- *Some other factors relate to survival ability of each histological cancer forms.*

Children live or die depending on age, histopathological forms of cancer, size, malignancy level, surgery, adjuvant therapies, invasion and metastasis, compliance.

-Neurological disorders and impacts of therapies:

Neurological and mental sequelae in surviving patients, intellectual development.

2.3. Data processing methods.

Data was collected, surveys were carried out, manipulation using Epi - Info 6.04 software. Using medical statistical algorithm analyzed standard deviation. Comparing the index of study groups by X^2 and t student with 95% reliability.

Chapter 3:RESULTS

From 1/1/2009 to 31/12/2013, National Hospital of Pediatrics treated 124 patients with cerebellar tumor: performing surgery and histological classification, the results were recorded below:

3.1. Clinical characteristics

3.1.1. Epidemic clinical features

Average age: 6.2±3.4. Male: Female = 1.58:1.

Brain tumors in the cerebellum is prevalently found in all ages, 2-8 years old group: 85(68.5%) patients.

3.1.2. Clinical traits

** The period of time from the initial cancer sign appearance to hospital*

This average time is 25.1± 7.7 days. The vast majority of patients admitted in the first month was 76/124 (61.3%), next two months was 20/124 (16.1%), and the following 2 months was 13/124 (10.5%), that was admitted more for more than a year because of suffering from the disease.

The period of time from the initial cancer sign appearance to hospital for astrocytoma is 86.2 days, for medulloblastoma is 49 days, for ependymoma is 31.7 days and for other tumor cohorts is 13 days.

** Symptoms*

Headaches 78/124 (63%), vomiting 25/124 (20.2%), limb weakness/ paralysis 10/124(8.1%), balance disorder 7/124 (5.6%), the remain is other symptoms in children.

** Clinical symptoms present in when admission:*

Vomiting and headache are common signs (89.5% and 81.5% respectively). Apraxia and faltering are common (89.5% and 87.9%).

Table 3.6. Clinical symptoms at admission

Symptoms		N	Percentage (%)
Symptom triggered by raised intracranial pressure and other neurological signs.	Headache	101	81,5
	Vomiting	111	89,5
	Blurred vision	10	8,1
	Diplopia	22	17,7
	Papilledema (n=114)	62	54,4
	Visual disorder	16	12,9
	Big head	12	9,7
	Convulsion	7	5,7
	Stiff neck	6	4,8
	Torticollis	15	12,1
	Limb weakness/ paralysis	36	29,0
	Pyramidal sign	16	12.9
	Hypotonia	42	33,9
	Cranial nervous paralysis	26	21,0
Symptoms of cerebellar dysfunction	Faltering	109	87,9
	Irregulation	111	89,5
	Nystagmus	19	15,3
	Limb shaking	40	32,3
	Language disorder	7	5,7

3.1.3. Some pathological characteristics on MRI films.

**The imaging features of brain tumors in the cerebellum on MRI films.*

There are 71.8% tumors in vermis and 12.9% in cerebellar hemisphere. They have average diameter 3-5cm, regular margin, non-homogenous, 28.2% of tumors have cysts, markedly enhances after gadolinium administration. Brain stem invasion 15.3%, third and lateral ventricular dilatation 85.5%, spinal cord metastasis 7.2%.

3.1.4. Histopathological characteristics.

3.1.4.1 Brain tumors in the cerebellum distribution.

Table 3.8. Distribution of the cerebellum regarding to histopathology and average age

Distribution / Cancer type	Number of patient (%)	Average age (Year)
Medulloblastoma	61 (49,2)	6,9 ± 3,2
Astrocytoma	42 (33,9)	6,9 ± 3,5
Ependymoma	17 (13,7)	3,3 ± 2,4
Other types	4 (3,2)	4,5 ± 1,9
Total	124 (100%)	6,3 ± 3,4

Medulloblastoma took approximately 50%, the latter are astrocytoma, ependymoma. The average age of astrocytoma was similar to medulloblastoma and higher than ependymoma's data.

**The distribution of cerebellar neoplasm according to histopathological features, gender and age groups.*

Astrocytoma and Medulloblastoma had high incidence in the 5-9 years old group (25.8% and 16.2%), thenependymoma was often found in younger children ages, 0-4 years old (13/17 patients). Medulloblastoma had an incidence rate in male two times higher than in female, especially from 5 to 9 years old, incidence of males was 4 time higher than females.

3.1.4.2. Malignant level of tumor regarding to histopathology (WHO)

There were 41.1% of patients having low cancerous level (Grade I and II), 56.5% high malignancy grade (Grade III and IV). The majority of astrocytoma was in grade I (83.3%), fewer in the third and fourth level (7.2%). Ependymoma commonly had malignant grade II (64.7%). One hundred percent of medulloblastoma was in grade IV.

3.1.5. The alteration between tumor types according to histopatholgical features and pathological images on MRI.

3.1.5.1. The shift between astrocytoma and medulloblastoma

**Changes in clinical presentation:*

The clinical symptoms of astrocytoma and medulloblastoma had no difference ($p>0.05$).

**The alteration on images of MRI films.*

Medulloblastoma cell mass located commonly in vermis while the latter cancer lodged in hemisphere or in anterior vermis and spreading lateral hemisphere ($p<0.01$). Medulloblastoma often had small size, more uniformal density, stronger enhances whereas

astrocytoma had regular margin ($p<0.05$). Cysts were often found in astrocytoma image, cord metastasis found in the latter type.

3.1.5.2. The shift between astrocytoma and ependymoma regarding to clinic and image on MRI films.

**The changes in clinical symptoms:*

Almost symptoms were similar ($p>0.05$), except headache signs in patients with astrocytoma were clearer ($p<0.05$).

**The changes in features in MRI films.*

Ependymoma was prevalently found in vermis, irregular margin, had brain stem invasion and cord metastasis. By contrast, astrocytoma often located in cerebellar hemisphere, regular margin, did not invade the brain nd had cord metastasis ($p<0.01$).

3.1.5.3. The alteration between medulloblastoma and ependymoma regarding to clinic and MRI images.

**The changes in clinical presentation,*

Headache, nausea/vomiting were common for medulloblastoma, while hypotonia and stiff neck were found in ependymoma ($p<0.05$).

**The alterations in features on MRI images.*

Ependymoma often located in vermis like medulloblastoma. Nevertheless, this tumor type did not show lodgment in cerebral hemisphere. Both types can invade the brain stem and metastasize spinal cord.

3.2. Assessment of treatment outcomes

3.2.1. General treatment effects

3.2.1.1. The death/survival situation of patients.

Table 3.17. The condition of survive or death in each years of study period.

Index / Year	Number of patients admitted	Number of patients was observed annually (summation)	Annual death	Surviving patients at the end of the year.
2009	28	28	17	11
2010	29	40	15	25
2011	25	50	18	32
2012	16	48	7	41
2013	26	67	8	59
2014	No record	59	4	55
Total	124 (100%)		69 (55,6%)	55 (44,4%)

Until the end point of research, there were 55 surviving patients (44.4%).

**The condition of surviving and death patients in annual observation*

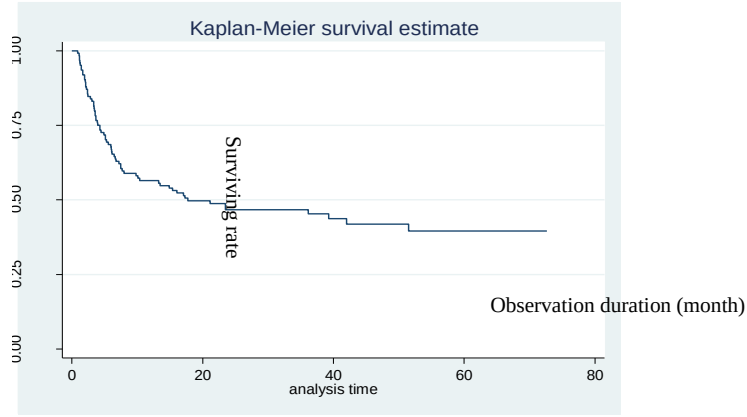
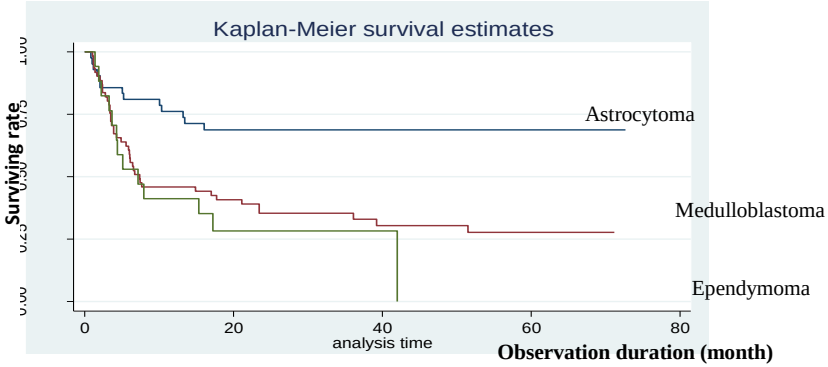


Figure 3.3. General Kaplan-Meier graph

The number of patients died in the first year, comparing with total dead pediatric patients was 54/69 (78.3%), estimation of the survival ability more than 5 years was approximately 38%.

3.2.1.2. Treatment outcomes according to histopathology



Comment: Astrocytoma had the highest surviving estimation, after 5 years, survival expectancy dropped down to 60%, medulloblastoma, after 5 years, decreased to 30%, the longest plausible observation of ependymoma patients was 41 months and exhibited a 23.5% survival rate.

Table 3.19.The comparison of death and survival in the end of study according to histopathology.

Types	Survival		Death		P
	n	%	n	%	
Astrocytoma	29	69,0%	13	31,0%	<0,001
Medulloblastoma	19	31,1%	42	68,9%	
Ependymoma	4	23,5%	13	76,5%	
Others	3	75,0%	1	25,0%	

Astrocytoma has surviving rate, in the end of study, absolutely greater than the latter types ($p<0.001$).

3.2.1.3. The assessment of surgery outcomes via MRI images.

*******The evaluation of surgical results via MRI*

There was 51.6% of patients with brain tumors in the cerebellum which had removed the tumor mass completely, the images after operation in 8.1% of patients cannot be detected since they had died before MRI or CT were performed.

*Patient rate according to the times of surgery.

The number of patients just required one operation was 89.5%, 97% needed two operations, only one patient needed the third surgery because of tumor reappearance.

3.2.2. Assessment of treatment outcomes according to protocol and disease forms.

3.2.2.1. Basic treatment effects of histopathological tumor regarding to each methods.

**Collection of treatment results of several therapies.*

There were 89 (71.8%) children that took operations without other therapies, 40% of them were alive at the end of study. These groups mainly had astrocytoma. Ten patients were given surgery operating with radiotherapy and 50% of them composing of 4 medulloblastoma and 1 third-grade ependymoma survived. Six patients took surgery and adjuvant chemotherapy and half of them who had medulloblastom and ependymoma, under the age of 6, had survived. There were 78.9% of 19 patients who took a combination of surgery, chemotherapy and radiotherapy survived, all of them were more than 6 years old and suffered from medulloblastoma.

**The number of surviving and death patients recorded in each years.*

At the time the study finished, 55 children were alive. In which, 7 patients survived in 2009; 2010: 11, 2011: 10, 2012: 9, 2013: 18.

3.2.2.2. Treatment outcomes of medulloblastoma

There were 61 patients with medulloblastoma, in which 35 (57.4%) children took surgery alone and consequently all died. The remained 26 patients were given a therapy combination, particularly, the combination of surgery, radio and chemotherapy has highest number of children (78.9%) alive. 19/61 (31.2%) children lived until the end of study.

3.2.2.3. Results of astrocytoma treatment.

There were 29/42 patients with astrocytoma (69%) were alive until the research finished.

3.2.2.4. Treatment outcomes of ependymoma.

Solely 4/17 (23.5%) patients with this disease survived until the study ended.

3.2.3. Metal and neurological abnormalities triggered by disease and therapies.

* *Sequelae of surviving patients*

Movement disorder was mostly seen (84.2%), cranial nervous paralysis took 47.4%.

* *Intellectual development after treatment*

An intelligence quotient (IQ) of children with cerebellar cancer, after intervention, was 94.8 points. Papillaryastrocytoma patient had a higher IQ score than patients with medulloblastoma. No radiotherapy group had greater IQ than the one taking that method ($p<0.05$). No chemotherapy group had higher IQ point than the chemo cohort ($p<0.05$). No chemo and therapy cohort was higher than chemotherapy and radiotherapy group in IQ score.

3.2.4. Some factors relate to death and survival of each cancer types according to histopathology.

* *Relationship with age in histopathological manner*

Children in the 0-4 years old group had highest death rate in medulloblastoma and ependymoma (86.7% and 84.6%). The number of surviving patient of 5-9 years old group was greatest: 30 (54.5%). Cohort age 10-15 in patients with astrocytoma had the highest survival rate (88.9%).

**Relating to tumor size*

There were 54/69 patients that died in the first year (78.3%), in which: size <3cm group took 75.0%, 3-5cm cohort made up 77.4% and 100% of patients having >5 cm cancer died.

**Relating to invasive tumor and metastasis.*

All patients who had brain stem and cord metastasis died in the first year 100%, 84.6% of patients of brain stem invasion group passed away in the first year , the latter died in the second year.

**Some factors mainly contribute to death and surviving number:*

Patients who could survive after one year off treatment were variable when differing in age group, tumor size, histopathological types, malignant level, complete removal of cancer or not and how well they followed the medication ($p<0.05$). Two group had more than and under 60 days of onset before admission were the same ($p=0.054$).

Chapter 4: DISCUSSION

1.1. Histological and clinical characteristics.

1.1.1. Clinical epidemiological features

In 5 years of study, 124/177 patients were diagnosed based on clinical, MRI imaging and histopathological classifications.

Age and gender

Brain tumors in the cerebellum was found in all ages, particularly the 2-5 years old group was the most prevalent. Average age of onset cancer was 6.2 ± 3.4 years old. Boys suffered more often than girls (ratio 1.58:1).

1.1.2. Brain cancer diagnosis

1.1.2.1. Clinical characteristic

Research illustrated that headaches, which was the primary signs, had the greatest frequency (62.9%), then vomiting 20.2%, balance disorder was merely found in 4 cases (5.6%). Regarding to John F. K et al (2011), the early signs of patients with cerebellar tumor were raised intracranial pressure triggered by disorders of cerebrospinal fluid together with cancerous volume; therefore the early signs were headache and vomiting, the next signs of cerebellar dysfunction were things like balance disorders and apraxia.

In regards to frequency of clinical symptoms at admission, it showed that notable signs of increased intracranial pressure were headache in 101 children (87.9%) andvomiting in 111 children (89.5%), then papilloedema in 62 children (54.4%). The significant symptoms of cerebellar dysfunction was staggering (87.9%) and apraxia (89.5%). Guy L. Odom (1956) from Duke University (USA) evaluated clinically 164 pediatric brain tumors in the cerebellum patients, he found that 84% of brain tumors in the cerebellumhad vomiting symptom, headache took 82%, balance disorder 72%, nystagmus 46%, and double vision 29%. The interchange of clinical presentations between astrocytoma and medulloblastoma: Headaches and vomiting were two profound symptoms. Headaches of two tumor types made 85.7% and 85.3% of children, the percentage of vomiting (or nausea) was 88.1% and 95.1% of children, papilloedema of two sorts was approximately 45.9%

comparing with 66.1% children. For cerebellar dysfunction, stagger in astrocytoma were found in 92.9% of patients while this number of medulloblastoma was 93.4%. Apraxia was commonly seen and similar in two tumor types 92.9% and 93.4% relatively. Based on these data, there were no differences between symptoms of intracranial hypertension and cerebellar syndromes of these two histopathological tumors ($p>0.05$). Comparison between clinical presentations of ependyoma, astrocytoma and medulloblastoma show us that headache in ependymoma was less commonly found than astrocytoma 5.7% ($p=0.024$). Vomiting of ependymoma differed from medulloblastoma ($p=0.042$). There was no difference in cerebellar dysfunction symptoms of all three cancer types.

1.1.2.2. Pathological feature on MRI images.

Cerebellar cancers often located in vermis (71.8%) and solely 12.9% in cerebellar hemisphere. Tumor masses can be found in both vermis and cerebellar hemisphere made up 15.3%. In 81.5% of cases, tumor size had 3-5cm diameter and the other (15.5%) were more than 5cm diameter. Daria Riva (2000) from Italy had investigated 53 brain tumors in the cerebellum cases whose average tumor size was 28mm smaller than the tumor size of our study (43.4mm), this may be due to late diagnosis of our patients.

Our detection results of cancer location can determine that astrocytoma was mostly found in the hemisphere, vermis and cerebellar hemisphere (61.9%) while medulloblastoma located mainly in cerebellar vermis (91.8)) ($p<0.01$). The density of astrocytoma was more identical than medulloblastoma ($p<0.01$). Cysts were solely seen in astrocytoma while medulloblastoma had none of them. Astrocytoma could not invade the brain stem, unlike medulloblastoma (4.7% and 16.4% respectively). 9.8% of medulloblastoma cases had spinal cord metastasis, whereas there was no case in astrocytoma. William T. O'Brien (2013) suggested that cerebellar astrocytoma located in vermis or migrated from vermis to hemisphere, most of them were large cysts. Our results about cancer location were similar to Henry S. Friedmen's research (2014): 95-90% of medulloblastoma developed in vermis, there were 75-90% of this type found in 92% of markedly enhances after gadolinium administration.

Lodgment of ependymoma was mainly in cerebellar vermis (88.2%), 11.8% of this case located in vermis and hemisphere, none case was detected in cerebellar hemisphere alone. Ependymoma did not have cysts like astrocytoma and metastasized down to spinal cord in 17.6% of cases.

The detection of MRI images was very important for cerebellar cancer, based on that, we can diagnosed histopathological types.

4.1.2.3. Histopathological traits of cerebellar cancer.

**Incidence rate according to histopathogogy*

Researches of incidence following histopathology demonstrated that medulloblastoma had the highest proportion (49.2%), the second position was spent for astrocytoma (33.9%), ependymoma made up 13.7%, and others took 3.2%. Our outcomes were similar with the data of Chang (1993), Gjerri (1998) andAkay K.M (2004).

**Malignant level according to histopathology.*

Regard to WHO histopathological classification, the high grade group made up 56.4%. This was similar with the outcome of Christian (2001): 53.2% of cerebellar cancers were high-grade.

1.2. Assessment of treatment outcomes

1.2.1. Evaluation of brain tumors in the cerebellum treatment

1.2.1.1. General situation of death and surviving patients

The study showed that the highest number of dead patients, in 2010, was 15/40 (37.5%) then in 2011 was 18/50 (36%), at the end of the research, it was 69 (55.6%). The ratio between dead cases of the first year and total number of death in five years was 78.3%. There were 18 patients which survived after 5 years, which took up 23.1% in total 78 cases at the end of the study – more than 5 years from the initiation of disease (admitted in 2009 and 2010).

Kaplan-Meier graph estimated general survival ability of 124 patients after 5 years was 38%. Compare with the investigation of Copeland in Houston (USA) whose survival ability of cerebellar patients after 5 years was 60%, our results were much lower. The study also illustrates the distinction in the number of patients died regarding to different histopathological types of cancer in 5 years of observation ($p<0.001$). The greatest death proportion in the end of the study was belong to ependymoma (76.5%), next was medulloblastoma (68.9%), astrocytoma had 31.0%, this number of other types was lowest (25%).

The Kaplan-Meier line chart estimated the survivability after 5 years of astrocytoma, medulloblastoma was 60% and 30% relatively. In the case of ependymoma, none of patients lived to 5 years, estimation of after 3 year surviving cases was 25%. According to Jacqueline (1984), if medulloblastoma patients removed cancer completely, and given adjuvant chemo and radiotherapy will live for 1 year (85.7%), 5 years (64.3%). The survival rate after 5 years of astrocytoma in the research was 50% being similar with data of Udjian (1989) 47%.

1.2.1.2. Assessment of surgery

There were 51.6% of patients that removed cancer completely and the other 38.7% was discarded partially. In the totalnumber of patientsunder surgery, 8.1% of them passed away while cranial MRI was not performed. The majority of patients (89.5%) just needed 1 operation, whereas 9.7% had 2 operations and only 1 person had to have 3 operations.

1.2.2. Assessment of histopathology according to treatment protocol

1.2.2.1. General evaluation of histopathological types of cancer.

The investigation demonstrated that 71.8% of patients were under surgery alone without adjuvant therapies. They embodied some low grade astrocytoma and people died after surgery (chemo and radiotherapy could not been performed). The death number in patients taking surgery alone was the highest (64%), occurring commonly in 2009, 2010 and 2011. There were 10 individuals taking radiotherapy after surgery and half of them passed away in 3 years. Six patients were given adjuvant chemotherapy and 50% of them have died before 5 years. The group taking combination of three therapies which contained 19 patients (15%) had lowest death rate (21% after 5 years). Based on these result, we found that the high number of deaths was high in the first year because they have not taken all therapies, namely surgery, chemotherapy and radiotherapy. Heiskanen andLehtosalo (USA) studied 118 cerebellar tumor patients taking surgery from 1968 to 1982 showed that from 1976, when imaging diagnosis using CLVT appeared, a shunt was placed between the ventricle and abdominal cavity and after one week patients were operated to remove the tumor mass, researchers found that patients did not die during operation, more than 10 year survival ability of astrocytoma and medulloblastoma were 97% and 13% respectively, by contrast, unfortunately, the number of patients with ependymoma could live more than 5 years made up only 7%.

1.2.2.2. Assessment of treatment for medulloblastoma

In 61 patients with medulloblastoma, there were 35 (57.4%) given surgery alone hade died. Some taking combination of surgery and radiotherapy had 5 death cases. 1 over 2 patients passed away after taking surgery and adjuvant chemotherapy. There were 19 patients (13.1%) taking three therapy sorts and 78.9% of them could survive until the study finished.

This results were similar to Jacqueline, and even took over in the data of combination of surgery and radiotherapy. However,more than 5 year survival rate was lower than Jacqueline’s one in all therapies. We realized that there were several factors corresponding with our therapies that were not good.

Kaplan-Meier chart showed that more than 5 year survival ability of medulloblastoma was 30%. This was similar with Heiskanen (1985): 27% of 39 patients with medulloblastomacan live more than 5 years.

1.2.2.3. Assessment of astrocytoma treatment

Of all patients diagnosed with astrocytoma, 69% of the patients could survive by the end of study. Kaplan-Meier chart of this cancer demonstrates 70% of patients could live after 5 years. Our outcome was lower than Heiskanen's (1985): 83.7% of patients had been alive.

1.2.2.4. Assessment of ependymoma treatment

In 17 ependymoma patients: 8/9 children were given surgery alone had died, 3 over 5 children taking combination of surgery and radiotherapy had died and 2 over 3 children taking surgery and chemo passed away. Hence, we did not have any cases taking all three therapies types, only 8/17 cases were given surgery combining with chemo or radiotherapy. Children had to be more than 6 years old to take radiotherapy so this number in ependymoma was very low since 76.5% of patients were under age 4. Only 1 patient survived until the end of the study, which was 41 months.

According to Pierre - Kahm (1983), if all therapies are performed, 39% of ependymoma children can live 5 years more, recurrence rate was 41%, and metastasis took 20%. This means survivability will increase when children are treated well

1.2.3. Metal and neurological abnormality after treatment

1.2.3.1. Sequenlae commonly found in alive patients

Research showed that there were 33% of surviving patients have different level of sequenlae. Particularly, each patients had 1-3 distinct sequenlae, movement disorder was the most prevalent one (84.2% of patients have got this), the percentage of cranial nervous paralysis was 47.4%.

1.2.3.2. Intellectual development after treatment

IQ index of patients who survive after treatment was quite high. IQ score level of astrocytoma patients was greater than medulloblastoma's one ($p<0.05$). The group taking full therapy combination had lower IQ index than the one did not have radiotherapy and chemotherapy. The IQ score of radiotherapy group was 5.2 points lower than non - radiotherapy one, the cohort given combination of radiotherapy and chemotherapy have IQ index 6.6 points lower than the non-radiotherapy and chemotherapy group.

1.2.4. Some important factors affect the death and survive of each brain tumors in the cerebellum histopathlogical type cases.

We have found out some factors relating to death and survival.

**Age groups*

The investigation showed that children in the age group 0-4 have the highest death rate in medulloblastoma and ependymoma (86.7% and 84.6%). The mortality rate of 10-15 years old cohorts was the lowest in astrocytoma (11.1%). Compared with age group impinging on mortality during first year, children age 0-4 had the greatest mortality rate. This outcome was similar with the research result of Udjian (1989) and Jeffrey (1982), the prognosis was worse in children under age 4. The younger the children, the lower the survival prognosis.

**Tumor size*

There were 69 patients that died, of which 54 (78.3%) cases occurred in the first year. 4 cases of < 3cm tumor size had passed away for 5 years (3 people in the first year, 1 in the second year). 3-5 cm tumor diameter group had 62 mortality cases, particularly, 48-10-4 occurred respectively in the first year, second year and the latter 3 years. In the first years, there were 3 patients belonging to >5 cm tumor size group that died. Obviously, the larger the tumor size, the worse the surgery outcomes. Moreover, cancer cells could metastasize to nearby benign tissue.

**Brain stem invasion and spinal cord metastasis.*

We found that all patients who had spinal cord metastasis died in the first year. Almost all patients, 11/13 patients having brain stem invasion passed away in the first year and 2 of them died in next year. The group suffering from both these events had 5 individuals and all of them died in the initial year.

**Histopathological types of cerebellar cancer.*

The study represented that in the first year the mortality rate of ependymoma was highest (58.5%), the second one was medulloblastoma (54.1%), them astrocytoma (31%) and finally other sorts (25%) with p =0.038. We also found that the survival rate of astrocytoma patients until the end of our study were higher than the one of epedymoma cases (p<0.001).

**Malignancy level of cancer*

The investigation of cancerous grade of histopathological cancer types in the first year, table 3.29 illustrated that the vast majority of children with third grade neoplasm had a mortality rate up to 80%, the second highest was grade IV with 56.9%, this proportion of level II and I was 53.3% and 22.2% relatively. This comparison had statistical meaning (p=0.003). This outcome was also compatible with international studies focusing on the early death of high grade cancer patients.

**Surgery to remove tumor*

We realized that the complete tumor removal had lower mortality rate than partial one ($p<0.001$). Nevertheless, all patients taking surgery alone passed away in the first year (except low grade astrocytoma), if adjuvant chemo or radiotherapy or both of them were not utilized.

CONCLUSION

Studying 124 children with brain tumors in the cerebellum at the National Hospital of Pediatrics from 2009 to 2014, we conclude that:

1. Clinical and histopathological characteristics of pediatric cerebellar cancer.

- Average age of onset: 6.2, mainly from 5 to 9 years old in medulloblastoma and astrocytoma, 0-4 years old in ependymoma. Boys suffered more often than girls 1.58/1.
- Patients admitted to hospital later than 58.1 days.
- General clinical presentations were vomiting 89.5%, headaches 81.5%, papilloedema 54.4%, apraxia 89.5%, ataxia 87.9%, and shaking limbs 32.2%.

Histopathological signs of medulloblastoma, astrocytoma were headaches, vomiting,papilloedema,apraxia, ataxia like general symptoms of cerebellar cancer, except in ependymoma, headaches and vomiting were less common.

- Tumor images in histological manner:

Medulloblastoma was prevalently found in vermis 91.8%, 28.6% of astrocytoma located in hemisphere, 38.1% in vermis and 33.3% in both two places. This is the unique type had cyst 78.6%. Ependymoma was often found in vermis (88.2%). Medulloblastoma and ependymoma had spinal cord metastasis and brain stem invasion.

- Histopathology: Medulloblastoma took 49.2%, 33.9% were astrocytoma, ependymoma made 13.7%, the latter 3.2% was other types.
- Malignant level: all medulloblastoma cells were in grade IV. 92.9% of astrocytoma had lowest level. The percentage of low grade ependymoma was 64.7%

2. Assessment of treatment outcomes.

- General outcomes:

Most of the patients, 69/124 (55.6%) had died, 78.3% of these cases occurred in the first year. While 18/57 survival children were observed in 5 years until the study finished. Kaplan-Meier graph estimated the survival rate after 5 years was 38%.

- Results in histopathological manner.

+ Most of the 35/61 medulloblatoma children taking surgery alone had died, the latter (26) children were given a combination of surgery and radio/chemotherapy or both radiotherapy and chemotherapy and could survived longer. Complete tumor removal patients lived significantly longer. After 1 year, the number of surviving children made up 45.9%. Kaplan-Meier graph estimated surviving rate after 5 years was 27%.

+ Astrocytoma: 42 children were given operation alone. After one year, 72% of them were alive. Kaplan-Meier graph estimated surviving rate after 5 years was 60%.

+ Ependymoma: 8/17 children taking only surgery while the latter (9) were given adjuvant chemo or radiotherapy. Only 4 children lived until the end of the research (23%) and all people were observed in 5 years died.

- Some factors corresponding to the mortality and survival of patients generally were age of onset, the time from the appearance of initial sign to diagnosis, tumor size, histopathological types, malignant level, removal results, compliance.

- Some cases had unrecoverable movement disorder, characteristic alteration, language disorder, cranial nervous paralysis after treatment. Metal index was normal with average IQ greater than 90%.

RECOMMENDATIONS

1. Early discovery, diagnosis and treatment of brain tumors in the cerebellum will reduce the mortality rate and improve living quality of patients.

2. Cerebellar treatment needs to start with the complete removal of tumors. Then, we cooperate with chemo and radiotherapy to gain a better outcome.

3. More advanced studies should be performed in treatment protocols and prognosis of each histopathological types and genetic disease in cerebellar cancer.

Some limitations of research: Wide spread and first study about the entirebrain tumors in the cerebellumaims to show the diagnosis circumstances, histological types and treatment in recent years, have not gone deeply in certain aspects to achieve more completed and clearer outcomes.

LIST OF RESEARCHES PUBLISHED RELATING TO THE THESIS

1. Tran Van Hoc, Nguyen Van Thang, Nguyen Thanh Liem (2012). Result treatment of medulloblastoma in children at the Nationa Hospital of pediatrics, Journal of Medical Research, vol 80, No 3, 52-58.
2. Tran Van Hoc, Nguyen Van Thang, Nguyen Thanh Liem (2014). Evaluate the initial results of treatment cerebellar astrocytoma in children at the Nationa Hospital of pediatrics, *Vietnam Medical Journal*, vol 414, 93 - 97.