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Retrospective audit of paediatric intracranial tumours treated in Universitas hospital from 2000-2020

By

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DECLARATIONS

"Submitted in fulfillment of the requirements in respect of the Master'sDegree MMed in the Department of Neurosurgery in the Faculty of Health Sciences at the University of the Free
State."

"I, Lelethu Bulelani Bango, declare that the coursework Master's Degreemini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification of the Master's degree MMED at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education."

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Abstract

The research involved a retrospective review of the number and types of paediatric tumours managed at Universitas Hospital, Bloemfontein, over 20 years. Universitas is the only referral hospital serving the Free State province and the surrounding areas, including the Northern Cape and Lesotho, in relation to paediatric tumours. The total population of the Free State, Northern Cape, andLesotho numbers at least 6 million, and the area has only one hospital to managepaediatric tumours.
Paediatric tumours are treated in cooperation by the neurosurgery and the paediatric oncology departments of Universitas Hospital. This collaboration is due to the multidisciplinary approach needed to treat this pathology adequately.The objective of this research was to review the different types of tumours encountered and managed by the hospital. An investigation was done into the demographics of patients presenting at the hospital from 2000 to June 2020. Thedata that was collected clarified the patient gender and age distribution, and alsothe outcomes achieved during the given period. A review of the management of the patients was done, and a comparison made of reviewed data and literature reporting on international statistics. The research was undertaken with the aim of optimising the management of pediatric oncology patients, and to streamline data collection. As Universitas is ateaching institution, achieving these aims may help upcoming registrars in both neurosurgery and paediatric oncology to have a better understanding of a disease that affects this fragile population.

The research conducted is a retrospective review of paediatric intracranial tumours admitted to Universitas hospital during the period ranging from 2000 to 2020 (June). It looks at the different types of tumours admitted and the management thereof by the departments involved; neurosurgery and paediatric oncology. During this period 274 patients were managed with 60% of the patients dying after receiving surgery and or adjuvant treatment. Of the 274 patients, most tumours were glial in origin with medulloblastomas and ependymomas being second and third most, respectively. Patients received radiotherapy and oncotherapy according to paediatric protocols; after a biopsy or resection by neurosurgery. Patients would also get cerebrospinal fluid diversion if required. This diversion was seen as prophylactic management in patients that could not receive a complete resection of the tumour. This research revealed a need for better notekeeping and storage of patient data when it comes to tumours, ensuring that future research will be of greater quality. Research also revealed that a more thorough examination of tumours in teenagers will need to be conducted. This research will help in compiling a better template in admission of all tumours in Universitas and thereby facilitate an extensive tumour registry for the neurosurgery department.

Keywords

Intracranial tumours
Adjuvant therapy
Post diagnosis lifespan
Infratentorial
Supratentorial
Oncotherapy
Radiotherapy
Gliomas
Medulloblastomas
Ependymoma
Astrocytoma

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Chapter 1

Literature review

Brain tumours are the second most common malignancy in children with the first being haematological malignancies like lymphomas and leukaemia.[3,6] There are quite a few predisposing factors or familial conditions that give rise to certain types of tumours. High grade gliomas and medulloblastomas are common in patients with Turcot, Li-Fraumeni and Gorlin syndromes.[3]Neurocutaneous disorders are usually inherited and also have an association with certain intracranial tumours. Neurofibromatosis is associated with gliomas, tuberous sclerosis with subependymal giant cell astrocytomas, von Hippel- Lindau disease with hemangioblastomas, and basal-cell naevus syndrome with medulloblastomas.[6] Some of the patients seen with these disorders associated with tumours are not classified as such after diagnosis. This is an area where our data-keeping and tumour registry will need to improve. The review of these syndromes needs extensive tests which are not always available at Universitas hospital. This is further hindered by the Genetics Department which is no longer fully operational. An operational Genetics Department would assist with review of syndromes and be able to acquire blood tests that would otherwise not be justified in other departments.

The incidence of brain tumours varies for different geographical regions across the world, although they remain relatively in the same range. In the United States, it is estimated that 17-22.5 % of children with cancer have a brain tumour.[2] One of the articles reviewed highlights that 4350 children between the age of 0-19 years are diagnosed with brain tumours.[3] Whereas another article shows that 2.5-3.5 per 100 000 is the incidence of brain tumours in children under the age of 15 years. It is also noticed that the incidence of brain tumours is higher in patients with a strong familial history of stroke and convulsions.[6] Brain tumours represent 16-23% of malignancies in children.[12] This is a very large percentage of tumours affecting a small area. This is most likely due to the amount of blood that is distributed to the brain;15-20% of the total blood volume of the body.

Brain tumours are the leading cause of death in paediatric patients with cancers. This makes them important especially since they cause the highest morbidity and mortality in children with cancer.[5,8] An additional problem is that the management of the tumours has long term sequelae that are sometimes unavoidable.[2,4,5] Some tumours are in areas where the surgical approach will lead to postoperative deficits. These are mainly posterior fossa tumours, which form a large proportion of tumours seen in paediatric neurosurgery patients. Children can develop ataxia or nystagmus that may not resolve. Another problem is that patients present after a prolonged period of illness and have had the specific neurological deficit for too long for it to resolve after surgery. The added insult of adjuvant therapy (chemotherapy or radiotherapy) ensures that the management remains complicated and the long term sequelae permanent.

The clinical presentation of children can be nonspecific. Therefore the clinician requires a high index of suspicion, especially if there's a clinical disorder associated or a family history of convulsions. It must also be remembered that if the fontanelles are still patent the signs of raised intracranial pressure will differ from those seen in adults. In infants the presentation may be lethargy, increasing head circumference and inability to have head control.[3] Depending on tumour location a child can present with various signs and symptoms; dropping objects to signify limb weakness due to supratentorial lesion, unsteadiness that will direct to a posterior fossa lesion in the cerebellum and delayed milestones or decreased progression academically. They may also present with short stature which requires work up as this may reveal an endocrine abnormality.[3,6] All these symptoms or signs require a high index of suspicion which some parents lack. With better education, we can hopefully prevent parents from arriving at hospital too late for meaningful intervention. Unfortunately, this is devastating to a family that will now need to look for a special school when they already couldn't afford to get a normal school for the child.

In children, 50% of brain tumours will occur in the posterior fossa. The most common tumours seen in children are medulloblastomas, gliomas, and ependymomas. Medulloblastomas account for 15-20% of paediatric brain tumours and are said to be the most common tumour.[3,5,6,] Gliomas, especially the high grade gliomas have the poorest prognosis of the tumours that affect children. This may be due to their location in the deep structures making them more difficult to operate or the fact that on diagnosis a lot of normal tissue is already infiltrated.[3,4] The diagnostic tools used are imaging; CT or MRI and histology for review post surgery. Review of tumour molecular biology can be used to classify tumours but this is still in its developmental stages. Review of molecular biology is not currently done in South Africa but it does assist in classifying patients into high-risk groups post-surgery, especially since some of the medulloblastomas have a better prognosis.[1]

The management of intracranial tumours in children is difficult in that the complications of surgery and adjuvant therapy have long term implications on both child and parents.[1,4,9]
The mainstay of management is gross total resection of tumours whenever possible. Gross total resection means that less tumour remains and a smaller surface area of the brain needs to be irradiated post-surgery. Although radiation mainly targets fast-growing cells, it also has a detrimental effect on the normal growing cells in the cell cycle. Children that undergo total resection have a longer event-free survival rate. Improvements in surgical techniques and adjuvants have meant that the survival of these children has increased by almost 20% after management.[1,2,3] If we can improve our surgical techniques then we will see the same improvement in a population; Free state, that probably doesn't have the same rehabilitation facilities to assist children post-surgery. Post-surgery or resection the children will undergo radiation or adjuvant therapy.[1,2,3,4,5] In children over the age of three, radiotherapy may be used for radio-sensitive tumours and the inclusion of chemotherapy if tumours are sensitive. Children below the age of 3 will receive chemotherapy instead of radiation. This is according to international standards due to the brain still growing actively at this stage of life.

I will be looking at the intracranial brain tumours that presented to Universitas from 1 January 2000 to 30 June 2020. I will review the number of cases presenting in this

time period and compare the data to information reviewed in other articles. This will hopefully assist in providing better ways to manage these patients and also review any problems that need resolution.

The three main tumours seen in children, as mentioned above, have various management strategies. The aim is always for gross total resection with minimal morbidity. The management of tumours in the department has always been according to literature. It is also based on the available experienced surgeon at the time. Currently, surgery for paediatric tumours has improved greatly as the experience of surgeons has and this allows for larger gross total resection. Universitas Hospital remains a teaching institute and this also means that there may be a variation in the gross total resection of tumours according to the surgical expertise available. Unfortunately, experience and interest can not be quantified but only retold.

Very few tumours were mainly associated with familial syndromes as mentioned above. It was difficult to find any other similarities or variables that had any significance in the study.

Identification of shortfalls

In the review of intracranial tumours, there is a need to find specific data on patients. This data is available in the database that the hospital has; Meditech. On review of Meditech, most patients will have information present about what occurred in their hospital admission. The information available is patient demographics such as gender, date of birth, address and contact numbers, or next of kin details. It also has the medication that a given patient is or was taking. Also included is information on the blood that was taken. It will list the date of admission and discharge and also any notes written by the different departments that have managed the patient. It also includes radiology reports on any imaging that the patient might have.

Although this information is readily available on the system, a researcher needs the patient details to search for the specific pathology. The notes are not saved under specific diagnoses so a researcher needs to search every patient seen by neurosurgery to begin reviewing specific patients with the problem that is going to be reviewed. This would have been a difficult task had it not been for the tumour registry that the Paediatric Oncology Department had readily available. This is one of the shortfalls I encountered as the neurosurgery department had not started a registry on paediatric tumours but has one on all adult patients.
To start a registry that would assist with further research, it seems the best method would be to provide a template on Meditech that will be accessed by diagnosis and make it easier for future research to be conducted. A researcher will just need to type the code for the template and then acquire all the necessary information on the patients.
This template would have to have all the headings required for a review of a patient with specific issues, such as tumours.

The information would have to be all variables; height, weight, tumour size, tumour location, management from resection to adjuvant therapy, and clinical symptoms and neurology both pre-operatively and post-operatively. It should also have any follow-up information, such as imaging or further management and histology.
All this will greatly improve the quality and access for further restrospective studies.

Further information that will need to be incorporated and reviewed will be the imaging itself; the radiology reports. These were solely dependent on the specific radiologist that was reviewing the computer tomography scan or the magnetic resonance imaging. This meant that certain details were left out of some reports. A template will either need to be made by radiology or by the neurosurgery department to facilitate the addition of all relevant information. The relevant information would be tumour size, location, midline shift, differential diagnosis, and any grading system used to quantify the given pathology. This would greatly improve all reviews of patients.
Another pitfall was that the imaging system was previously changed in the hospital. All the information from that previous system; Isite was lost and tumours and the radiology reports could not be reviewed. A consolidated place to keep all this patient information would result in information always being available for future researches.

It was also difficult to review the histology of given patients. The patients needed specific diagnoses and gradings that were in line with the latest international guidelines. This was not available mainly due to resource limitations; unable to currently use molecular grading systems as this is not yet available to us. This will improve our future research but in preparation, we should already develop a system that will accommodate and regulate accurate review.

The biggest pitfall is one that is very difficult to overcome without co-operation and constant review by individuals and departments. It is the note-keeping of specific patient details. There needs to be a formal template made to ensure that all patients have the same details. The registrars or doctors making notes should all ensure that every detail is recorded. This is the biggest challenge as only a few departments ensure that this happens.
Neurosurgery is currently efficient at ensuring that notes are available on the system. This has also greatly improved over the twenty years of review as prior generations had very scanty notes. This was also determined by the individual that was managing the patient and should be improved to a level that all notes have as much information available and all the information is similar if not identical.

Another component lacking was the reasons certain things were done. This was not placed on the information system; Meditech. Meaning that a concise or overall follow up of patients was not adequately achieved. It means that such information will need to be included and strictly adhered to at all times. Neurosurgery has currently developed this and is ensuring that all patient details are recorded and decisions clarified electronically.

To ensure that all future research has improved quality, it will be the responsibility of departments to ensure that all personnel know what is required concerning note-

keeping. This means that the nursing and theatre staff will have to keep better records and ensure that all available information is notated.
It will also fall to seniors in every department to teach and ensure that new arrivals adhere to the requirements. They should also explain the importance of all these procedures and explain that these are in measure to ensure that their researches as registrars will be easier to do and yield better results.

There is a need for further research and review of paediatric intracranial tumours. Better research will lead to the discovery of better ways to manage patients and education on how to avoid mistakes that were previously done. If departments want to improve and compete at an international level then these are the building blocks to such an improvement.

An important factor, easily ignored or forgotten, is the data collection and review by the biostatistician. It was very difficult to ascertain what information and how it should be compiled to give to the biostatistician. This meant that certain information had to be rechecked and resubmitted, causing a delay in the final accumulation and review of the data. If students are better informed in this regard, it will not only make the research easier to do but also peak the interests of young, future researchers. Although this is taught and emphasized in initial courses when starting with your postgraduation degree, it seems that this is lost and not easily reflected when the need arises to finally to your protocol and manuscript.
The main aims needed to achieve better research should be instilled from the initial contact with registrars. This should not only be done with courses but also by seniors that have already been through the process and completed their studies.

What will improve the collection of all this information is quite a difficult task. The biggest difficulty is how you include information that will assist researchers and improve patient management in notes that will also be used for legal purposes. This may eventually cause a conflict as medical professionals may be inclined to omit relevant or important information that may have made research into specific topics easier. At present, the best idea for better data collection may be to have a consolidated universal template that will be filled out by all departments involved in patient management. Unfortunately, Meditech may not be able to accommodate such a template. And finally, it will be up to an individual to ensure that the best information possible is included in the database and this is something that will be difficult to achieve.
Currently, the neurosurgery department is looking into solving this issue and providing a template that will be placed on the database; Meditech. This was mainly due to the difficulties seen in not only compiling my research but also the research needed by the incoming, future graduates.

An evident gap in the review of the tumours was the review of patients that were aged from thirteen to eighteen. Although this was an inclusion criterion in my research, it was mainly due to minimal notes available on this age group. This was caused by the exclusion of this age group from the Paediatric Oncology tumour registry and the unavailability of these patients in a specific Neurosurgery Department tumour registry. This creates a good opportunity for any future research that needs to be done.

Another area that may need research is the identification of resources that are available to parents after discharge. Currently, the Free State has no public rehabilitation facility that is available to parents with children that have great postoperative morbidity. A review needs to be done of the income of parents that present to the hospital. A follow up by the social worker to see what conditions these children return to will also help to identify where the hospital or state can help in facilitating the much-needed rehabilitation of these children. We have seen that the physiotherapy and occupational therapy these children receive post-operatively is of great benefit to them. However, in most cases the rehabilitation they receive post-operatively in hospital is probably the last contact with rehabilitation they receive. This could be attributed to the lack of rehabilitation in their hometowns. It can also be because parents can not afford to take children to the contact sessions that are planned post-discharge from the hospital.
Since many of these questions remain unanswered, the best way to go about answering will be a review of conditions. This will cause a strain on an already overwhelmed health system but is the best way of ensuring patients receive the best care possible.

Aim

1. To review information gathered on paediatric patients presenting to Universitas hospital; review the gender predilection, age at presentation, tumour characteristics, years of follow up and complications pre-and post-operatively.
2. To compare the information to international standards presented in the literature.
3. Review the difference in management and outcomes as the years progressed to see if there was any improvement in managing patients.

The research is motivated by the need to learn more about our patient population and to review where the department of neurosurgery can improve in the treatment of paediatric patients with tumours. This improvement will lead to our local standards being at the same level as international protocols or standards of operations.
An in-depth look at the patients we receive will reveal where improvements need to be made.
A review of the tumours presenting and collection of the specific histology, characteristics and presentation of patients will help us see whether a need for an outreach program is necessary. This may be hindered by the lack of resources, mainly staff to carry out such programs as already the department in Universitas is not fully equipped to manage the patients that present at the hospital.

Improvement in the management will require a review of what was previously done in the past and thereby finding ways to better implement the new means of treating patients according to international standards.

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Chapter 2: manuscript

Retrospective Audit of Paediatric Intracranial Tumours Managed at Universitas Hospital from 2000(January) to 2020(June)

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Abstract
The research conducted is a retrospective review of paediatric intracranial tumours admitted to Universitas hospital during the period ranging from January 2000 to June 2020. It looks at the different types of tumours admitted and the management thereof by the departments involved; neurosurgery and paediatric oncology. During this period 274 patients were managed with 60% of the patients dying after receiving surgery and or adjuvant treatment (chemotherapy or radiotherapy). Of the 274 patients, most tumours were glial in origin with medulloblastomas and ependymomas being second and third most common. Patients received radiotherapy and oncotherapy according to paediatric protocols. This is usually after a biopsy or resection by neurosurgery. Patients would also get cerebrospinal fluid diversion if required. This diversion was seen as prophylactic management in patients that could not receive a complete resection of the tumour. This research revealed a need for better note keeping and storage of patient data when it comes to tumours, ensuring that future research will be of greater quality. Research also revealed that a more thorough examination of tumours in teenagers will need to be conducted. This research will help in compiling a better template in the admission of all tumours in Universitas and thereby facilitate an extensive tumour registry for the Neurosurgery Department.

Introduction

The research involved a retrospective review of the number and types of paediatric brain tumours managed at Universitas Hospital, Bloemfontein, over 20 years. Universitas is the only referral hospital for Paediatric Oncology and Neurosurgery serving the Free State province and the surrounding areas, including the Northern Cape and Lesotho. The total population of the Free State, Northern Cape, and Lesotho numbers at least 6 million, and the area has only this hospital to manage paediatric brain tumours.
Paediatric brain tumours are treated in cooperation by the Neurosurgery and the Paediatric Oncology Departments of Universitas Hospital. This collaboration is due to the multidisciplinary approach needed to treat the patients adequately. The objective of this research was to review the different types of brain tumours encountered and managed by the hospital. An investigation was done into the demographics of patients presenting at the hospital from 2000 to June 2020. The data that was collected clarified the patient gender and age distribution, and also the outcomes achieved during the given period. A review of the management of the patients was done, and a comparison was made of reviewed data and literature reporting on international statistics.
The research was undertaken with the aim of optimising the management of pediatric oncology patients and streamline data collection. As Universitas is a teaching institution, achieving these aims may help upcoming registrars in both neurosurgery and paediatric oncology to have a better understanding of a disease that affects this fragile population.

Materials and methods

The researcher collected data from the tumour registry kept by the Department of Paediatric Oncology at Universitas Hospital. The registry contains data of all children who have been treated by the oncology department. In addition to the registry, the researcher collected information needed for this research from the electronic database of the hospital, Meditech. Patient notes were reviewed and the detailed data needed were collected in Excel format, and sent for review by the Biostatistics Department at the University of Free State. The allocated biostatistician assisted by applying statistical procedures to information that had been compiled, and which will be reported on in this research project. The data will be represented in tables and percentages that are easy to interpret.
The researcher was, however, unable to review certain aspects of presenting patients, as certain information was no longer present on the database or was never included in the initial assessment of patients.

Inclusion and exclusion criteria

The research included all patients below the age of 156 months who presented at Universitas Hospital from 2000 (January) to 2020 (June). These patients represent the accumulation of patients referred to the hospital from the surrounding referral hospitals, including Northern Cape and Lesotho patients. The number also includes patients who were referred from Pelonomi Regional Hospital, as most patients presenting at Pelonomi were transferred to the Paediatric Oncology Unit at Universitas.
Patients who had died acutely after the initial review were also included. Exclusion criteria were patients who were older than 156 months on presentation at Universitas and those who were managed privately after an initial emergency review at the hospital. Patients who were followed up after 2000, but who had already been diagnosed before 2000, were also excluded from the research.

Methods

The information was collected from the oncology tumour registry and the hospital database. The information that was gathered was reviewed in an Excel spreadsheet and assessed by biostatisticians. The results will be reviewed in the research report.

Variables

The variables reviewed are numerical and categorical. The numerical variables assessed are continuous, namely, age, height, weight, and lifespan post-diagnosis of a tumour.
The discrete numerical variables are the number of patients and the number of different types of tumours.
The ordinal (categorical) variables are the different tumour grades. This information was limited, as the hospital cannot diagnose according to the new molecular classification, and reports contained minimal notes that could be used to review specific grading systems.

The nominal (categorical) variables include patient sex, tumour type, degree of tumour resection, and management offered.

Outcomes

The outcomes review of the research was influenced by the amount of information available, especially the notes on the Meditech system. The information available in the tumour registry is of great importance to paediatric oncologists.
The main outcomes assessed were whether patients survived post-diagnosis and for how long. A review of the management patients received, and for how long they survived after management could not be quantified for review by biostatisticians, because of a limitation relating to a lack of clarity of available notes. Although the notes improved in later years, they often remain inadequate and not clearly illustrated.
Patient outcomes were mainly influenced by the type of tumour and the degree of tumour resection that occurred.
Patients with less aggressive tumours and better gross total resection seemed to have a longer post-diagnosis lifespan, which is also reflected in the literature.

Results

A review of 274 children with intracranial tumours was done, of whom 126 were female and 148 male patients (46% and 54% respectively).
Over the period of 20 years, an average of 13.5 patients were managed per year, with a maximum of 22 patients seen in 2009, and a minimum of 9 patients seen in 2015. The patients seen in 2020 were not counted as this was not a full-year review. The median number seen over the past 20 years is 15.
The age distribution of the 274 patients ranged from 0 months (children who presented within 30 days of birth) to 189 months at diagnosis. The researcher reviewed a lower quartile of 46 months and an upper quartile of 126 months, giving a median age of 189 months.
In total 164 patients died post diagnosis and/or management – 60.22% of the total of 274 patients. These deaths occurred from either tumour progression or post inpatient or post outpatient management. The deaths were recorded at various times post diagnosis: arrival at the hospital, post surgery, post radiation therapy, or post oncotherapy. A small number died post discharge home.
The balance of 110 patients are still alive, and have been transferred to other institutions or are receiving management at Universitas, in the Paediatric Oncology Department. A large number of those still living have had maximal resection of less aggressive tumours, with or without cerebrospinal fluid diversion, ventriculoperitoneal shunt or endoscopic third ventriculostomy.
The post-diagnosis lifespan ranged from a minimum of 0 months (patients who died immediately or less than 30 days after diagnosis) to a maximum of 226 months. The median lifespan post diagnosis was 8 months, with the lower quartile at 2 months and the upper quartile at 35 months.
As Universitas is the main referral hospital in the Free State, a review of referring hospitals would have to be made on CT scan availability. Institutions without CT scan facilities referred 111 patients (40.51%), leaving 163 (59.49%) patients presenting with CT scans. MRI was only available at Pelonomi(Bloemfontein),

Kimberley Hospital (Northern Cape) and in Lesotho, and most of the workup was done when these patients arrived at Universitas, which facilitated prompt intervention, such as surgery or adjuvant therapy, such as radiation or chemotherapy. Table 1 in the addendum provides a representation of the patients referred to Universitas from its districts, surrounding provinces, and countries. Most patients originated from Lesotho – 67 patients (24.45%) – and Northern Cape referred 46 patients (16.56%). Referrals from the surrounding districts may be fewer than reported because these districts have no imaging facilities available.

A wide variety of tumour types were visible on review. At least 19 different types of tumours were seen in the data that was collected, as reported in Table 2 in the addendum. Tumours were divided into larger groups according to the WHO classification of 2021.[1] When the tumours are divided further, into infratentorial and supratentorial locations in the brain, it enabled assessment of the findings of the post-diagnosis lifespan. On review, 148 tumours (54.21%) appeared infratentorial and 125 tumours (45,29%) appeared supratentorial.

This number is close to that reported by literature, namely that about two-thirds of tumours seen in children are situated in the posterior fossa or infratentorially.[2-5]

The post-diagnosis lifespan of the infratentorial tumours ranged from a minimum of 0 months to a maximum of 211 months. The lower and upper quartiles were 2 and 31.5 months respectively.

The post-diagnosis lifespan of supratentorial tumours ranged from a minimum of 0 months to a maximum of 226 months. The lower and upper quartiles of these tumours were 2 and 41 months respectively. Supratentorial tumours showed a slightly higher upper quartile, at 8 months. This finding may be attributed to the greater ease of approaching supratentorial tumours via surgery, therefore, allowing a more extensive gross total resection. In infratentorial tumours, gross total resection is hindered by the proximity of the brainstem, which results in a less extensive resection.

It was difficult to assess the specific locations of tumours in the brain, as 15 different locations are represented. The locations seen by this study were infratentorially: cerebellopontine angle, cerebellar and brainstem lesions, and fourth ventricle.

Supratentorial locations seen were frontal, temporal, and parietal lobes and intraventricular (excluding fourth ventricular, as these were added to infratentorial), pineal region, and basal ganglia region. The main gross tumour locations that occurred are listed in descending order: posterior fossa tumours, 73 (26.28%); tumours in the brainstem, 61 (21.96%); situated in the cerebrum, 38 (13.68%); and suprasellar, 32 (11.52%). Some of these locations overlap and the difficulties experienced in reviewing them correctly was mainly due to a lack of imaging or notes available to assess the locations personally. The various locations are represented in Table 3. These areas can be further divided into supratentorial, infratentorial, brainstem, spinal cord and other areas as seen in the larger headings in Table 3.

Some tumours appeared rarely, and this is confirmed by the literature. Among those that appear most commonly, gliomas made up 26.57% (73) of the total, which is contrary to reports in the literature, which describes a 30% occurrence of low grade tumours, medulloblastomas and ependymomas.

In the WHO 2021[1] classification, gliomas are divided into adult and paediatric types. These tumours are the same even though the classification has decided to separate them into different categories. These types are divided further into high and low-grade tumours. In this research, the low-grade and high-grade tumours were divided and, as shown in Table 2, labelled as brain astrocytoma (low grade) and gliomas (high grade). Medulloblastomas were the second most common, with 41 patients (14.96%) and astrocytomas (low-grade gliomas) were the third most common, with 36 patients (13.13%). Although, it would probably be better to group both low grade and high grade astrocytomas as one big group, for biostatistical reasons the researcher separated the big group; gliomas or glial tumours. The fourth-highest number was attributed to tumours identified on clinical diagnosis only, which represented 12.02%, or 35 patients. Cases using the clinical diagnosis are difficult to interpret, as they can be either infra- or supratentorial. It also means that no biopsy was done to determine what tumour was seen on imaging; this is mainly done in brainstem lesions that are dangerous to biopsy. The number of tumours diagnosed clinically could also be affected by patients dying before diagnosis or surgery.

Ependymomas were the fifth most common tumours, with 24 patients (8.76%). Although astrocytomas, medulloblastomas, and ependymomas were not represented in perfect thirds, as illustrated in literature, they did occur more often than other less common tumours.

In sixth and seventh places were craniopharyngiomas, with 21 patients (7.9%), and pineal tumours with 14 (4.74%), respectively.

Craniopharyngiomas form part of sellar tumours, which include pituitary tumours, which are rare in the pediatric population. Pineal tumours comprise pineocytomas and pineoblastomas.

The rest of the tumours were scarcely represented, as seen in Table 2 (attached to the addendum). These tumours could not be represented into biostatistically significant values, though their frequency is a true reflection of their representation in literature.

As mentioned, the tumour grading system was not calculated for this study. Much information was unavailable, due to restrictions due to technology and minimal information recorded. Tumours are still being graded according to histology. Molecular grading has not been used yet, thereby, preventing the use of specific terms in the latest classification of tumours.

Of the 274 patients, 4% (11) had metastasis from either ependymoma, pineal region tumours, or medulloblastomas at presentation. These tumour subtypes are the most likely to present which metastases.

In total 23 patients (8,39%) were transferred back to referring hospitals for further management, most likely supportive but was unable to specify in the notes. The only facility in the region served by Universitas that offers adjuvant therapy is, currently, Kimberley Hospital, which has an Oncology Department. This department mainly offers chemotherapy and radiotherapy for adults; all paediatric oncology is managed at Universitas Hospital.

Of the 274 patients, 51 had no notes available on the various databases available to the researcher, a situation that made it difficult to assemble a great deal of the data.

When it came to adjuvant management, 70 patients (25.64%) received chemotherapy. This number could be influenced by the fact that patients under 3

years of age are not eligible for radiotherapy – 123 patients (45.23%) received radiotherapy, while 194 of the patients (71.06%) received surgery of some kind, either a biopsy, resection (complete or incomplete), or cerebrospinal fluid diversion.
Fifteen patients (5.47%) refused management of any kind, including surgery. This may be due to patient fear or a belief in traditional medication. Parents refusing management, against a child's best interest, should be investigated further in future research.
Of the 274 patients, 134 (48.9%) completed their treatment, whether it was surgery or adjuvant. Definitive treatment (complete resection or patient with no growing tumour according to Collin's law) was achieved by 17 patients (6.20%) and their next followup was at the next clinic or followup imaging, months later. Tumour recurrence was seen in 34 patients (12.41%), and cases were divided into local recurrence (occurring in the same area in the brain), and distant metastasis, most likely the spinal canal. Of the 34 patients, 25 patients (75.53%) had local recurrence and 9 patients (26.47%) had distant metastasis. Management of patients with recurrence was divided into surgery (1 patient), radiotherapy (3 patients), and palliation (28 patients). Two of the patients died at home.
The management of tumours overlaps, and patients receive different management. Some receive surgery – whether resection or biopsy – with or without radiation and chemotherapy as adjuvant treatment.

In total 125 patients (45.62%) received resection of some kind – complete or incomplete. Of the 123 patients, 105 (38.32% of 274 patients) received radiotherapy and 70 received chemotherapy. 66 patients (24.09%) had only biopsies for diagnostic purposes with no further resection due to either danger associated with complete resection, or tumours being amenable to radiotherapy. Most patients who underwent only biopsies, incomplete resection, or emergency review with signs of raised intracranial pressures received prophylactic surgery. Prophylactic surgery was seen as a cerebrospinal fluid diversion in the form of a shunt or a scope.

Discussion

Paediatric intracranial tumours are important, because, according to the literature review, they are the second most common malignancy, after haematological cancers. They also play a big role in the socioeconomics of a country, as they not only affect children but also, indirectly, parents, who need to take time off work. They may be unable to work for a prolonged period of time, as hospital stay is extended by both post-surgery palliation and further adjuvant therapy. This means that parents also have to schedule follow-up visits for further management, which can affect their employment. These effects of paediatric tumours are, however, not in the scope of this research, and can be evaluated further in future research. Paediatric tumours also involve a psychological component that includes extended family members. The death of a child is a tragedy, and the financial implications of funerals can be severe. At least 60% of children with intracranial tumours do not survive

Another important aspect of this study was the evaluation of specific tumours. Due to government tenders and hospital financing, it is difficult to have one specific imaging modality system. This results in historical imaging being lost when the systems change. Universitas switched from Isite to the currently used Xeroview, which resulted in an inability to review tumour sizes or even previous clinical diagnoses. This problem can be overcome by good clinical note-taking, which seems to have improved over the years, but which can improve through review and encouragement of registrars to record as much information as possible in their clinical notes.

A large percentage of Free State hospitals – 41% – lack CT scan facilities. Some facilities with CT scan facilities, lack radiologists to review imaging and facilitate swift referral for further management of patients. A delay in referral and imaging leads to a delay in definitive treatment for patients who may have terminal conditions or tumours that are not surgically resectable. This situation is not in the scope of this research and should be reviewed by the Departments of Neurosurgery, Paediatric Oncology, and Radiology. Doing so may be a difficult task, as few medical professionals in South Africa are interested in specialising.

The literature, which mostly reports on studies conducted abroad, shows that many children with intracranial tumours die. This was confirmed by this research, as reported above. However, with an upper quartile figure of 35 months for post-diagnosis lifespan, it seems that, with adequate and quick referral, there is an opportunity to deliver life-prolonging management. On review, the greatest contributor to prolonging lifespan post diagnosis was complete resection, especially of less aggressive tumours.

Fortunately, over the past few years, it seems that the Neurosurgery department has improved in their ability to perform complete resections of tumours.

There was a minor difference in the occurrence of tumours in the different sexes. It is interesting that more boys were affected, considering the population has more girls. This finding may be attributed to some tumours, mainly germ cell tumours, having a high predilection for male patients.

In total 15 patients refused management. Although this is only 5.47% of the 274 patients in this study, this response should be reviewed. Usually, in such cases, the oncology and neurosurgery departments call on a social worker, but it remains difficult to convince parents who are adamant about relying on traditional healers or consultation with elders. Only with better education and communication will parents be persuaded to allow their children to receive the best medical management possible. This response by parents could also be due to adverse socio-economic circumstances, as parents, as breadwinners, cannot attend to the child for the duration of the recommended treatment, or commit to subsequent follow-ups, which may involve recurrence and requires longer-term management.

Most of the data collected by this study is in line with international standards or statistics. Although minor changes were noted in the distributions of tumours, it seems that glial tumours were most prevalent, as expected. Medulloblastomas and ependymomas were also among the major tumours appearing in the posterior fossa. A large percentage of tumours had, as the only data, clinical diagnoses which were via imaging. With improved surgical skills and better review of tumours by pathology, this situation may reduce below the 12% recorded by this research. New developments, such as molecular genetics, are

starting to be used, though it may be a long time before the Free State, in general, or Universitas, in particular, has such facilities. Molecular genetics will assist to divide tumours into those amenable to adjuvant therapy, and those that require gross total resection.

A high number of gliomas was seen – 26.57% – of which 22.6 % were located in the brainstem or infratentorially. These tumours are quite aggressive and explain why there is such a high number of deaths due to paediatric brain tumours. Very few brainstem gliomas are amenable to surgery, and few patients are subjected to biopsies, as this is associated with high morbidity and mortality. This means that there will continue to be large numbers of tumours that are only diagnosed clinically. However, the lifespan post diagnosis of these patients may be prolonged with adjuvant therapy and so-called prophylactic surgery.

In discussions with the biostatistician, it was difficult to review the different tumours according to the specific post-diagnosis lifespan – there were just too many variables associated with arranging the data in a way that would allow good interpretation and results. This means future research may need a larger pool of tumours, which may be established by starting prospective research of tumours arriving or being managed at Universitas Hospital.

This research was also unable to review or discuss the different grading of tumours, as minimal note-taking meant tumours were not classified. It may also be the case that the Anatomical Pathology Department does not have facilities to enable tumours to be graded according to the latest WHO definitions or nomenclature. This shortcoming will have to be addressed in the future and rectified.

This experience also extended to specific clinical data, such as height and weight, which was excluded from the discussion because certain patients had no values recorded upon initial review. Optimising note-taking will assist to resolve this issue.

The management of paediatric brain tumours at Universitas Hospital corresponds with international standards. Medical professionals perform biopsies with either gross total resection, followed by adjuvant therapy or adjuvant therapy for tumours that are internationally known to be amenable. The only major difference between practice at Universitas and hospitals abroad is the availability of neurosurgeons, theatre time, and resources to enable immediate resection of tumours at presentation. Many tumours are managed with permanent cerebrospinal fluid diversion or ventriculoperitoneal shunt, which is not in accordance with international standards. This practice is, however, influenced by the lack of resources available at Universitas Hospital, where there is limited paediatric ICU beds available and, therefore, staff cannot operate on tumours at the soonest possible time and prevent associated external ventricular drain infections. Patients who are deteriorating neurologically receive ventriculoperitoneal shunts while awaiting definitive management of their tumours. Concerning adjuvant(chemotherapy and radiotherapy) therapy, in the rest of the world, only children older than 3 years are offered radiation, which is in keeping with South Africa's current paediatric oncology standard operation protocol. This is offered to children with radiosensitive tumours according to international protocols.

Statements

Acknowledgments

1. Cornel van Rooyen, biostatistician
2. Health Sciences Research Ethics Committee (HSREC), University of the Free State

Ethics

Ethics were reviewed and approved by HSREC and Free State Department of Health (approval attached).

Conflict of interest

No conflict of interest, whether personal or financial, was present.

Author contributions

1. Professor A. van Aswegen supervised the research
2. Professor D. Stones provided data from the Paediatric Oncology tumour registry

Data available

1. Excel sheets of patient information and biostatistician evaluation attached
2. Meditech, which is available on the hospital system
3. Professor D. Stones' tumour registry, available at the office and attached

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Chapter 2: Manuscript

Retrospective Audit of Paediatric Intracranial Tumours Managed at Universitas Hospital from 2000 to 2020

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Abstract

The research conducted is a retrospective review of paediatric intracranial tumours admitted to Universitas hospital during the period ranging from 2000 to 2020 (June). It looks at the different types of tumours admitted and the management thereof by the departments involved; neurosurgery and paediatric oncology. During this period 274 patients were managed with 60% of the of patients dying after receiving surgery and or adjuvant treatment. Of the 274 patients, most tumours were glial in origin with medulloblastomas and ependymomas being second and third most, respectively. Patients received radiotherapy and oncotherapy according to paediatric protocols; after a biopsy or resection by neurosurgery. Patients would also get cerebrospinal fluid diversion if required. This diversion was seen as prophylactic management in patients that could not receive a complete resection of the tumour. This research revealed a need for better notekeeping and storage of patient data when it comes to tumours, ensuring that future research will be of greater quality. Research also revealed that a more thorough examination of tumours in teenagers will need to be conducted. This research will help in compiling a better template in admission of all tumours in Universitas and thereby facilitate an extensive tumour registry for the neurosurgery department.

Introduction

The research involved a retrospective review of the number and types of paediatric tumours managed at Universitas Hospital, Bloemfontein, over 20 years. Universitas is the only referral hospital serving the Free State province and the surrounding areas, including the Northern Cape and Lesotho, in relation to paediatric tumours. The total population of the Free State, Northern Cape, and Lesotho numbers at least 6 million, and the area has only one hospital to manage paediatric tumours.

Paediatric tumours are treated in cooperation by the Neurosurgery and the Paediatric Oncology Departments of Universitas Hospital. This collaboration is due to the multidisciplinary approach needed to treat this pathology adequately.

The objective of this research was to review the different types of tumours encountered and managed by the hospital. An investigation was done into the demographics of patients presenting at the hospital from 2000 to June 2020. The data that was collected clarified the patient gender and age distribution, and also the outcomes achieved during the given period. A review of the management of the patients was done, and a comparison made of reviewed data and literature reporting on international statistics. The researcher would like to see if the common tumours mentioned in literature are similar to those seen locally in Universitas Hospital.

The research was undertaken with the aim of optimising the management of pediatric oncology patients, and to streamline data collection. As Universitas is a teaching institution, achieving these aims may help upcoming registrars in both neurosurgery and paediatric oncology to have a better understanding of a disease that affects this fragile population.

Materials and methods

The researcher collected data from the tumour registry kept by the Department of Paediatric Oncology at Universitas Hospital. The registry contains data of all children who have been treated by the oncology department. In addition to the registry, the researcher collected information needed for this research from the electronic database of the hospital, Meditech. Patient notes were reviewed and the detailed data needed were collected in Excel format, and sent for review by the biostatistics department at

the University of Free State. The allocated biostatistician assisted by applying statistical procedures to information to that had been compiled, and which will be reported on in this research project. The data will be represented in tables and percentages that are easy to interpret.

The researcher was, however, unable to review certain aspects of presenting patients, as certain information was no longer present on the database or was never included in the initial assessment of patients.

Inclusion and exclusion criteria

The research included all patients below the age of 13 who presented at Universitas Hospital from 2000 to 2020 (June). These patients represent the accumulation of patients referred to the hospital from the surrounding referral hospitals, including Northern Cape and Lesotho patients. The number also includes patients who were referred from Pelonomi Regional Hospital, as most patients presenting at Pelonomi were transferred to the oncology department at Universitas.

Patients who had died acutely after the initial review were also included.

Exclusion criteria were patients who were older than 13 years at presentation at Universitas, and those who were managed privately after initial emergency review at the the hospital. Patients who were followed up after 2000, but who had already been diagnosed before 2000, were also excluded from the research.

Methods

The information was collected from the oncology tumour registry and the hospital database; Meditech. The information that was gathered was reviewed in an Excel spreadsheet and assessed by biostatisticians. The results will be reviewed in the research report.

Variables

The variables reviewed are numerical and categorical. The numerical variables assessed are continuous, namely, age, height, weight, and lifespan post diagnosis of a tumour.

The discrete numerical variables are the number of patients and the number of different types of tumours.

The ordinal (categorical) variables are the different tumour grades. This information was limited, as the hospital cannot diagnose according to the new molecular classification, and reports contained minimal notes that could be used to review specific grading systems.

The nominal (categorical) variables include patient sex, tumour type, amount of tumour resection, and management offered.

Outcomes

The outcomes review of the research was influenced by the amount of information available, especially the notes on the Meditech system. The information available in the tumor registry is of great importance to paediatric oncologists.

The main outcomes assessed were whether patients survived post diagnosis, and for how long. A review of the management patients received, and for how long they survived after management could not be quantified for review by biostatisticians, because of a limitation relating to a lack clarity of available notes. Although the notes improved in later years, they often still remain inadequate and not clearly illustrated.

Patient outcomes were mainly influenced by the type of tumour and the amount of tumour resection that occurred. Patients with less aggressive tumors and better gross total resection seemed to have a longer post-diagnosis lifespan, which is also reflected in the literature.

Results

A review of 274 children with intracranial tumours was done, of whom 126 were female and 148 male patients (46% and 54% respectively).

Over the period of 20 years, an average of 13.5 patients were managed per year, with a maximum of 22 patients seen in 2009, and a minimum of 9 patients seen in 2015. The patients seen in 2020 were not counted as this was not a full-year review. The median number seen over the past 20 years is 15.

The age distribution of the 274 patients ranged from 0 months (children who presented within 30 days of birth) to 189 months at diagnosis. The researcher reviewed a lower quartile of 46 months and an upper quartile of 126 months, giving a median age of 189 months.

In total 164 patients died post diagnosis and/or management – 60.22% of the total of 274 patients. These deaths occurred from either tumour progression or post inpatient or post outpatient management. The deaths were recorded at various times post diagnosis: arrival at the hospital, post surgery, post radiation therapy, or post oncotherapy. A small number died post discharge home.

The balance of 110 patients are still living, and have been transferred to other institutions or are receiving management at Universitas, in the oncology department. A large number of those still living have had maximal resection of less aggressive tumours, with or without cerebrospinal fluid diversion, ventriculoperitoneal shunt or endoscopic third ventriculostomy.

The post-diagnosis lifespan ranged from a minimum of 0 months (patients who died immediately or less than 30 days after diagnosis) to a maximum of 226 months. The median lifespan post diagnosis was 8 months, with the lower quartile at 2 months and the upper quartile at 35 months.

As Universitas is the main referral hospital in the Free State, a review of referring hospitals would have to be made on CT scan availability. Institutions without CT scan facilities referred 111 patients (40.51%), leaving 163 (59.49%) patients presenting with CT scans. MRI was only available at Kimberley Hospital (Northern Cape) and in Lesotho, and most of the workup was done when these patients arrived at Universitas, which facilitated prompt intervention, such as surgery or adjuvant therapy, such as radiation or oncotherapy. Table 3 in the addendum provides a representation of the patients referred to Universitas from its districts, surrounding provinces, and countries. The most patients originated from Lesotho – 66 patients (24.09%) – and Northern Cape referred 46 patients (16.56%). Referrals from the surrounding districts may be fewer than reported because these districts have no imaging facilities available.

A wide variety of tumour types were visible on review. At least 19 different types of tumours were seen in the data that was collected, as reported in Table 1 in the addendum. Tumours were divided into larger groups according to the WHO classification of 2021.[1] When the tumours are divided further, into infratentorial and supratentorial locations in the brain, it enabled assessment of the findings of the post-diagnosis lifespan. On review, 148 tumours (54.21%) appeared infratentorial and 125 tumours (45,29%) appeared supratentorial. This number is close to that reported by literature, namely that about two thirds of tumours seen in children are situated in the posterior fossa or infratentorially.[2-5]

The post-diagnosis lifespan of the infratentorial tumours ranged from a minimum of 0 months to a maximum of 211 months. The lower and upper quartiles were 2 and 31.5 months respectively.

The post-diagnosis lifespan of supratentorial tumours ranged from a minimum of 0 months to a maximum of 226 months. The lower and upper quartiles of these tumours were 2 and 41 months respectively. Supratentorial tumours showed a slightly higher upper quartile, at 8 months. This finding may be attributed to the greater ease of approaching supratentorial tumours via surgery, therefore, allowing a more extensive gross total resection. In infratentorial tumours, gross total resection is hindered by the proximity of the brainstem, which enables a less extensive resection.

It was difficult to assess the specific locations of tumours in the brain, as 15 different locations are represented. The locations seen by this study were infratentorially: cerebellopontine angle, cerebellar and brainstem lesions, and fourth ventricle.

Supratentorial locations seen were frontal, temporal, and parietal lobes and intraventricular (excluding fourth ventricular, as these were added to infratentorial), pineal region, and basal ganglia region. The main gross tumour locations that occurred are listed in descending order: posterior fossa tumours, 73 (26.28%); tumours in the brainstem, 61 (21.96%); situated in the cerebrum, 38 (13.68%); and suprasellar, 32 (11.52%). Some of these locations overlap and the difficulties experienced in reviewing them correctly was mainly due to a lack of imaging or notes available to assess the locations personally. The various locations are represented in Table 2.

Some tumours appeared rarely, and this is confirmed by the literature. Among those that appear most commonly, gliomas made up 26.57% (73) of the total, which is contrary to reports in the literature. In the WHO 2021[1] classification, gliomas are divided into adult and paediatric types. These types are divided further into high and low-grade tumours. In this research, the low-grade and high-grade tumours were divided and, as shown in Figure 1, labeled as brain astrocytoma (low grade) and gliomas (high grade). Medulloblastomas were the second most common, with 41 patients (14.96%) and astrocytomas (low-grade gliomas) were third most common, with 36 patients (13.13%). The fourth-highest number was attributed to tumours identified on clinical diagnosis only, which represented 12.02%, or 35 patients. Cases using the clinical diagnosis are difficult to interpret, as they can be either infra- or supratentorial. It also means that no biopsy was done to determine what tumour was seen on imaging; this is mainly done in brainstem lesions that are dangerous to biopsy. The number of tumours diagnosed clinically could also be affected by patients dying before diagnosis or surgery.

Ependymomas were the fifth-highest occurring tumours, with 24 patients (8.76%). Although astrocytomas, medulloblastomas, and ependymomas were not represented in perfect thirds, as illustrated in literature, they did occur more often than other less common tumours.

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Statements

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3. Professor D. Stones' tumour registry, available at office and attached

References

1. Louis DN, Perrie A, Wesseling P, Brat DJ, Cree IA, Figarella-Granger D et al. Neuro-oncology: 2021 WHO classification of tumors of the central nervous fhttps://doi.org/10.1093/neuonc/noab106
2. Chintagumpala M, Gajjar A. Brain tumors. Paediatr Clin N Am. 2015;62(2015):167-178.
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5. Lacayo A, Farmer PM. Brain tumors in children: A review. Ann Cli. Lab Sci. 1991;21(1):26-35.

Appendix # 1: HSREC clearance

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

19-Jan-2021

Dear **Dr Lelethu Bango**

Ethics Clearance: **retrospective audit of paediatric intracranial tumours treated in Universitas hospital from 2000-2020**

Principal Investigator: **Dr Lelethu Bango**

Department: **Neurosurgery Department (Bloemfontein Campus)**

Submission Page

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2020/1442/2601**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Prof. A. Sherriff
Chair : Health Sciences Research Ethics Committee

appendix # 2: DOH clearance

health
Department of Health
FREE STATE PROVINCE

02 December 2020

Dr L Bango
Depart. Of Neurosurgery
UFS

Dear Dr L Bango

Subject: Retrospective audit of paediatric intracranial tumours treated in Universitas hospital from 2000-2020.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / makenamr@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 7/12/2020

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

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4 August 2021

To Whom It May Concern

MINI-DISSERTATION: **DR LB BANGO**
STUDENT NUMBER: **2004012296**
REGISTRAR TRAINING NUMBER: **O-09-01-08**
UFS-HSD2020/1442/2601

I hereby give permission that dr LB Bango may do the under mentioned manuscript:

"Retrospective audit of paediatric intracranial tumours treated in Universitas Academic Hospital from 2000 to 2020"

Kind regards

DR A VAN ASWEGEN
HOCD: NEUROSURGERY

Department of Neurosurgery: School of Medicine
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Appendix #4: approved protocol

Research protocol

Retrospective audit of paediatric intracranial tumours treated in Universitas hospital from 2000-2020

Researchers

Dr. LB Bango: primary researcher
Dr. A Van Aswegen: research supervisor
Prof. D Stones: contributing supervisor

Introduction

Brain tumours are the second most common malignancy in children with the first being hematological malignancies like lymphomas and leukemia.[3,6,] There are quiet a few predisposing factors or familial conditions that give rise to certain types of tumours. High grade gliomas and medulloblastomas are common in patients with Turcot, Li-Fraumeni and Gorlin syndromes.[3,] Neurocutaneous disorders are usually inherited and also have an association with certain intracranial tumours. Neurofibromatosis is associated with gliomas, tuberous sclerosis with subependymal giant cell astrocytomas, von Hippel- Lindau disease with hemangioblastomas, and basal-cell nevus syndrome with medulloblastomas.[6]

The incidence of brain tumours varies for different geographical regions across the world, although they remain relatively in the same range. In the United States theres an estimated 17-22.5 % of children with cancer having a brain tumour.[2] One of the articles reviewed highlights that 4350 children between the age of 0-19 years are diagnosed with brain tumours.[3] Whereas another article shows that 2.5-3.5 per 100 000 is the incidence of brain tumours in children under the age of 15 years. It is also noticed that the incidence of brain tumours is higher in patients with a strong familial history of stroke and convulsions.[6] Brain tumours represent 16-23% of malignancies in children.[12]

Brain tumours are the leading cause of deaths in paediatric patients with cancers. This makes them very important especially since they cause the highest morbidity and mortality in children with cancer.[5,8] The added problem is that the management of the tumours has long term sequelae that is sometimes unavoidable.[2,4,5]

The clinical presentation of children can be nonspecific. Therefore the clinician requires a high index of suspicion, especially if there's a clinical disorder associated

or family history of convulsions. It must also be remembered that the fontanelles are

still patent and signs of raised intracranial pressure will differ to those seen in an adult. In infants the presentation may be lethargy, increasing head circumference and inability to have head control.[3] Depending on tumour location a child can present with various signs and symptoms; dropping objects to signify limb weakness due to supratentorial lesion, unsteadiness that will direct to a posterior fossa lesion in cerebellum and delayed milestones or decreased progression academically. They may also present with short stature which requires work up as this may reveal an endocrine abnormality.[3,6,]

In children 50% of brain tumours will be seen in the posterior fossa. The most common tumours seen in children are medulloblastomas, gliomas, and ependymommas. Medulloblastomas account for 15-20% of paediatric brain tumours, and as said to be the most common tumour.[3,5,6,] Gliomas, especially the high grade gliomas have the poorest prognosis of the tumours that affect children. This may be due to their location in the deep structures making them more difficult to operate or the fact that on diagnosis a lot of normal tissue is already infiltrated.[3,4] The diagnostic tools used are imaging ; CT or MRI and post review of histology of tumour molecular biology can be used to classify tumours. Review of molecular biology is not currently done in South Africa but it does assist in classifying patients into high risk groups post surgery, especially since some of the medulloblastoma have a better prognosis.[1]

The management of intracranial tumours in children is difficult in that the complications of surgery and adjuvant therapy have long term implications on both child and parents.[1,4,9]
The mainstay of management is gross total resection of tumour whenever possible. Children that undergo total resection have a longer event free survival rate. Improvements in surgical techniques and adjuvants has meant that the survival of these children has increased by almost 20% after management.[1,2,3]
Post surgery or resection the children will undergo radiation or adjuvant therapy, if over the age of 3 and subsequent chemotherapy[1,2,3,4,5].
Children below the age of 3 will receive chemotherapy instead of radiation.

I will be looking at the intracranial brain tumours that presented to Univeristas from 1 January 2000 to 30 June 2020. I will review the amount of cases that presented in the time and compare the data to information reviewed in other articles.

The three main tumours seen in children as mentioned above have various management strategies. The aim is always for gross total resection with minimal morbidity. The management of tumours in the department as always been according to literature. It is also based on the available experienced surgeon at the time. Currently surgery for paediatric tumours has improved greatly as Dr Van Aswegen as a keen interest in tumour surgery. This was not the case when he was studying because there was no dedicated surgeon who had an interest. Unfortunately experience and interest can not be quantified but only retold.

I was unable to find information with regards to any racial preference or predilection of tumours. There was mostly an association with familial syndromes as mentioned above. The need for race would be to try and ascertain whether certain tumours are more prevalent in certain races or whether certain races presented at more advanced stages of disease.

Aim

1. To review information gathered on paediatric patients presenting to Universitas hospital; review the gender predilection, age at presentation, tumour characteristics, years of follow up and complications pre- and post-op.
2. To compare the information to international standards presented in literature
3. Review the difference in management and outcomes as the years progressed to see if there was any improvement

Methodology

Data collection to be gathered from available sources in the hospital such as meditech and registry supplied by Prof. Stones. A review of the information present on excel or in tabular form will be done with assistance from biostaticians.
A review of the tumours that presented in the time and the management thereof will be done. Also follow up according to outcomes and complications.

Study design

Retrospective audit: review of the data collected on all children admitted to Universitas who presented with intracranial tumours

Study population

All the children admitted to Univeristas with intracranial tumours

Sample selection

Children admitted to Universitas Hospital from 1 January 2000- 31 May 2020,presenting with intracranial tumours
The number of children currently on system meeting the above criteria are 350.

Measurement

Review of the differences in gender predilection of the children presenting with various tumours
Also a review of the age at presentation
Review the tumours that the children presented with and whether it is the same as literature. A comparison of tumour types, size, location of tumours and symptoms and signs at presentation to hospital.

Problems may arise where there isnt enough documentation of procedures performed, histology received or patient lost to follow up or deceased outside the hospital. May need social worker to follow up patients that are lost but will have to add that information is not written in the documentation that is present if there is no other method of finding it.

Minimal information documented on deficit or learning disabilities has been supplied in the neurosurgery notes. Will review if paediatrics has written notations of these children's disabilities as this may make it difficult to follow up their functional outcomes if nothing is documented.
Some tumours are diagnosed on imaging only; diffuse intrinsic pontine gliomas

Data analysis

Collect data from meditech notes written by paediatrics and neurosurgery and Prof Stones's registry of children presenting with intracranial tumours and supply list to biostatitics to assist with calculation of statistics which will be compiled into graphs and tables by the researcher.

Implementation

To review the outcomes of children treated in facility and to see whether any improvement can be made in their management compared to international standards. Improved follow up of patients will lead to an improved management and outcome. It will be easier to then review what the best management for the patient will be and how best to ensure that they are not lost to follow up.
To start a registry in neurosurgery that will compare children presenting with tumours

Time schedule

Protocol assesment 27/7/20
Hand in to biostatician after assessment 6/8/20
Ethics application 15/8/20
RIMS review from 15-22/8/20
Data collection November-February 2021

Budget

Printing costs and stationary R 500-1000

Ethical considerations

Confidentiality may be a problem since I will be able to review patient information but the data given to the biostaticians will only have patient numbers. The names and surnames will not be distributed.

Pilot study

The information that is required to perform the study is already available and just requires placement in an excel format to give to the biostaticians.

Permission

Head of department Neurosurgery: Prof A van Aswegen
Department of Paediatrics: Prof D Stones
Biostatician Dr C Van Rooyen
Approval of HSREC and Free State Department of Health

References

1. Roger J Parker. Childhood brain tumors: accomplishments and ongoing challenges. J Child Neurol.2008 October; 23(10); 1122-1127
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3. M Chintagumpala and A Gajjar. Brain tumors. Paediatr Clin N Am 62(2015) 167-178
4. J Glod et al. pediatric brain tumors: current knowledge and therapeutic opportunities. J Pediatr Hematol Oncol. 2016 May; 38(4): 249-260
5. IF Pollack et al. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr 2019 March; 23:261-273
6. A Lacayo and PM Farmer. Brain tumors in children: A review. Annals of clinical and laboratory science 1991; 21(1): 26-35
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9. SG Suresh et al. Profile and outcome of pediatric brain tumors-experience from a tertiary care pediatric oncology unit in South India. J Pediatr Neurosci 2017 Jul-Sep;12(3):237-244
10. MH Siregar et al. Clinical, radiological, and histopathological features and prognostic factors of brain tumors in children. J. Phys: Conf Series 1073(2018)
11. AJ Bishop et al. Infant brain tumors: incidence,survival, and the role of radiation based on surveillance, epidemiology, and end results(seer)data. Int. J. Radiation Oncology Biol. Phys 2012; 82(1): 341-347

Referral areas		
	Frequency	**Percentage**
Xhariep	66	24.09
Thabo Mofutsanyane	29	10.42
Fezile Dabi	8	2,88
Lejweleputswa	31	11.16
Northern Cape	46	16.56
North West	10	3.65
Eastern Cape	7	2.55
Lesotho	67	24.45

Supplementary: Table 1

Appendix #5

Tumour type	**Frequency**	**Percentage**
Astrocytoma (low grade)	36	13.13
Brain tumour: clinical diagnosis	33	12.02
Gliomas (high grade, incl BSGs)	73	26.57
Medulloblastoma	41	14.96
Ependymoma	24	8.76
Pineal tumours	14	4.74
Sellar region tumours:Craniopharyngioma	21	7.9
Meningioma	6	2.16
Choroid plexus tumours	6	2.16
Other miscellaneous:		
Other CNS embryonal tumours: AT/RT	2	0.72
Embryonal NOS	1	0.36
Dermoid cyst	1	0.36
Glioneuronal & neuronal tumours	4	1.81
Dysgerminomma	1	0.36
Hamartoma	1	0.36
Cranial & paraspinal nerve tumours	3	1.09
Hematolymphoid tumours: Lymphoma	1	0.36
Ependymal cyst	1	0.36
PNET tumour	3	1.09

Supplementary tables: Table 2

Appendix # 5

Gross tumour location	**Frequency**	**Percentage**
Supratentorial		
Frontal	5	1.8
Cerebral / Intraaxial supratentorial/supratentorial	38	13.68
Temporal	1	0.36
Suprasellar / tuber cinerium	32	11.52
Intraventricular	17	6.12
Parietal	1	0.36
Pineal region	17	6.12
Midline /central	2	0.72
Right orbit	1	0.36
Thalamus/thalamic	14	5.04
Infratentorial		
Brainstem	61	21.96
Cerebellar	5	1.8
Cerebellopontine angle	1	0.36
Posterior fossa	73	26.28
Intraspinal / Spinal extension/medulla oblongata/spinal cord	6	2.16

Supplementary: Table 3

Appendix #5

addendum #5: map for table 1

Appendix #6: peer reviewed journal

- (https://scholars.direct)
  - (https://scholars.direct/review-policy.php)
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    - Footnotes
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Track your manuscript status online (manage-manuscript.php) or send us a mail to: editorialoffice@scholars.direct (mailto:editorialoffice@scholars.direct)

2. Word Limit: No page limit or word limit.

3. Format: All manuscripts submitted can be either submitted in PDF or Word Document. The manuscripts with formulas can be submitted in LaTeX format. Figures can be submitted in JPEG/TIFF/PNG/PDF formats.

4. Paragraph Settings: No specific requirement because the paragraphs will be adjusted as per our standards.

5. Font: The standard font for manuscript preparation is Times New Roman 10. Any size variations can be represented to distinguish headings and sub headings.

6. Line and Page Numbers: Line & Page Numbers are optional.

7. Page Layout: No specific requirement.

8. Language: All the manuscripts must be submitted in English.

9. Footnotes: Footnotes are acceptable.

10. Keywords: Keywords are not mandatory for any type of manuscripts. If provided, keywords can be separated by semi colon.

11. Abbreviations: Abbreviations if present in the manuscript can be listed to make easy understanding upon the terminologies.

12. Equations: For mathematical equations, use Math type.

Note: If the manuscript has more number of equations please send the manuscript only in Word or preferably LaTeX format.

13. Representation, Units and Nomenclature: As applicable.

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Scholars.Direct has the references style, but the author need not work on reference format. Our formatting experts will work on it and arrange references according to our format. The reference style required by the journal will be applied to the published version by Scholars.Direct. Details of reference such as Author(s) name(s), journal title / book title, year of publication, volume & issue / book chapter must be provided.

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Check if title page contain the following portions:

List of all authors.

The corresponding author should be identified with an asterisk. Authors from different departments must mention the numbers with superscript.

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Corresponding author: The complete details of the corresponding along with postal code must be provided.

Note: Title Page remains mandatory for all type of submissions.

Abstract

The Abstract should serve both as a general introduction to the topic and as a brief, non-technical summary of the main results and their implications. It should not contain references. Abstract must be free from citations.

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Keywords

A minimum of 3-6 keywords could be used in the manuscript. This will help narrow the searching options for the manuscript.

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Research articles include an abstract, an introduction, figures or tables, sections with brief subheadings, materials and methods, supplementary materials, which should also include information needed to support the paper's conclusions.

Introduction: The introduction should put the manuscript into context and must be clear so that readers are able to understand the aims, purpose and significance of your research. The background must be capable of explaining the background work and must be properly cited.

Materials and Methods: The Journal has no explicit requirements for materials and methods section. According to the authors' preferences and the experiments conducted Authors can be organize it as best suits the research. Individual experiments must be elaborated under appropriate subheadings.

Results: Results must be appropriate to the conducted research experiments. Results of the individual experiments must be elaborated under appropriate subheadings. All the figures and tables provided must be labeled accordingly in the order of sequence they follow.

Discussion: The Discussion section must be succinct and usually do not contain subheadings.

References: Please look at the formatting corner for appropriate guidelines in preparing references.

Acknowledgements: Acknowledgements should be concise, should not include thanks to anonymous referees and editors or extroverted comments. Grant Numbers and the Grant details must be acknowledged if any.

Review Article and Mini Review

No word limit and organization remains same for Review and Mini Review.

Introduction: The introduction should put the manuscript into context and must be clear so that readers are able to understand the aims, purpose and significance of your research. The background must be capable of explaining the background of work, review literature, focus of the review and must be properly cited.

Sub Headings: The Journal has no explicit requirements for this section. According to the authors' preferences the main body of the text could be organized as it best suits the review. Headings may be further categorized under subheadings.

Conclusion: The conclusion section must be concise and usually do not contain subheadings. The conclusion must be capable of summarizing the purpose of the review and discuss briefly about the highlights of review.

References: Please look at the formatting corner for appropriate guidelines in preparing references.

Acknowledgement: Acknowledgement should be concise, should not include thanks to anonymous referees and editors or extroverted comments. Grant Numbers and the Grant details must be acknowledged if any.

Cases

Introduction: The introduction should put the manuscript into context and must be clear so that readers are able to understand the aims, purpose and significance of your Case study. The background must be capable of explaining the background of work, review literature, focus of the case and must be properly cited.

Case Presentation: This section is a formal communication presented regarding a patient's clinical information. Citations might be included in this section.

Discussion: The discussion section must be concise and usually do not contain subheadings. The authors must discuss briefly the case summary, management plans, success of the treatment or failure and causes of success or failure.

References: Please look at the formatting corner for appropriate guidelines in preparing references.

Acknowledgements: Acknowledgements should be concise, should not include thanks to anonymous referees and editors or extroverted comments. Grant Numbers and the Grant details must be acknowledged if any.

Clinical Image

This is the shortest type of articles that describe a significant image of clinical medicine.

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They are not structured articles. Letters are pertinent to material published in science or that discusses problems of general interest and intended to reflect the range of opinions received.

Note: References are optional.

All other kind of Submissions

All other type of submissions such as editorials, short notes, perspectives/opinions, commentaries are not structured manuscripts. They may be of author's choice of research interest, general interest or intended to reveal the range of

opinions received.

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Figures may be multi-componential provided with proper sub labeling such as A), B) and so on. The legends for the multi-componential figures may be single or provided in detail with sub labeled descriptions. The units used in the figure must be represented in the legend separately.

Figures with identifiable facial features must be masked or provided with duly signed consent. This will allow the Journal to avoid any future conflicts. Authors may request the Editorial office to mask the figure during the production of manuscript post acceptance.

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We recommend usage of tools to draw chemical structures such as ChemDraw, Chem Doodle, etc. Such tools could be applied even to draw gene and molecular level representations.

Citations may be represented in square brackets with sequence to the order of text followed in the figure legends.

Any problem with the Figures or the Legends, we request your immediate attention and resolve in coordination with Editorial office on time.

Tables Format

All the tables must be created using Table -creation tool or in excel sheet. Tables in image format are not acceptable. Avoid coloring of the Tables.

Tables must be sequentially numbered in the body text. The headings may be emphasized in Bold. Try avoiding huge number of Tabular data. All the tables must be properly Labeled and the abbreviations if any provided in the Tabular data must be listed below the Tables. Please also label the symbolic mark representations with clear legends.

Appendix Tables must be separately created using Table-creation tool or excel sheet and labeled as Supplementary data. While numbering those Tables in the body text, it must be denoted as Supplementary table 1, Supplementary table 2, etc.

Table legends must be brief and concise. No two table legends must be similar in a single manuscript. All the table legends must be distinct and unique.

Supplementary/Appendix Format

Supplementary Appendix is a part of original submission, submitted by authors to provide more information about their work. Supplementary Appendix may contain detailed information including, statistical data, mathematical derivations, data and programmes, text based appendix index, protocols, tabular data, figures and descriptions, etc.,

Supplementary Appendix must include a title as well as list of all authors. If the supplementary indexes do not have any precise title, then the manuscript title may be used. For any details in terms of section headings, typescript formatting, figure and tables preparation, please follow the general guidelines provided. Supplementary Information must not be merged with the manuscript submission rather it is submitted as a separate document. Supplementary information must not have any references included in article references. The supplementary information also undergoes the regular peer review process along with the manuscript and would be published as a separate downloadable attachment.

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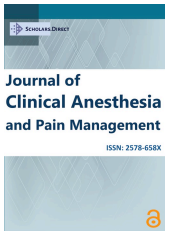

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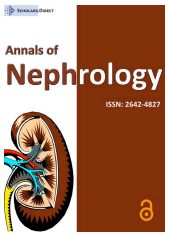

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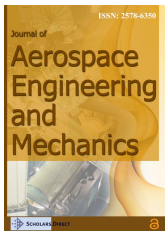

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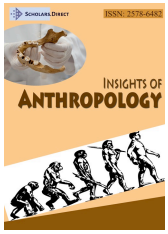

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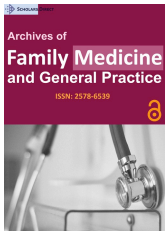

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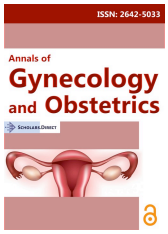

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appendix # 7: plagiarism report

Protocol

by Lelethu Bango

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Research protocol

Retrospective audit of paediatric intracranial tumours treated in Universitas hospital from 2000-2020

Researchers

Dr. LB Bango: primary researcher
Dr. A Van Aswegen: research supervisor
Prof. D Stones: contributing supervisor

Introduction

Brain tumours are the second most common malignancy in children with the first being hematological malignancies like lymphomas and leukemia.[3,6,] There are quiet a few predisposing factors or familial conditions that give rise to certain types of tumours. High grade gliomas and medulloblastomas are common in patients with Turcot, Li-Fraumeni and Gorlin syndromes.[3,] Neurocutaneous disorders are usually inherited and also have an association with certain intracranial tumours. Neurofibromatosis is associated with gliomas, tuberous sclerosis with subependymal giant cell astrocytomas, von Hippel- Lindau disease with hemangioblastomas, and basal-cell nevus syndrome with medulloblastomas.[6]

The incidence of brain tumours varies for different geographical regions across the world, although they remain relatively in the same range. In the United States theres an estimated 17-22.5 % of children with cancer having a brain tumour.[2] One of the articles reviewed highlights that 4350 children between the age of 0-19 years are diagnosed with brain tumours.[3] Whereas another article shows that 2.5-3.5 per 100 000 is the incidence of brain tumours in children under the age of 15 years. It is also noticed that the incidence of brain tumours is higher in patients with a strong familial history of stroke and convulsions.[6] Brain tumours represent 16-23% of malignancies in children.[12]

Brain tumours are the leading cause of deaths in paediatric patients with cancers. This makes them very important especially since they cause the highest morbidity and mortality in children with cancer.[5,8] The added problem is that the management of the tumours has long term sequelae that is sometimes unavoidable.[2,4,5]

The clinical presentation of children can be nonspecific. Therefore the clinician requires a high index of suspicion, especially if there's a clinical disorder associated or family history of convulsions. It must also be remembered that the fontanelles are

still patent and signs of raised intracranial pressure will differ to those seen in an adult. In infants the presentation may be lethargy, increasing head circumference and inability to have head control.[3] Depending on tumour location a child can present with various signs and symptoms; dropping objects to signify limb weakness due to supratentorial lesion, unsteadiness that will direct to a posterior fossa lesion in cerebellum and delayed milestones or decreased progression academically. They may also present with short stature which requires work up as this may reveal an endocrine abnormality.[3,6,]

In children 50% of brain tumours will be seen in the posterior fossa. The most common tumours seen in children are medulloblastomas, gliomas, and ependymommas. Medulloblastomas account for 15-20% of paediatric brain tumours, and as said to be the most common tumour.[3,5,6,] Gliomas, especially the high grade gliomas have the poorest prognosis of the tumours that affect children. This may be due to their location in the deep structures making them more difficult to operate or the fact that on diagnosis a lot of normal tissue is already infiltrated.[3,4] The diagnostic tools used are imaging ; CT or MRI and post review of histology of tumour molecular biology can be used to classify tumours. Review of molecular biology is not currently done in South Africa but it does assist in classifying patients into high risk groups post surgery, especially since some of the medulloblastoma have a better prognosis.[1]

The management of intracranial tumours in children is difficult in that the complications of surgery and adjuvant therapy have long term implications on both child and parents.[1,4,9]
The mainstay of management is gross total resection of tumour whenever possible. Children that undergo total resection have a longer event free survival rate. Improvements in surgical techniques and adjuvants has meant that the survival of these children has increased by almost 20% after management.[1,2,3]
Post surgery or resection the children will undergo radiation or adjuvant therapy, if over the age of 3 and subsequent chemotherapy[1,2,3,4,5].
Children below the age of 3 will receive chemotherapy instead of radiation.

I will be looking at the intracranial brain tumours that presented to Univeristas from 1 January 2000 to 30 June 2020. I will review the amount of cases that presented in the time and compare the data to information reviewed in other articles.

The three main tumours seen in children as mentioned above have various management strategies. The aim is always for gross total resection with minimal morbidity. The management of tumours in the department as always been according to literature. It is also based on the available experienced surgeon at the time. Currently surgery for paediatric tumours has improved greatly as Dr Van Aswegen as a keen interest in tumour surgery. This was not the case when he was studying because there was no dedicated surgeon who had an interest. Unfortunately experience and interest can not be quantified but only retold.

I was unable to find information with regards to any racial preference or predilection of tumours. There was mostly an association with familial syndromes as mentioned above. The need for race would be to try and ascertain whether certain tumours are more prevalent in certain races or whether certain races presented at more advanced stages of disease.

Aim

1. To review information gathered on paediatric patients presenting to Universitas hospital; review the gender predilection, age at presentation, tumour characteristics, years of follow up and complications pre- and post-op.
2. To compare the information to international standards presented in literature
3. Review the difference in management and outcomes as the years progressed to see if there was any improvement

Methodology

Data collection to be gathered from available sources in the hospital such as meditech and registry supplied by Prof. Stones. A review of the information present on excel or in tabular form will be done with assistance from biostaticians.
A review of the tumours that presented in the time and the management thereof will be done. Also follow up according to outcomes and complications.

Study design

Retrospective audit: review of the data collected on all children admitted to Universitas who presented with intracranial tumours

Study population

All the children admitted to Univeristas with intracranial tumours

Sample selection

Children admitted to Universitas Hospital from 1 January 2000- 31 May 2020,presenting with intracranial tumours
The number of children currently on system meeting the above criteria are 350.

Measurement

Review of the differences in gender predilection of the children presenting with various tumours
Also a review of the age at presentation
Review the tumours that the children presented with and whether it is the same as literature. A comparison of tumour types, size, location of tumours and symptoms and signs at presentation to hospital.

Problems may arise where there isnt enough documentation of procedures performed, histology received or patient lost to follow up or deceased outside the hospital. May need social worker to follow up patients that are lost but will have to add that information is not written in the documentation that is present if there is no other method of finding it.

Minimal information documented on deficit or learning disabilities has been supplied in the neurosurgery notes. Will review if paediatrics has written notations of these children's disabilities as this may make it difficult to follow up their functional outcomes if nothing is documented.
Some tumours are diagnosed on imaging only; diffuse intrinsic pontine gliomas

Data analysis

Collect data from meditech notes written by paediatrics and neurosurgery and Prof Stones's registry of children presenting with intracranial tumours and supply list to biostatitics to assist with calculation of statistics which will be compiled into graphs and tables by the researcher.

Implementation

To review the outcomes of children treated in facility and to see whether any improvement can be made in their management compared to international standards. Improved follow up of patients will lead to an improved management and outcome. It will be easier to then review what the best management for the patient will be and how best to ensure that they are not lost to follow up.
To start a registry in neurosurgery that will compare children presenting with tumours

Time schedule

Protocol assesment 27/7/20
Hand in to biostatician after assessment 6/8/20
Ethics application 15/8/20
RIMS review from 15-22/8/20
Data collection November-February 2021

Budget

Printing costs and stationary R 500-1000

Ethical considerations

Confidentiality may be a problem since I will be able to review patient information but the data given to the biostaticians will only have patient numbers. The names and surnames will not be distributed.

Pilot study

The information that is required to perform the study is already available and just requires placement in an excel format to give to the biostaticians.

Permission

Head of department Neurosurgery: Prof A van Aswegen
Department of Paediatrics: Prof D Stones
Biostatician Dr C Van Rooyen
Approval of HSREC and Free State Department of Health

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Protocol

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Protocol

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appendix #7: plagiarism report

FINAL MANUSCRIPT

by Lelethu Bango

Submission date: 27-Jul-2021 06:35PM (UTC+0200)
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Character count: 21858

Retrospective Audit of Paediatric Intracranial Tumours Managed at Universitas Hospital from 2000 to 2020

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Introduction

The research involved a retrospective review of the number and types of paediatric tumours managed at Universitas Hospital, Bloemfontein, over 20 years. Universitas is the only referral hospital serving the Free State province and the surrounding areas, including the Northern Cape and Lesotho, in relation to paediatric tumours. The total population of the Free State, Northern Cape, and Lesotho numbers at least 6 million, and the area has only one hospital to manage paediatric tumours.

Paediatric tumours are treated in cooperation by the neurosurgery and the paediatric oncology departments of Universitas Hospital. This collaboration is due to the multidisciplinary approach needed to treat this pathology adequately.

The objective of this research was to review the different types of tumours encountered and managed by the hospital. An investigation was done into the demographics of patients presenting at the hospital from 2000 to June 2020. The data that was collected clarified the patient gender and age distribution, and also the outcomes achieved during the given period. A review of the management of the patients was done, and a comparison made of reviewed data and literature reporting on international statistics.

The research was undertaken with the aim of optimising the management of pediatric oncology patients, and to streamline data collection. As Universitas is a teaching institution, achieving these aims may help upcoming registrars in both neurosurgery and paediatric oncology to have a better understanding of a disease that affects this fragile population.

Materials and methods

The researcher collected data from the tumour registry kept by the Department of Paediatric Oncology at Universitas Hospital. The registry contains data of all children who have been treated by the oncology department. In addition to the registry, the researcher collected information needed for this research from the electronic database of the hospital, Meditech. Patient notes were reviewed and the detailed data needed were collected in Excel format, and sent for review by the biostatistics department at the University of Free State. The allocated biostatistician assisted by applying

statistical procedures to information to that had been compiled, and which will be reported on in this research project. The data will be represented in tables and percentages that are easy to interpret.

The researcher was, however, unable to review certain aspects of presenting patients, as certain information was no longer present on the database or was never included in the initial assessment of patients.

Inclusion and exclusion criteria

The research included all patients below the age of 13 who presented at Universitas Hospital from 2000 to 2020 (June). These patients represent the accumulation of patients referred to the hospital from the surrounding referral hospitals, including Northern Cape and Lesotho patients. The number also includes patients who were referred from Pelonomi Regional Hospital, as most patients presenting at Pelonomi were transferred to the oncology department at Universitas.

Patients who had died acutely after the initial review were also included.

Exclusion criteria were patients who were older than 13 years at presentation at Universitas, and those who were managed privately after initial emergency review at the the hospital. Patients who were followed up after 2000, but who had already been diagnosed before 2000, were also excluded from the research.

Methods

The information was collected from the oncology tumour registry and the hospital database; Meditech. The information that was gathered was reviewed in an Excel spreadsheet and assessed by biostatisticians. The results will be reviewed in the research report.

Variables

The variables reviewed are numerical and categorical. The numerical variables assessed are continuous, namely, age, height, weight, and lifespan post diagnosis of a tumour.

The discrete numerical variables are the number of patients and the number of different types of tumours.

The ordinal (categorical) variables are the different tumour grades. This information was limited, as the hospital cannot diagnose according to the new molecular classification, and reports contained minimal notes that could be used to review specific grading systems.

The nominal (categorical) variables include patient sex, tumour type, amount of tumour resection, and management offered.

Outcomes

The outcomes review of the research was influenced by the amount of information available, especially the notes on the Meditech system. The information available in the tumor registry is of great importance to paediatric oncologists.

The main outcomes assessed were whether patients survived post diagnosis, and for how long. A review of the management patients received, and for how long they survived after management could not be quantified for review by biostatisticians, because of a limitation relating to a lack clarity of available notes. Although the notes improved in later years, they often still remain inadequate and not clearly illustrated.

Patient outcomes were mainly influenced by the type of tumour and the amount of tumour resection that occurred. Patients with less aggressive tumors and better gross total resection seemed to have a longer post-diagnosis lifespan, which is also reflected in the literature.

Results

A review of 274 children with intracranial tumours was done, of whom 126 were female and 148 male patients (46% and 54% respectively).

Over the period of 20 years, an average of 13.5 patients were managed per year, with a maximum of 22 patients seen in 2009, and a minimum of 9 patients seen in 2015. The patients seen in 2020 were not counted as this was not a full-year review. The median number seen over the past 20 years is 15.

The age distribution of the 274 patients ranged from 0 months (children who presented within 30 days of birth) to 189 months at diagnosis. The researcher

reviewed a lower quartile of 46 months and an upper quartile of 126 months, giving a median age of 189 months.

In total 164 patients died post diagnosis and/or management – 60.22% of the total of 274 patients. These deaths occurred from either tumour progression or post inpatient or post outpatient management. The deaths were recorded at various times post diagnosis: arrival at the hospital, post surgery, post radiation therapy, or post oncotherapy. A small number died post discharge home.

The balance of 110 patients are still living, and have been transferred to other institutions or are receiving management at Universitas, in the oncology department. A large number of those still living have had maximal resection of less aggressive tumours, with or without cerebrospinal fluid diversion, ventriculoperitoneal shunt or endoscopic third ventriculostomy.

The post-diagnosis lifespan ranged from a minimum of 0 months (patients who died immediately or less than 30 days after diagnosis) to a maximum of 226 months. The median lifespan post diagnosis was 8 months, with the lower quartile at 2 months and the upper quartile at 35 months.

As Universitas is the main referral hospital in the Free State, a review of referring hospitals would have to be made on CT scan availability. Institutions without CT scan facilities referred 111 patients (40.51%), leaving 163 (59.49%) patients presenting with CT scans. MRI was only available at Kimberley Hospital (Northern Cape) and in Lesotho, and most of the workup was done when these patients arrived at Universitas, which facilitated prompt intervention, such as surgery or adjuvant therapy, such as radiation or oncotherapy. Table 3 in the addendum provides a representation of the patients referred to Universitas from its districts, surrounding provinces, and countries. The most patients originated from Lesotho – 66 patients (24.09%) – and Northern Cape referred 46 patients (16.56%). Referrals from the surrounding districts may be fewer than reported because these districts have no imaging facilities available.

A wide variety of tumour types were visible on review. At least 19 different types of tumours were seen in the data that was collected, as reported in Table 1 in the addendum. Tumours were divided into larger groups according to the WHO

classification of 2021.[1] When the tumours are divided further, into infratentorial and supratentorial locations in the brain, it enabled assessment of the findings of the post-diagnosis lifespan. On review, 148 tumours (54.21%) appeared infratentorial and 125 tumours (45,29%) appeared supratentorial. This number is close to that reported by literature, namely that about two thirds of tumours seen in children are situated in the posterior fossa or infratentorially.[2-5]

The post-diagnosis lifespan of the infratentorial tumours ranged from a minimum of 0 months to a maximum of 211 months. The lower and upper quartiles were 2 and 31.5 months respectively.

The post-diagnosis lifespan of supratentorial tumours ranged from a minimum of 0 months to a maximum of 226 months. The lower and upper quartiles of these tumours were 2 and 41 months respectively. Supratentorial tumours showed a slightly higher upper quartile, at 8 months. This finding may be attributed to the greater ease of approaching supratentorial tumours via surgery, therefore, allowing a more extensive gross total resection. In infratentorial tumours, gross total resection is hindered by the proximity of the brainstem, which enables a less extensive resection.

It was difficult to assess the specific locations of tumours in the brain, as 15 different locations are represented. The locations seen by this study were infratentorially: cerebellopontine angle, cerebellar and brainstem lesions, and fourth ventricle.

Supratentorial locations seen were frontal, temporal, and parietal lobes and intraventricular (excluding fourth ventricular, as these were added to infratentorial), pineal region, and basal ganglia region. The main gross tumour locations that occurred are listed in descending order: posterior fossa tumours, 73 (26.28%); tumours in the brainstem, 61 (21.96%); situated in the cerebrum, 38 (13.68%); and suprasellar, 32 (11.52%). Some of these locations overlap and the difficulties experienced in reviewing them correctly was mainly due to a lack of imaging or notes available to assess the locations personally. The various locations are represented in Table 2.

Some tumours appeared rarely, and this is confirmed by the literature. Among those that appear most commonly, gliomas made up 26.57% (73) of the total, which is contrary to reports in the literature. In the WHO 2021[1] classification, gliomas are

divided into adult and paediatric types. These types are divided further into high and low-grade tumours. In this research, the low-grade and high-grade tumours were divided and, as shown in Figure 1, labeled as brain astrocytoma (low grade) and gliomas (high grade). Medulloblastomas were the second most common, with 41 patients (14.96%) and astrocytomas (low-grade gliomas) were third most common, with 36 patients (13.13%). The fourth-highest number was attributed to tumours identified on clinical diagnosis only, which represented 12.02%, or 35 patients. Cases using the clinical diagnosis are difficult to interpret, as they can be either infra- or supratentorial. It also means that no biopsy was done to determine what tumour was seen on imaging; this is mainly done in brainstem lesions that are dangerous to biopsy. The number of tumours diagnosed clinically could also be affected by patients dying before diagnosis or surgery.

Ependymomas were the fifth-highest occurring tumours, with 24 patients (8.76%). Although astrocytomas, medulloblastomas, and ependymomas were not represented in perfect thirds, as illustrated in literature, they did occur more often than other less common tumours.

In sixth and seventh places were craniopharyngiomas, with 21 patients (7.9%), and pineal tumours with 14 (4.74%), respectively. Craniopharyngiomas form part of sellar tumours, which include pituitary tumours, which are rare in the pediatric population. Pineal tumors comprise pineocytomas and pineoblastomas.

The rest of the tumours were scarcely represented, as seen in Table 1 (attached to the addendum). These tumours could not be represented into biostatistically significant values, though their frequency is a true reflection of their representation in literature.

As mentioned, the tumour grading system was not calculated for this study. Much information was unavailable, due to restrictions due to technology and minimal information recorded. Tumours are still being graded according to histology. Molecular grading has not been used yet, thereby, preventing use of specific terms in the latest classification of tumours.

Of the 274 patients, 4% (11) had metastasis from either ependymoma, pineal region tumours, or medulloblastomas. These tumour subtypes are the most likely to present in metastases.

In total 23 patients (8,39%) were transferred back to referring hospitals for further management. The only facility in the region served by Universitas that offers adjuvant therapy is, currently, Kimberley Hospital, which has an oncology department. This department mainly offers chemotherapy and radiotherapy for adults; all paediatric oncology is managed at Universitas Hospital.

Of the 274 patients, 51 had no notes available on the various databases available to the researcher, a situation that made it difficult to assemble a great deal of the data.

When it came to adjuvant management, 70 patients (25.64%) received chemotherapy. This number could be influenced by the fact that patients under 3 years of age are not eligible for receiving radiotherapy – 123 patients (45.23%) received radiotherapy, while 194 of the patients (71.06%) received surgery of some kind, either a biopsy, resection (complete or incomplete), or cerebrospinal fluid diversion.

Fifteen patients (5.47%) refused management of any kind, including surgery. This may be due to patient fear or a belief in traditional medication. Parents refusing management, against a child's best interest, should be investigated further in future research.

Of the 274 patients, 134 (48.9%) completed their treatment, whether it was surgery or adjuvant. Definitive treatment (complete resection or patient in recession) was achieved by 17 patients (6.20%) and only presented at the next imaging, months later.

Tumour recurrence was seen in 34 patients (12.41%), and cases were divided into local recurrence (occurring in the same area in the brain), and distant metastasis, most likely the spinal canal. Of the 34 patients, 25 patients (75.53%) had local recurrence and 9 patients (26.47%) had distant metastasis. Management of patients with recurrence was divided into surgery (1 patient), radiotherapy (3 patients), and palliation (28 patients). Two of the patients died at home.

Much of the management of tumours overlap, and patients receive different management. Some receive surgery – whether resection or biopsy – with or without both radiation and chemotherapy.

In total 125 patients (45.62%) received resection of some kind – complete or incomplete. Of the 123 patients, 105 (38.32% of 274 patients) received radiotherapy,

and 70 received chemotherapy. 66 patients (24.09%) had only biopsies for diagnostic purposes with no further resection due to either danger associated with complete resection, or tumours being amenable to radiotherapy.

Most patients who underwent only biopsies, incomplete resection, or emergency review with signs of raised intracranial pressures received prophylactic surgery. Prophylactic surgery was seen as a cerebrospinal fluid diversion in the form of a shunt or a scope.

Discussion

Paediatric intracranial tumours are important, because, according to the literature review, they are the second most common malignancy, after haematological cancers. They also a play a big role in the socioeconomics of a country, as they not only affect children, but also, indirectly, parents, who need to take time off work. They may be unable to work for a prolonged amount of time, as hospital stay is extended by both post-surgery palliation and further adjuvant therapy. This means that parents also have to schedule follow-up visits for further management, which can affect their employment. These effects of paediatric tumours are, however, not in the scope of this research, and can be evaluated further in future research. Paediatric tumours also involve a psychological component that includes extended family members. The death of a child is a tragedy, and the financial implications of funerals can be severe. At least 60% of children with intracranial tumours do not survive

Another important aspect of this study was the evaluation of specific tumours. Due to government tenders and hospital financing, it is difficult to have one specific imaging modality system. This results in historical imaging being lost when the systems change. Universitas switched from Isite to the currently used Xeroview, which resulted in an inability to review tumour sizes, or even previous clinical diagnoses. This problem can be overcome by good clinical note-taking, which seems to have improved over the years, but which can improve through review and encouragement of registrars to record as much information as possible in their clinical notes.

A large percentage of Free State hospitals – 41% – lack CT scan facilities. Some facilities with CT scan facilities, lack radiologists to review imaging and facilitate swift referral for further management of patients. A delay in referral and imaging

leads to a delay in definitive treatment for patients who may have terminal conditions, or tumours that are not surgically resectable. This situation is not in the scope of this research, and should be reviewed by the Departments of Neurosurgery, Paediatric Oncology, and Radiology. Doing so may be a difficult task, as few medical professionals in South Africa are interested in specialising.

The literature, which mostly reports on studies conducted abroad, shows that many children with intracranial tumours die. This was confirmed by this research, as reported above. However, with an upper quartile figure of 35 months for post-diagnosis lifespan, it seems that, with adequate and quick referral, there is an opportunity to deliver life-prolonging management. On review, the greatest contributor to prolonging lifespan post diagnosis was complete resection, especially of less aggressive tumours. Fortunately, over the past few years, it seems that neurosurgery departments have improved in their ability to perform complete resections of tumours.

There was a minor difference in the occurrence of tumours in the different sexes. It is interesting that more boys were affected, considering the population has more girls. This finding may be attributed to some tumours, mainly germ cell tumours, having a high predilection for male patients.

In total 15 patients refused management. Although this is only 5.47% of the 274 patients in this study, this response should be reviewed. Usually, in such cases, the oncology and neurosurgery departments call on a social worker, but it remains difficult to convince parents who are adamant about relying on traditional healers or consultation with elders. Only with better education and communication will parents be persuaded to allow their children to receive the best medical management possible. This response by parents could also be due to adverse socio-economic circumstances, as parents, as breadwinners, cannot attend to the child for the duration of the recommended treatment, or commit to subsequent follow-ups, which may involve recurrence and requires longer-term management.

Most of the data collected by this study is in line with international standards or statistics. Although minor changes were noted in the distributions of tumours, it seems that glial tumours were most prevalent, as expected. Medulloblastomas and

ependymomas were also among the major tumours appearing in the post fossa. A large percentage of tumours had, as the only data, clinical diagnoses which were via imaging. With improved surgical skills and better review of tumours by pathology, this situation may reduce below the 12% recorded by this research. New developments, such as molecular genetics, are starting to be used, though it may be a long time before the Free State, in general, or Universitas, in particular, has such facilities. Molecular genetics will assist to divide tumours into those amenable to adjuvant therapy, and those that require gross total resection.

A high number of gliomas was seen – 26.57% – of which 22.6 % were located in the brainstem or infratentorially. These tumours are quite aggressive and explain why there is such a high number of deaths due to paediatric tumours. Very few brainstem gliomas are amenable to surgery, and few patients are subjected to biopsies, as this is associated with high morbidity and mortality. This means that there will continue to be large numbers of tumours that are only diagnosed clinically. However, the lifespan post diagnosis of these patients may be prolonged with adjuvant therapy and so-called prophylactic surgery.

In discussions with the biostatistician, it was difficult to review the different tumours according to the specific post-diagnosis lifespan – there were just too many variables associated with arranging the data in a way that would allow good interpretation and results. This means future research may need a larger pool of tumours, which may be established by starting prospective research of tumours arriving or being managed at Universitas hospital.

This research was also unable to review or discuss the different grading of tumours, as minimal note-taking meant tumours were not classified. It may also be the case that the pathology department does not have facilities to enable tumours to be graded according to the latest WHO definitions or nomenclature. This shortcoming will have to be addressed in the future, and rectified. This experience also extended to specific clinical data, such as height and weight, which was excluded from the discussion because certain patients had no values recorded upon initial review. Optimising note-taking will assist to resolve this issue.

The management of pediatric tumours in at Universitas Hospital corresponds with international standards. Medical professionals perform biopsies with either gross total resection, followed by adjuvant therapy or adjuvant therapy for tumours that are internationally known to be amenable. The only major difference between practice at Universitas and hospitals abroad is the availability of neurosurgeons, theatre time, and resources to enable immediate resection of tumours at presentation. Many tumours are managed with permanent cerebrospinal fluid diversion or ventriculoperitoneal shunt, which is not in accordance with international standards. This practice is, however, influenced by the lack of resources available at Universitas Hospital, where there is no paediatric ICU available and, therefore, staff cannot operate on tumours at the soonest possible time and prevent associated external ventricular drain infections. Patients who are deteriorating neurologically receive ventriculoperitoneal shunts while awaiting definitive management of their tumours. With regard to adjuvant therapy, in the rest of the world, only children older than 3 years are offered radiation, which is in keeping with South Africa's current paediatric oncology standard operation protocol.

Statements

Acknowledgments

1. Cornel van Rooyen, biostatistician
2. Health Sciences Research Ethics Committee (HSREC), University of the Free State

Ethics

Ethics were reviewed and approved by HSREC and Free State Department of Health (approval attached).

Conflict of interest

No conflict of interest, whether personal or financial, was present.

Author contributions

1. Professor A. van Aswegen supervised the research
2. Professor D. Stones provided paediatric oncology tumour registry

Data availabile

1. Excel sheets of patient information and biostatistician evaluation attached
2. Meditech, which that is available on the hospital system
3. Professor D. Stones' tumour registry, available at office and attached

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