UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES

MMed Part III (Minor Dissertation)

"EPENDYMAL TUMOURS IN CHILDHOOD: OUTCOMES AND PROGNOSTIC FACTORS."

by

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfilment of the requirements for the degree

MMed Radiation Oncology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission: 13 September 2016

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DECLARATION

I, Dr. Zanele Nkosi, hereby declare that the work on which this minor dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ACKNOWLEDGEMENTS

I am grateful to have completed this research and would like to extend my gratitude to the following people:

- My dearest husband, Basil Enicker. Thank you for your constant love, support and encouragement. To my little boy Lisolethu, all I do is for you. You two are my inspiration and you continue to push me to strive to be the best I can be.
- My mother Nomsa Nkosi. You are such an inspiration. I aspire one day to be half the woman you are. Thank you for believing in me and for all the sacrifices you have made in order to provide me with the best education. To dad, Zee, Ayanda, Monde, Merica, Nyaki and Nkanyezi. Thank you for your love and your belief in me.
- Thank you to my supervisors. Professor Jeanette Parkes and Dr. Alistair Hunter for the guidance and support throughout this whole process. You sacrificed a lot of your time to make this work possible and I greatly appreciate this.
- Professor Stannard. Your valuable input is greatly appreciated.
- To the filing room staff in the Radiation Oncology Department. You were a great help in locating medical folders and making them available for review. Thank you.

PART A

ABSTRACT

EPENDYMAL TUMOURS IN CHILDHOOD: OUTCOMES AND PROGNOSTIC FACTORS

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ABSTRACT

OBJECTIVES: To retrospectively review the patient demographics, disease profile and treatment outcomes of paediatric patients treated for ependymoma at our institution.

STUDY DESIGN AND METHODS: 51 eligible patients were treated between 1980 and 2013. The median age at presentation was 6 years. The majority of patients were male (66,7%), had infratentorial tumours (62,7%) and had low-grade tumours (70,6%). Gross total resection (GTR) was achieved in 22 patients (43,1%). Thirty-eight patients received adjuvant radiotherapy (76,5%) and 10 (19,6%) received adjuvant chemotherapy.

RESULTS: The 5-year overall survival (OS) was 63,3 % (median follow up of 46 months). The 5 year progression free survival (PFS) was 50,70%. Seventeen (33,3%) patients experienced treatment failure, of which 13 (76,5%) represented local failure. The median time to first relapse was 20 months. The 5 year PFS for children > 3 was 50,0 % and 27,7% for children ≤ 3 years of age ($p = 0.0356$). GTR had a superior 5-year OS of 73,9% over subtotal resection with a value of 56,7% ($p = 0.0016$). Similarly an improved 5-year PFS of 70,3% versus 29,1% was observed with GTR over subtotal resection ($p = <0.0001$). Patients who received adjuvant radiotherapy (RT) had significantly better outcomes than those in whom RT was not given ($p = <0.0001$, 5 year OS of 69,7% versus 37,5%).

CONCLUSION: This review confirms the finding that GTR is associated with improved outcomes and that adjuvant radiation therapy positively impacts survival. The worse outcomes in the younger age group requires further evaluation and possible change in treatment protocol for this group of patients.

PART B

STRUCTURED LITERATURE REVIEW

OBJECTIVES OF LITERATURE REVIEW

The objective of this literature review is to provide the reader with background information on the topic of the outcomes of paediatric patients treated for ependymoma and justification for the research I have undertaken. I will present work already published in this field. Comparisons will be made through analysis of previously published data on this topic and the findings of this study. This may allow identification of what is new, different or confirmatory and may identify areas where further research is required.

LITERATURE RESEARCH STRATERGY

For this literature review, articles relating to paediatric ependymoma outcomes were sought using the following search engines; PubMed, Google, and Google Scholar, provided through the University of Cape Town library resources. Articles were chosen based on relevance to the topic under review. Only publications in English were considered for the literature review.

In the last few decades, the majority of published literature on paediatric ependymoma consisted of case reports and small, single institution retrospective analyses. Due to the rarity of this tumour, these series frequently had small numbers of patients, often failing to reach numbers of significant statistical power. More recently the large paediatric co-operative groups have been able to publish larger series and randomized controlled trials, which are superior in the hierarchy of evidence. A systematic review of intracranial ependymomas has been previously published. The majority of literature on this topic has been from developed countries. There is little available literature published to give insight on paediatric ependymoma in the African setting or in other developing countries.

INTERPRETATION OF LITERATURE

In order to understand and discuss the results of the current study, a detailed review of the available literature on this topic was performed and discussed. This literature review will summarise and form discussions around the following sub headings:

a) Background information

b) Epidemiology

c) Histological grading and cytogenetics

d) Treatment, outcomes and treatment related prognostic factors

e) Patient and tumour related prognostic factors

f) Challenges in paediatric neuro-oncology in low/middle income countries

g) Conclusion

a) BACKGROUND

Ependymomas are a group of neuroepithelial tumours that arise within or adjacent to the ependymal lining of the ventricular system. Less commonly these tumours can occur within the brain parenchyma, arising from rests of fetal ependymal cells during development.

The aetiological factors that play a role in the development of these tumours are not fully understood. It was previously postulated that exposure to the simian virus 40 (SV40) could be a risk factor for development of ependymoma tumours. This was based upon identification of the virus in tumour tissue. However a causal relationship has not been confirmed [1]. An increased association of intramedullary spinal cord ependymoma has been reported in patients with neurofibromatosis 2 (NF2) [2].

Pevney and Rao reported that ependymal cells are remnants of the proliferative ventricular zone and they hypothesized that these cells are adult multipotent stem cells. This was supported by the fact that ependymomas express both neuronal and glial markers [3]. It is postulated that because ependymal cells are maintained as proliferating neural progenitors beyond the postnatal period, this leaves them susceptible to oncogenic transformation [4].

b) EPIDEMIOLOGY

Ependymal tumours are an uncommon group of tumours representing approximately 5,7% of all primary brain and CNS tumours in children aged 0- 14 years, according to the latest data by CBTRUS [5]. Ependymomas represent approximately 6% of all intracranial CNS tumours and 25% of all primary spinal cord tumours in the paediatric age group [6].

The median age at presentation is between 4 and 7 years of age [7,8,9]. The majority of studies show a slight male predominance [9,10,11]. The most common location for ependymoma is the infratentorial compartment (intracranially). These tumours occur less commonly in the supratentorial region or the spinal cord [8,12,13]. Low grade tumours (grade 2) form the vast majority of this group of tumours in the paediatric age group [12,13]. Disseminated disease at diagnosis is relatively uncommon, occurring in <18% of patients at diagnosis [14,15].

c) HISTOLOGICAL GRADING AND CYTOGENETICS

Bailey and Cushing [16] first recognized ependymomas as a distinct entity in 1926. The 2007 World Health Organization (WHO) classification of tumours of the central nervous system has classified ependymomas into 3 grades. WHO grade I includes myxopapillary ependymoma and subependymoma. WHO grade II includes classic ependymoma and WHO grade III includes anaplastic ependymomas [17]. Ependyoblastomas are highly malignant tumours that were previously considered as a variant of ependymoma. These tumours are however now classified in the group of primitive neuroectodermal tumours. In 2016, the WHO released the new classification of tumours of the central nervous system. This classification sees the addition of a genetically defined ependymoma subtype known as RELA fusion positive ependymoma. This variant forms the majority of supratentorial tumours in children. Another modification to the 2016 classification of ependymoma is the removal of the cellular variant of classic ependymoma, as it was considered to overlap extensively with standard ependymoma.[18]

Ependymomas are a heterogeneous group of tumours that show variability in their clinical behavior and outcome. The difficulty in predicting tumour behavior and outcome in these patients based on clinical and histological factors has led to the exploration of biological and molecular markers as well as genomic understanding of these tumours. In the last decade, strides have been made in this regard and findings are influencing the management and prognostication of this group of patients.

Cytogenetic studies have shown numerous chromosomal aberrations in ependymal tumours. The most common aberration, occurring in 30-50% of tumours, is that of chromosome 22. This includes monosomy 22 as well as deletions of 22q [4]. Hirose et al reported on different patterns of chromosomal aberrations in relation to tumour location. Gain of 1q with losses on 6q, 9 and 13 were the common aberrations in intracranial tumours while gains on chromosome 7 with various other chromosomal abnormalities including frequent loss of 22q occurred

almost exclusively with spinal cord tumours. This suggests that spinal cord tumours progress along different pathways than that of intracranial ependymomas [19].

Recently two distinct subtypes of posterior fossa ependymomas have been identified. These are known as Subtype A (CIMP +) and B (CIMP -). These two subtypes differ in the age of the patient at presentation, location of the tumour, biological signaling pathways, genomic instability and prognosis. Subtype A tends to occur in younger patients. Most of the patients in this group are male (70%) and the tumours frequently are found extending into the cerebellopontine angle. Tumours in this group have relatively little genomic instability. Gain of chromosome 1 or loss of chromosome 22 occur frequently in this group. In contrast, tumours of Subtype B predominantly occur in older patients and are usually located in the spinal cord or midline of the cerebellum. In contrast to Subtype A, tumours of Subtype B have a much higher degree of genomic instability with extensive chromosomal aberrations. Prognostically, Subtype A tumours have a worse clinical outcome then those of Subtype B. 56% of patients belonging to the Subtype A group will develop recurrence and 35% will die of their disease within 5 years compared to Subtype B, where 25% of patients will develop recurrence while 5% will die of their disease within 5 years [4]. The importance of this distinction of ependymomas into the two subtypes has therapeutic implications. Cytotoxic therapy functions by promoting damage to DNA. This induces cancer cells with mutations and disorganized genomes to undergo apoptosis. With the understanding that Subtype A (CIMP +) tumours have a nearly normal genetic code, it is thus not surprising that cytotoxic therapy based on DNA damage has shown no efficacy in clinical trials.

The recent publication of a molecular classification of ependymal tumours in 2015 by K.Pajtler and H Witt, classified ependymomas into 9 distinct molecular subgroups using DNA methylation profiling[20] . These molecular subgroups are genetically, epigenetically, transcriptionally, demographically and clinically distinct. There are 3 subgroups within each anatomical compartment of the CNS, which includes spine, infratentorial and supratentorial). This molecular

classification has proven to outperform the current histopathological classification with regard to clinical associations and risk stratification of patients. The supratentorial compartment consists of the supratentorial subependymoma (balanced genome), the supratentorial anaplastic ependymoma (YAP1- fusion) and the supratentorial anaplastic (RELA-fusion) subgroups. The subgroups of the infratentorial compartment include posterior fossa subependymoma (balanced genome), the posterior fossa anaplastic ependymoma (balanced genome) and the posterior fossa anaplastic ependymoma (chromosomal instability). Spine subependymoma (6q deletion), spine myxopapillary ependymoma (chromosomal instability) and spine anaplastic ependymoma (NF2 mutation) are the 3 molecular subgroups of spine ependymomas. The subgroups that predominantly occur in children include the posterior fossa anaplastic ependymoma (balanced genome), the supratentorial anaplastic ependymoma YAP1- fusion and the supratentorial anaplastic RELA-fusion subgroup. Patients within the supratentorial anaplastic RELA-fusion and posterior fossa anaplastic ependymoma (balanced genome) subgroup have a poor prognosis with a 5 year PFS of 29% and 33% respectively and a 5 year OS of 75% and 68% respectively. All the other molecular subgroups showed a varied 5 year PFS of between 50% and 100% and all had a 5 year OS of 100%.

This new molecular classification of ependymomas will be of value in the design of future prospective clinical trials that tailor patient treatment according to risk stratification. It will allow evaluation of adjuvant therapies such as radiotherapy, chemotherapy and molecular targeted therapies in the context of specific molecular groups. This will ultimately help treating physicians tailor treatment accordingly

and aim to improve the outcomes of patients diagnosed with these tumours.

d) TREATMENT, OUTCOMES AND TREATMENT RELATED PROGNOSTIC FACTORS

The treatment of ependymoma involves multimodality treatment by a multidisciplinary team. Surgery is the primary treatment modality. Maximal safe surgical resection is aimed for by neurosurgeons with special care not to compromise neurological and functional outcome. Extent of resection has been validated as one of the most important prognostic factors. Van Veelen-Vincent et al reported superior outcomes in paediatric pateints treated for intracranial ependymoma between January 1980 and December 1998 in whom a gross total resection (GTR) was achieved [10]. The 5 year OS rate was 80% in the completely excised tumour group compared to 51% for incomplete resection group (p value <0.03). The 5 year event free survival (EFS) was 53% in the completely excised tumour group compared to 33% in the incomplete resection group (p value <0.04) [10]. Numerous studies have shown similair findings of an OS and prgrssion free survival (PFS)/EFS benefit with gross tumour resection [11,14, 21,22]. A PFS benefit, but no OS benefit was demonstrated in some publications [7,23].

The importance of a total resection has led to the investigation of second look surgery in order to achieve a GTR. Second look surgery can be perfomed postoperatively after primary surgery when residual tumour has been confirmed by postoperative imaging. Alternatively it can be done after adjuvant chemotherapy in patients with residual tumour after primary surgery to facilitate ease of resectability by the possible cytoreductive effect of chemotherapy. Massimino et al published results showing that second-look surgery proved feasible with no major morbidity and local tumor control was comparable in patients undergoing 1 or more resections [24].

It must be noted that interpretation of published data on extent of resection is greatly influenced by the definitions used for GTR, near total resection (NTR) and subtotal resection (STR), both as described from the neurosurgical report as well as from neuro-radiological findings. This has made data comparison and interpretation difficult over the years as varying definitions have been used in different studies. A standardised definition for the extent of tumour resection (based on postoperative imaging) needs to be developed so accurate comparisons can be made.

The role of postoperative radiotherapy is well established and is based on historic retrospective studies, which have shown superior progression free survival in patients who received adjuvant radiation therapy compared to surgery alone [14,25,26].

In the past craniospinal irradiation was the favoured radiotherapy volume chosen for paediatric ependymoma due to the risk of spinal seeding associated with this tumour. Currently, treatment guidelines recommend localized radiation therapy in patients with non-metastatic disease. Numerous studies support the finding that the major route of failure for localized ependymomas is a local recurrence [9,14,27,28]. In addition the low rate of metastatic relapse [9,14,29] does not warrant craniospinal irradiation.

The role of chemotherapy is not well established in the treatment of ependymoma. Grundy et al published results on paediatric intracranial ependymoma patients who were 3 years old and younger at diagnosis and received chemotherapy postoperatively in order to defer radiotherapy thus preventing the neurocognitive effects on the developing brain. The 5-year incidence of freedom from radiotherapy for patients with non-metastatic disease was 42%. However this came at a cost of a high rate of recurrence. Fifty of the 80 (62,5%) patients with non-metastatic disease progressed and 9 out of 9 (100%) of the patients with metastatic disease progressed. The median time to progression for all patients was 1,6 years. The 3 year event free survival reported in this study was 47,6[30]. This compares unfavourably to the EFS of 74,7% reported by Merchant et al in a study looking at immediate adjuvant radiotherapy in children 3 years and younger [31]. Merchant et al also showed that

although the mean IQ of children less than 3 at the start of radiation therapy was lower than children over the age of 3, the IQ of the younger children improved over time. The level of function and lack of treatment related effects in the younger and more vulnerable group with high dose radiation therapy is encouraging [31].

The five-year overall survival rates for paediatric patients treated for ependymoma range from 44% to 79% [7,8,9,10,29,37]. The five-year progression free survival rates range from 25% to 74% [9,11,30,42]. Local failure remains a major problem with ependymal tumours. Recurrence is noted in 27% to 65% of patients [7,10,14,29].

e) PATIENT AND TUMOUR RELATED PROGNOSTIC FACTORS

Many publications on the prognostic factors related to ependymal tumours are retrospective in nature and include limited numbers of patients due to the low incidence of this tumour. In addition, many of these studies span a few decades, which hampers the interpretation of the results due to changes in histological grading systems, diagnostic evaluation and treatment policies. Therefore interpretation of definitive prognostic factors proves difficult. Below, the literature regarding accepted and controversial prognostic factors is discussed.

1. Age

Treating ependymomas in the paediatric setting presents a challenge for the treating physicians especially for the younger paediatric population who are less then 3 years of age. Maximum safe surgical resection followed by radiation therapy is the accepted treatment for majority of patients who present with these tumours. However children who receive radiation therapy are at risk of developing varying degrees of neuro-cognitive impairment and endocrinopathies due to the effect of the radiation on the immature, rapidly growing brain [32,33,34]. These adverse effects

were thought to be much more deleterious in children under the age of 3 years. Trials that have investigated the use of chemotherapy to delay radiation therapy have had inferior results to those achieved for patients treated with immediate postoperative radiation therapy [35,36]. Currently, it is accepted practice to treat children below the age of 3 years with conformal radiotherapy. Merchant et al reported that conformal radiotherapy achieved high rates of disease control in pediatric patients with ependymoma and resulted in stable neurocognitive outcomes [31].

Improved outcomes have been documented in the older paediatric population treated for ependymoma [9,27,37]. It has been postulated that the difference in cytogenetic aberrations between younger and older patients may be responsible for the age related outcome [19]. High levels of expression of the genes LDHB and STAM in younger patients have been thought to lead to increased cellular proliferation that could account for the unfavourable outcome seen in younger patients [38]. In addition, Comi et al reported that younger patients presented later and with bigger tumours than older children [39]. Lastly an association between younger age with high-grade (anaplastic) tumours has been suggested [37].

2. Histological grade

   Much controversy exists regarding the influence of tumour grade on survival. One of the major problems regarding tumour grading is the discrepancy between pathologists. Robertson PL et al showed discrepancies between the institution's diagnosis and the centralized review diagnosis, present in 69% of cases of that study [7]. Another factor to consider, is that until the revision of the WHO classification of 1993, anaplasia was not used to classify grading. Additionally ependymoblastomas , which have an aggressive behaviour were previously classified as ependymomas and have since been classified as primitive neuroectodermal tumours [40]. The last important factor to consider

is that a single grading system needs to be used in all studies to allow comparison and consensus on the definition of anaplasia needs to reached by neuro-pathologists.

Various published papers have failed to show a correlation between tumour grading and outcomes [10,41,42]. Conversely the following papers demonstrated a progression free survival benefit in low-grade tumours [9,21,43]. Korshunov et al, in 2004, suggested both a PFS and OS benefit with low grade tumours when compared to high grade (anaplastic) tumours [23].

3. Tumour location

Ependymomas located in the spinal region are associated with improved survival outcomes when compared to intracranial tumours [8,12,29]. The prognostic significance of infratentorial versus supratentorial tumour location is less clear. Some literature has suggested that supratentorial ependymomas have a worse prognosis [12,29,23,44]. Reasons suggested for worse outcome of the supratentorial location is that ependymomas in this region often have peripheral infiltrative growth into the brain parenchyma [45] and are less often completely encapsulated, making complete surgical resection difficult [46]. Cage et al reported that infratentorial tumours have better outcome due to the fact that lesions in this region cause symptoms sooner then their supratentorial counterparts and thus treatment can be initiated earlier [47]. Conversely the following trials have suggested worse outcomes with infratentorial ependymomas [42,48]. Numerous reports show no difference in survival between infratentorial and supratentorial tumours [8,27,49,50].

In addition, within each tumour site, subgroups have been identified that make surgical resection difficult. Ernestus et al identified midline supratentorial tumours as a subgroup associated with a lower resection rate and higher operative mortality [51]. Lateral recess tumours which originate

from the lateral part of the fourth ventricle infratentorially pose a difficulty in obtaining a good resection as they tend to displace or involve neurovascular structures [52].

Cytogenetics has deepened our understanding of the differences between spinal and intracranial ependymomas as distinct entities and could account for the difference in outcomes of the two tumour locations. Spinal ependymomas display a common genetic signature with high levels of expression of HOXB5, PLA2G5 and ITIH2. CDKN2A is amongst the most frequently expressed genes in spinal ependymoma when compared to intracranial tumours [38]. Compared to spinal tumours, intracranial ependymomas show high expression of NF2. This could be due to NF2 gene deletion or mutations that are predominantly found in spinal ependymomas [2]. In addition, gain of 1q and losses on 6q,9 and 13 are frequent with intracranial ependymomas, whereas gains on chromosome 7 occur almost exclusively in spinal ependymomas [38].

4. Staging

Spread of ependymoma occurs predominantly through local invasion and less commonly by cerebrospinal fluid dissemination. Disseminated disease at diagnosis is relatively uncommon. Previously published literature has documented disseminated disease at diagnosis in 5-17% of tumours [9,14,27,44].

A 1996 publication by Rezai et al, studied the prognostic criteria for dissemination in patients diagnosed with ependymomas. In the total cohort, 11,4% of patients developed dissemination and this was associated with increased mortality. It was reported that patients at risk of dissemination during the course of their disease were younger patients, patients who did not have a gross tumour resection, patients with high grade or myxopapillary tumours and patients with high proliferation indices [53].

Agaoglu FY et al showed an overall and disease free survival benefit for patients with non- metastatic disease compared to those with metastatic disease [9].

f) CHALLENGES IN PAEDIATRIC NEURO ONCOLOGY IN LOW MIDDLE INCOME COUNTRIES

Paediatric neuro-oncology management is complex. It relies on a well functioning health care system with a specialised paediatric oncology centre with the relevant specialists and sub specialists, support staff , as well as an infrastructure and physical resources needed for the management of these tumours. Many low/middle income countries are lacking in the expertise and resources available for paediatric neuro-oncology management when compared to developed nations. Studies done in the United States of America have estimated that the cost of hospitilisation, surgery, chemotherapy, radiation therapy, labarotory studies and pharmacy services amounts to $32000 - $45000 for the first year after a brain tumour diagnosis, with subsequent annual costs of $4000 - $8000 [54]. This represents an unrealistic burden for developing countries where an estimated 26% of the population survives on less than $US 1 per day [55]. The move to molecular subgrouping of ependymomas in order to tailor treatment accordingly, will add to the already huge financial burden experienced by developing countries in treating these tumours due to the high cost of biological/molecular testing. Another major challenge in developing countries is that the ratio of medical specialists to population is poor. As an example, in 2007, the number of paediatric neurosurgeons in selected countries throughout the world was estimated and nine out of then ten surveyed countries that failed to meet the minimum recommended ratio of paediatric neurosurgeons were in developing regions [56]. The lack of resources in developing countries continues to be a challenge. Recent studies estimate thst 29 countries in Africa and 13 in Asia completely lack radiotherapy capabilities [57,58] and radiotherapy forms an intergral part of treatment of brain tumours. Analysis of the WHO's 2010 international survey of medical devices showed that high income countries have 142 times the MRI capability of low income nations, 53 times the CT scan capability and 555 times the

PET CT scan capability, as adjusted for population [59]. Lastly the development of cancer registries in developing countries has been substandard. Cancer registries provide information on epidemiological patterns of cancer that are endemic to particular regions or populations, provide information on disease burden, identify possible disease causes and help establish priorities for combatting cancer in resource constrained areas. Data from 2006 estimate that only 8% of the population in Asia, 11% in Africa and 21% in Latin America are covered by cancer registries. This is in stark contrast to 99% of the population in the United States of America and Canada and 86% in Australia and New Zeland [60].

g) CONCLUSION

Ependymomas represent a heterogenous group of tumours. Determining prognostic factors that impact on survival for this group of tumours over the decades has resulted in some conflicting results. Complete resection of tumour, older patient age and non metastatic ependymoma have been regarded as favourable prognostic factors. Tumour location (supratentorial versus infratentorial) and histological grading still remains controversial with conflicting results. Cytogenetics looks to be the future in determining prognostication of these tumours and determining treatment.

Further research is needed in this field with international collaboration required in order to be able to recruit the required numbers of patients for future studies. Consensus on definitions used by neuropathologists for tumour grading and for definitions on extent of resection by neuro surgeons and neuro radiologists is needed. Randomised controlled studies as well as investigation into genetic subtyping will further contribute to our understanding of this tumour and its behaviour and will guide us in effective treatment.

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PART C

PUBLICATION READY MANUSCRIPT

EPENDYMAL TUMOURS IN CHILDHOOD: OUTCOMES AND PROGNOSTIC FACTORS

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ABSTRACT

OBJECTIVES: To retrospectively review the patient demographics, disease profile and treatment outcomes of paediatric patients treated for ependymoma at our institution.

STUDY DESIGN AND METHODS: 51 eligible patients were treated between 1980 and 2013. The median age at presentation was 6 years. The majority of patients were male (66,7%), had infratentorial tumours (62,7%) and had low-grade tumours (70,6%).Gross total resection(GTR) was achieved in 22 patients (43,1%). Thirty-eight patients received adjuvant radiotherapy (76,5%) and 10 (19,6%) received adjuvant chemotherapy.

RESULTS: The 5-year overall survival (OS) was 63,3 % (median follow up of 46 months). The 5 year progression free survival (PFS) was 50,70%. Seventeen (33,3%) patients experienced treatment failure, of which 13 (76,5%) represented local failure. The median time to first relapse was 20 months. The 5 year PFS for children > 3 was 50,0 % and 27,7% for children ≤ 3 years of age (p = 0.0356). GTR had a superior 5-year OS of 73,9% over subtotal resection with a value of 56,7% (p = 0.0016). Similarly an improved 5-year PFS of 70,3% versus 29,1% was observed with GTR over subtotal resection (p = <0.0001). Patients who received adjuvant radiotherapy had significantly better outcomes than those in whom RT was not given (p = <0.0001, 5 year OS of 69,7% versus 37,5%).

CONCLUSION: This review confirms the finding that GTR is associated with improved outcomes and that adjuvant radiation therapy positively impacts survival. The worse outcomes in the younger age group requires further evaluation and possible change in treatment protocol for this group of patients.

INTRODUCTION

Ependymomas are classified as glial tumours and arise from ependymal cells lining the ventricle of the brain and central canal of the spinal cord. They constitute approximately 8 and 25 % of all paediatric intracranial and spinal cord tumours respectively [1].

Despite improvements in neuro- radiological imaging, micro-neurosurgical techniques and radiotherapy planning and delivery, ependymomas continue to be associated with significant morbidity and mortality. The overall 5-year survival rate for both intracranial and spinal ependymomas in the paediatric population is reported to range between 55 and 65% [2,3]. Ependymomas are a heterogeneous group of tumours that show variability in their clinical behaviour and outcomes thus making treatment of these tumours challenging for physicians. The difficulty in predicting tumour behaviour and outcome in these patients based on clinical and histological factors has led to the exploration of biological and molecular markers as well as genomic studies of these tumours. The new molecular classification of ependymomas [4] will allow patient treatment to be tailored according to risk stratification. It will allow evaluation of adjuvant therapies such as radiotherapy, chemotherapy and molecular targeted therapies in the context of specific molecular groups. This will ultimately help treating physicians tailor treatment accordingly and aim to improve the outcomes of patients diagnosed with these tumours.

There is a paucity of data from the developing world, including South Africa, with regards to outcome following management of these tumours. The purpose of this study was to report on the demographic profile, management trends and outcome of paediatric ependymomas in a single institution over a 33-year period.

MATERIALS AND METHODS

The Groote Schuur Hospital Radiation Oncology electronic patient registry (EPR) and the National Health Laboratory Service (NHLS) database were used to identify all cases of histologically confirmed ependymoma seen at the Groote Schuur Hopsital (GSH) / Red Cross Children's Hospital (RCCH) complex between January 1980 and December 2013. Patients were eligible for the study if they had a histological diagnosis of ependymoma and were between the ages of 0 and 13 years at the time of diagnosis. Patients were required to have received all or part of their treatment at the GSH/RCCH complex. Patients with a histological diagnosis of ependymoblastoma were excluded.

The University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee granted approval for this research. The medical folders of all eligible patients were reviewed for information relating to patient and tumour characteristics, treatment received, outcome and follow up.

During the study period, all treatment decisions were made in a multidisciplinary meeting involving paediatric oncologists, neurosurgeons, radiologists, anatomical pathologists, endocrinologists and radiation oncologists. The major factors that played a role in the treatment decision-making were the patient's age, Eastern

Cooperative Oncology Group (ECOG) or Karnofsky performance status, tumour location, histological grade and extent of surgical resection.

Imaging of the brain and whole spine with a CT scan or magnetic resonance imaging (MRI), as well as cytological assessment of cerebrospinal fluid (CSF) were used to assess for evidence of metastatic disease. The histopathological grade was based on the World Health Orginisation (WHO) classification system [5]. Grade 1 tumours include subependymoma and myxopapillary ependymoma. Grade II tumours refers to classic ependymoma. These 2 grades are considered benign. Grade III ependymoma includes anaplastic ependymoma (malignant).

The extent of surgical resection was determined primarily using postoperative imaging (MRI and or CT scan) with contrast enhancement; however the neurosurgeons operative report was used where imaging was not available. Gross total resection (GTR) included no enhancement on contrast enhanced postoperative imaging. Near total resection (NTR) was defined as residual tumour measuring 1,5cm^3 or less and subtotal resection was defined as tumour measuring more than 1,5cm^3. Biopsy only refers to cases where the neuro-surgeon has taken a biopsy sample with no debulking and the postoperative imaging confirms this.

External beam radiotherapy was delivered using a Cobalt 60 machine or a linear accelerator. Proton therapy (cyclotron) was used in 4 cases for the radiotherapy boost between the period of 1998 and 2002. During the study period, there was a shift in the radiation technique being used for the treatment of these patients. Craniospinal irradiation (CSI) with a local boost was the favoured treatment technique in the earlier years of the study. This changed to a localized radiation therapy technique post 1991.

Carboplatin, Vincristine and Etoposide were the agents used in patients who received chemotherapy as part of their treatment. It was used in the setting of delaying radiation therapy in patient's ≤ 3 years of age prior to 2014.

Statistical calculations were performed using Prism Graph pad (version 6.00; Graphpad software^{R}, San Diego, Cal). Overall survival (OS) was defined as the time from date of pathological diagnosis till date of death or date of last contact for the patients lost to follow up. Progression free survival (PFS) was defined as the time from date of pathological diagnosis to the date of progression or relapse. The Kaplan–Meier method was used to generate survival curves. The log rank test was used to compare the survival outcomes by age, gender, location, histological grade, stage and treatment received. A p-value of < 0.05 was deemed statistically significant.

RESULTS

There were a total of 58 patients diagnosed with ependymoma during the study period, of which 7 were excluded from this analysis due to insufficient data or missing folders.

Patient and tumour characteristics

Patient and tumour characteristics and treatment received are summarized in table 1.

The predominant gender in this analysis was males with a male predominance of 2,4:1. The median age at diagnosis was 6 years (range 1-13). Intracranial tumours

occurred more commonly than spinal tumours with intracranial ependymoma diagnosed in 43 patients (84,3%) and spinal ependymoma in 8 patients (15,7%). Of the intracranial ependymomas, infratentorial tumour location was the predominant tumour location occurring in 32 patients (74,4%). The tumours were low grade (1 and 2) in 36 patients (70,6%) with the remaining 15 patients (29,4%) having high grade, anaplastic tumours. Six patients (11,8%) had evidence of central nervous system (CNS) dissemination at diagnosis.

Treatment parameters

Gross total and near total resection was achieved in 22 patients (43,1%). Subtotal resection was obtained in 25 patients (51%) and biopsy only was done in 4 patients (7,8%). Documentation of the verification of extent of resection with postoperative imaging in patient's folders was found in 40 patients (78,4%). Thirty-nine patients (76,5%) received radiation therapy as a part of their treatment. Of these, 19 patients (56,4%) received localized radiation therapy while the remaining 17 patients (43,6%) received craniospinal radiation therapy. The median dose for localized radiation was 54,00Gy (range 30,00Gy to 59,40Gy). Two of the patients receiving localized radiation therapy received palliative radiation therapy, one for an extensive, inoperable spinal tumour (30,00Gy) and one patient with an infratentorial, anaplastic ependymoma who received only 40,00Gy, after deterioration in performance status postoperatively. The median dose to the craniospinal axis was 32,00Gy (range 30,00gy to 38,00Gy) and the median total dose of CSI was 52,00Gy. Chemotherapy formed part of the treatment in 10 (19,6%) patients. Eight of the patients were 3 years and under at diagnosis and the chemotherapy was used to delay radiotherapy until the child was older in order to prevent neuro-cognitive side effects in the

developing brain. The reason for chemotherapy in the two remaining patients is unclear.

Outcomes and survival

The 5 year OS was 63,3% for the whole series with a median follow up of 46 months (Figure 1). The 5 year PFS for the whole series was 50,7% (Figure 2).

Increasing age was associated with an improved PFS (Figure 3). The 5 year PFS for children > 3 years was 50,0 % and 27,7% for children ≤ to 3 years of age (p = 0.0356). Localised disease had an improved PFS with a median PFS of 73% compared to a median PFS of 13,3% (p = 0.046) in patients with extensive disease. Although increasing tumour grade showed a trend towards inferior OS, this failed to reach statistical significance (p = 0.253). The 5 year OS for spinal tumour location was 85,3%, for supratentorial tumours was 75,3% and for infratentorial tumours was 49,3%, however this failed to reach statistical significance (p = 0.291).

GTR/NTR had a superior 5 year OS of 73,9% over subtotal resection with a 5 year OS of 56,7% (p = 0.0016) [figure 4]. Similarly an improved 5-year PFS of 70,3% was observed with GTR/NTR while subtotal resection had a value of 29,1% (p = <0.0001). Patients who received adjuvant radiation therapy had a significantly better outcome than those in whom radiation therapy was not given (p =0.0064, 5 year OS of 69,7% versus 37,5%[figure 5]; and p = <0.0001, median PFS of 87 months versus 2 months). The radiation therapy technique (localized versus CSI) given did not have a statistically significant impact on OS or PFS (p = 0.826 and p = 0.498).

Treatment failure occurred in 17 patients (33,3%) with 7 patients diagnosed with a recurrence after a radiographic complete response and 10 patients with progressive

disease. The median time to recurrence or progression was 20 months (range 2 to 73 months). The majority of recurrences/progression occurred early (within the first 3 years) in the post treatment period (94,1%) with only 1 patient developing recurrence after 3 years .The treatment failures all represented local failure only except for two patients (11,8%) who developed disease at another site in the brain and two patients (11,8%) who had local disease with evidence of metastatic deposits. At the end of the study period, 4 (23,6%) of these patients still remained alive, 3 patients (17,6%) had been lost to follow up and 10 patients had demised (58,8%). The median follow up the 4 patients who remain alive is 94 months.

DISCUSSION

To the best of our knowledge, this is the first study giving insight into paediatric ependymoma management and outcomes in South Africa. The rarity of this tumour is proved by the fact that only 58 patients were diagnosed over a 33-year period. Patient demographics of paediatric pateints diagnosed with ependymoma in this study are in keeping with international data, which shows a male preponderance for this tumour [2,3,6], that the majority of tumours occur intracranially [3,7,8] and show a low rate of tumour dissemenation at presenation [3,9,10]

The 5 year OS and PFS for the whole series of 63,3% and 50,7% respectively which compared satisfactorily to other retrospective studies done over the same wide time frame as that spanning this study [2, 3, 9, 10].

A relapse rate of 33,3% observed in this study is lower then other reported studies reviewing patients with both intracranial and spinal ependymomas [3,7,8]. One of the factors that could account for this is could be the high number of patients lost to follow up and the short period of follow up. Eleven patients (21,6%) were lost to

follow up within the first 3 years. We found that the majority of treatment failures represented local failure and relapses tended to occur early in the treatment period (within 3 years). This has been corroborated in other studies [3,9,11,12].

GTR/NTR was achieved in 22 patients (43,1%) in this study. The GTR rate has been reported as slightly higher in previously published papers, ranging between 50 and 63% [3,9,10,13]. These numbers could be skewed by the fact that verification of the extent of resection was documented by postoperative imaging in only 40 patients (78,4%). With the remaining patients who had postoperative imaging, we were unable to find the images to verify and measure residual tumour when present, and/or the post-operative residual was not documented in terms of cm^3 in the patient folder and we had to rely on the neurosurgical report for the extent of resection. This represents one of the limitations of this study.

Although the prognostic significance of the extent of tumour resection was controversial in older papers, it has now been validated as one of the most important prognostic factors with gross total resection of tumour having the best outcomes [3,9,14,15]. Our study was able to confirm the latter finding. The controversies in older papers were likely related to the lack of clear definitions for GTR, NTR and subtotal resection, as well as due to the lack of objective imaging criteria.

The role of postoperative radiation therapy has been established for ependymomas and is based on historic studies that showed improved survival in patients treated with adjuvant radiation therapy compared to surgery alone [9,27]. Thirty-nine patients (76,5%) in this study received adjuvant radiation therapy and had a

statistically significant superior 5-year OS and PFS compared to subtotal resection and biopsy only. Historically all patients who received radiotherapy for ependymal tumours, received craniospinal radiotherapy due to the risk of spinal seeding associated with this tumour. Current guidelines for radiation therapy do not support the use of craniospinal irradiation for localized ependymoma. Numerous studies support the finding that the major route of failure for localized ependymomas is a local recurrence [3,9,10,11]. In addition the low rate of metastatic relapse [3,8,9] does not warrant craniospinal irradiation, which in itself represents a higher risk of adverse effects due to the larger treatment volume irradiated. We are in agreement with these current recommendations as this study showed no difference in survival based on whether patients received localized or craniospinal radiotherapy.

Studies are currently looking at subsets of patients who may not require adjuvant radiotherapy or in whom radiotherapy can be deferred and used as part of salvage therapy. Hukin et al. published results of a prospective trial in which 10 patients with intracranial ependymoma who achieved GTR during surgery, received no adjuvant treatment [16]. Eight of these patients had supratentorial tumours and three patients tumours were anaplastic. Seven (70%) of these patients remained tumour free after a median follow up of 48 months. The remaining 3 patients were successfully salvaged (two with surgery and one with surgery and adjuvant radiotherapy). This study has shown promising results in terms of possibly deferring radiotherapy in paediatric patients with supratentorial ependymoma, in whom a GTR has been radiologically confirmed. This strategy could spare patients for an indeterminate time from the neuro-cognitive and endocrine sequalae associated with radiotherapy. However this strategy does require close follow up with imaging in order to identify recurrences early and offer salvage therapy. This study did not divide the patients

into molecular sub-groups, which would help identify the sub-groups of supratentorial, completely resected tumours in whom radiotherapy can be deferred. This should be looked at in a future study.

The literature reports that younger children have worse outcomes [2,3,9,14,17]. This has been duplicated in our study in terms of PFS. One of the reasons for this finding has been thought to be due to delaying radiation therapy in children who are 3 years of age and younger in order to prevent the neuro-cognitive sequelae of radiotherapy. Duffner at al. reported low 5-year survival rates of 25,7% in children less than 2 years of age who received chemotherapy in order to delay radiotherapy [18]. Similarly Nazar et al. reported a 5-year OS of 18,8% in children less than 2 compared to a 5 year OS of 52,3% in children older than 2 years [17]. Another factor that may contribute to the adverse prognosis of younger patients is the delay in diagnosis in this group of patients. A review of the presenting features of 40 children with ependymal tumours by Comi et al. found that the older children presented earlier and with smaller tumours [19].
An association between younger age with high grade (anaplastic) tumours has been suggested [16]. It has been postulated that the difference in cytogenetic aberrations between younger and older patients may be responsible for the age related outcome [20].

Ependymal tumours of the spine have been reported to have superior survival then intracranial ependymal tumours [2,7,8]. Although there was a trend for improved survival with spinal cord tumours in this analysis, this failed to reach statistical significance. The prognostic significance of supratentorial versus infratentorial

tumours is less clear. The literature has shown conflicting results in this regard. Numerous reviews have supported supratentorial tumours having a worse outcome [7,8,11] and it are postulated that this is related to the difficulty resecting these tumours for the following reasons. Firstly, Fokes and Earle looked at the pathologic aspects of ependymomas and showed that supratentorial tumours often had an infiltrative growth into the brain parenchyma while infratentorial tumours grow exophytically, thus making surgical resection more difficult with supratentorial ependymomas [21]. Secondly, supratentorial tumours are more likely to be only partially encapsulated and lobulated, whereas infratentorial ependymomas are often completely encapsulated thus making complete resection easier. [22]. Cage et al. reported that infratentorial tumours have better outcomes as they cause symptoms sooner then their supratentorial counterparts and thus treatment can be initiated earlier [23]. Conversely, a worse outcome for infratentorial ependymomas was reported in other studies [24,25]. One hypothesis for this finding is that infratentorial tumours have a relatively high rate of brainstem and cerebellum invasion making GTR difficult. Kritcheff et al reported a 34,6% rate of brainstem/cerebellum invasion. Several papers found no difference in survival between these two regions [10,26,27,28].

In addition within each tumour site, subgroups have been identified that may influence the ease of surgical resectability. Ernestus et al. identified midline supratentorial tumours as a subgroup associated with a lower resection rate and higher operative mortality [29]. Lateral recess tumours, which originate from the lateral part of the fourth ventricle infratentorially can be difficult to resect completely as they tend to displace or involve neurovascular structures [30].

Histological grading as a prognostic factor, still remains controversial. There are a number of issues related to this. Firstly there are major discrepancies between neuro-pathologists with regard to tumour grading and the exact features that define anaplasia. Secondly, different publications use different grading systems in their reviews thus making interpretation of the literature difficult. Lastly ependymoblastomas were previously classified with ependymomas and as they are aggressive tumours, they may have negatively influenced the outcomes of ependymomas in the past. This study failed to show a statistically significant impact of tumour grade on outcome and this had been corroborated in other studies [31,32]. Conversely other authors have reported a statistically significant effect of increasing tumour grade on outcomes [33, 34].

The limitations of this study include the retrospective nature of the review, insufficient or missing data in patient folders and the high number of patients lost to follow up.

CONCLUSION

This retrospective review adds weight to the already established finding that gross total resection improves survival in paediatric ependymoma patients and should be aimed for during surgery. Although some authors are identifying, investigating and reporting on subgroups of patients that can be treated with surgery alone (such as supratetorial tumours that have been completely excised), this review showed statistically significantly improved outcomes with adjuvant radiotherapy and this should form an integral part of the treatment. Localised radiotherapy is sufficient in treating patients with localized disease, reserving craniospinal for patients with

evidence of metastatic deposits. The finding in this and other studies, that younger patients have a worse prognosis requires further investigation into the biological and cytogenetic aberrations in this age group which could account for this and allow possible revisions in treatment protocols in order to improve this the outcome in this group. The results from this study are comparable to those around the world despite the limitations faced by South Africa as a developing country.

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TABLES AND SURVIVAL CURVES

PARAMETER	NUMBER, (%) OF PATIENTS (51)
Age (years)	
Median	6
Range	1-13
≤ 3	15 (29,4%)
≥ 4	36 (70,6%)
Gender	
Male	34 (66,7%)
Female	17 (33,3%)
Tumour location	
Infratentorial	32 (62,7%)
Supratentorial	11 (21,6%)
Spinal	8 (15,7%)
WHO Histological grade	
I	2 (3,9%)
II	34 (66,7%)
III	15 (29,4%)
Extent of disease,	
Localised	40 (78,4%)
Metastatic	6 (11,8%)
Unknown/No staging	5 (9,8%)
Treatment modality	
Surgery alone	8 (15,7%)
Surgery and chemotherapy	4 (7,8%)
Surgery and radiotherapy	33 (64,7%)
Surgery and chemotherapy and radiotherapy	6 (11,8%)

Table 1

Patient demographics, tumour charactersistics and treatment received.

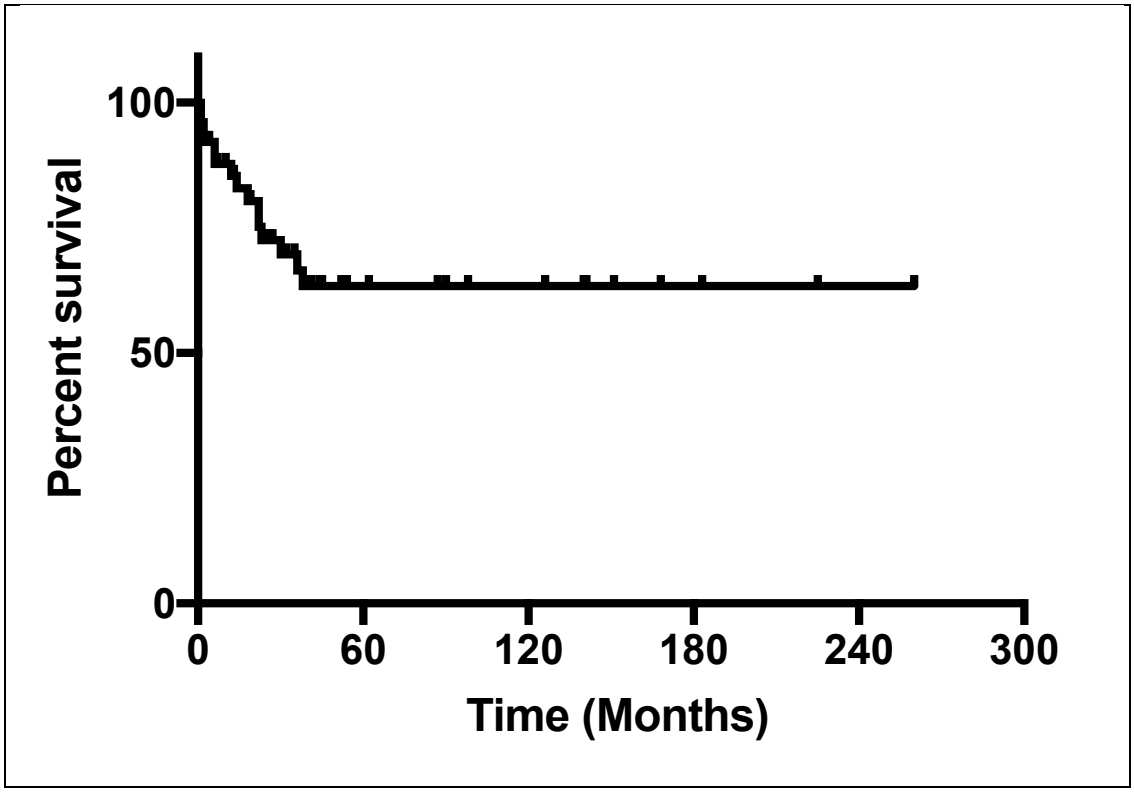

Figure 1
Overall survival of 51 patients diagnosed with ependymoma.

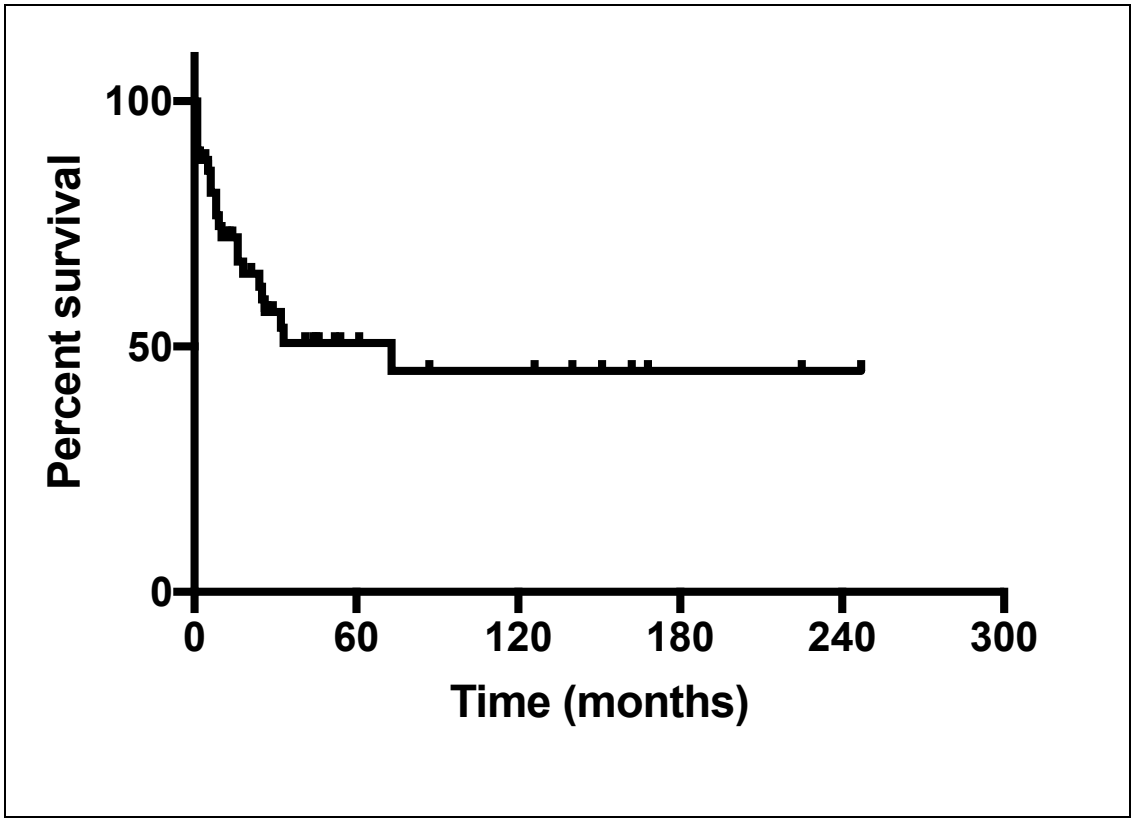

Figure 2
Progression free survival of 51 patients diagnosed with ependymoma.

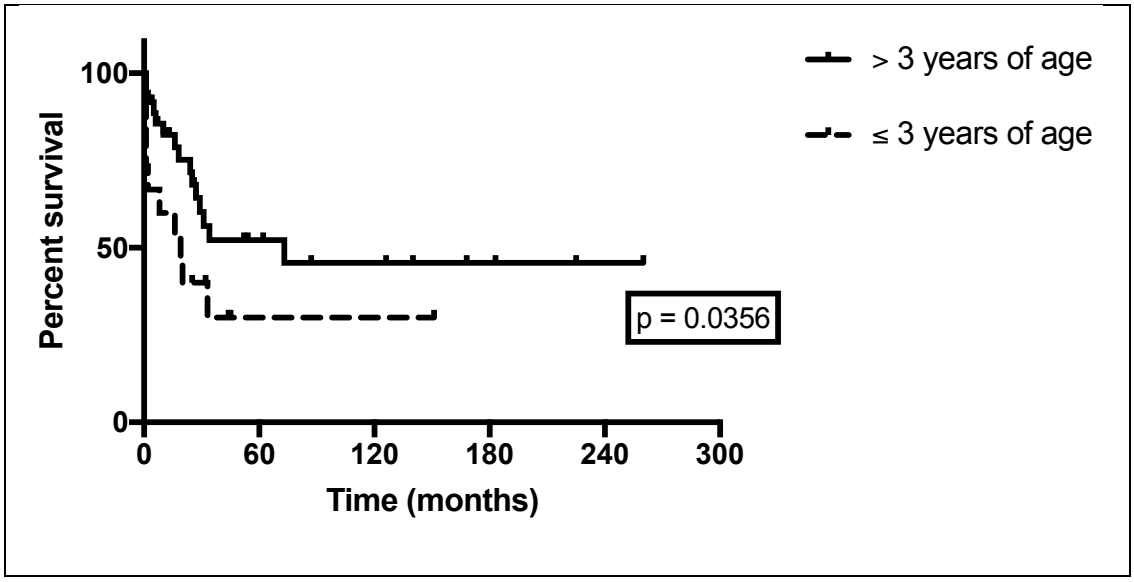

Figure 3
Progression free survival of patients ≤3 years old and > 3 years of age.

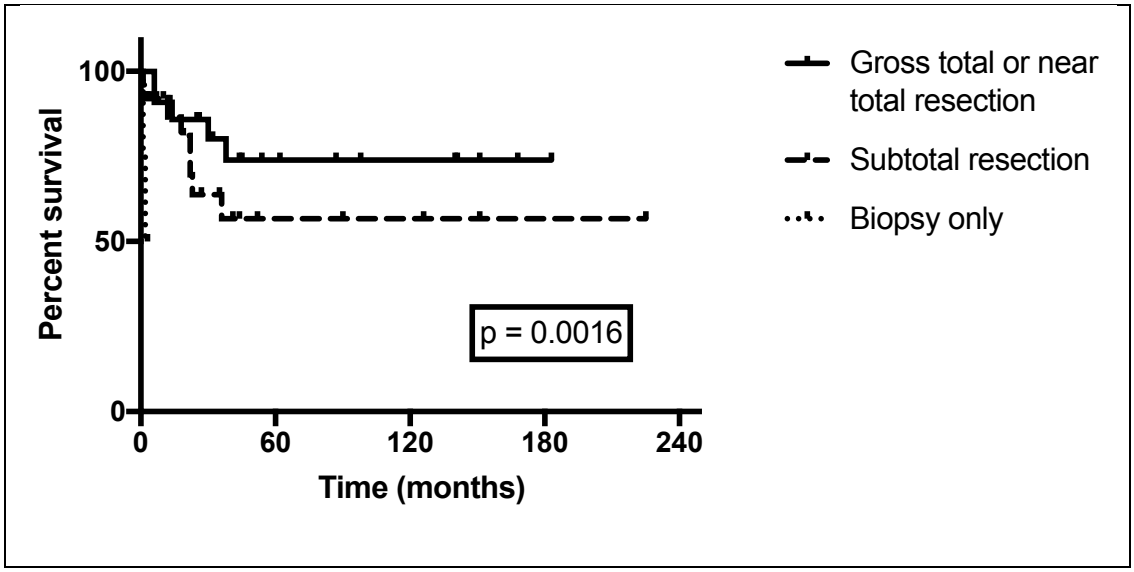

Figure 4
Overall survival of patients according to extent of surgical resection.

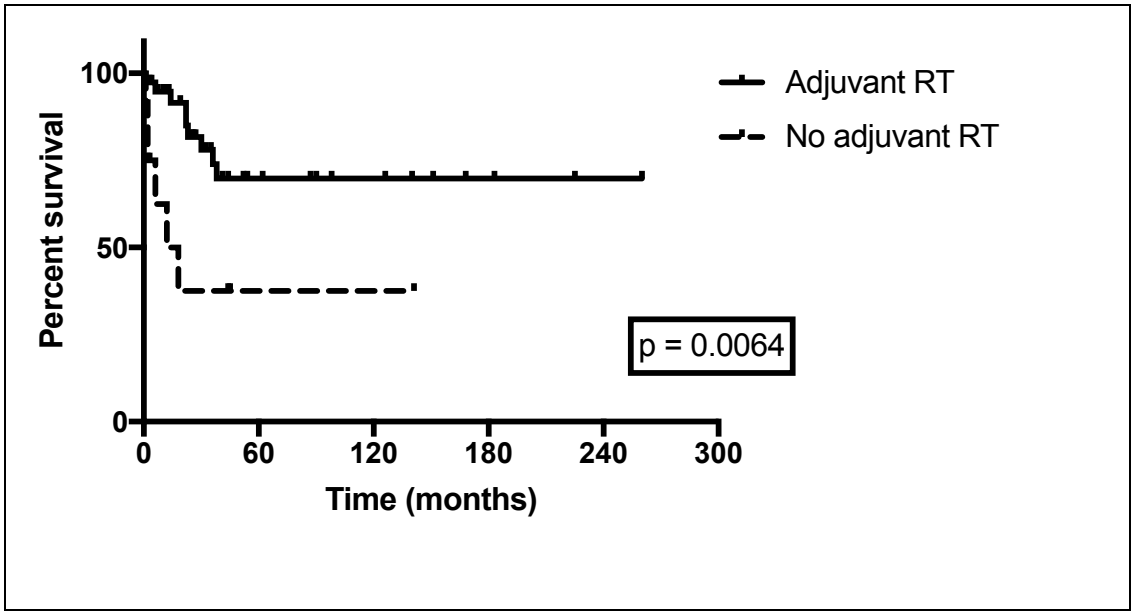

Figure 5
Overall survival of patients according to whether they received adjuvant radiation therapy or not.

LIST OF ABBREVIATIONS

- CSF: Cerebrospinal fluid
- CSI: Craniospinal irradiation
- ECOG: Eastern Coopertive Oncology Group
- EFS: Event free survival
- EPR: Electronic patient registry
- GSH: Groote Schuur Hospital
- GTR: Gross total resection
- NHLS: National Health Laboratory Service
- NTR: Near total resection
- OS: Overall survival
- PFS: Progression free survival
- RCCH: Red Cross Childrens Hospital
- STR: Subtotal resection

PART D

APPENDICES

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 November 2014

HREC REF: 757/2014

Dr J Parkes
Radiation Oncology
LE32

Dear Dr Parkes

PROJECT TITLE: A RETROSPECTIVE REVIEW OF THE OUTCOME OF PAEDIATRIC PATIENTS TREATED FOR EPENDYMOMA IN THE GROOTE SCHUUR HOSPITAL (GSH)/ RED CROSS CHILDREN'S HOSPITAL (RCCH) COMPLEX FROM 1980-2013. (MMed-candidate-Dr Z Nkosi)

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 05 November 2014.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student Dr Zanele Nkosi will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

AUTHOR GUIDELINES FOR THE SOUTH AFRICAN MEDICAL JOURNAL (SAMJ)

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

. Research
. Reviews
. Clinical trials
. Editorials
. In Practice (Previously Forum incl. Case Reports)
. Correspondence
. Obituaries
. Book reviews
. Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

. Guest editorial
. Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have

all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.
If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchershave been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative

Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The Agreement form should be uploaded along with other submissions files and any submission will be considered incomplete without it *[forthcoming]*.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

. An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
. Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
. Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports

- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.

- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies

- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.
Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.
From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.
In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.
In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Consensus/Position statement
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated

- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December

2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the

copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should be structured according to Agree II.
Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.
All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.

- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.

- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Copy the DOI between { }, which will always start with 10.
  - Provide as follows: DOI:10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. DOI:10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number
SA: SA Law Reports
11: Page or section number
(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
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- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

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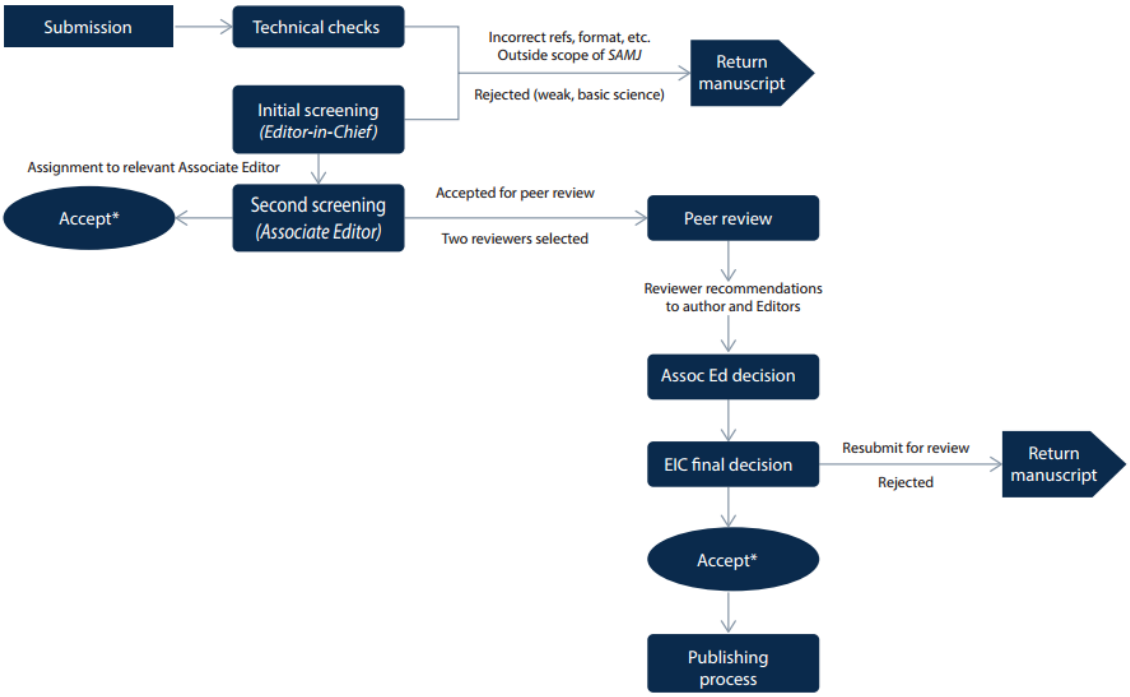

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