CHEMOTHERAPY IN RETINOBLASTOMA: DISEASE PROFILE & THERAPY OUTCOME IN TANZANIA, 2008-2010.

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MMed (Clinical Oncology) Dissertation
Muhimbili University of Health and Allied Sciences
October, 2013

CHEMOTHERAPY IN RETINOBLASTOMA: DISEASE PROFILE & THERAPY OUTCOME IN TANZANIA, 2008-2010.

By

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A dissertation submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine (Clinical Oncology) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences
October, 2013

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled ***Chemotherapy in Retinoblastoma: Disease Profile & Therapy Outcome in Tanzania, 2008-2010,*** in (Partial) fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences.

_____

Prof. T. Ngoma

(Supervisor)

_____

Date

DECLARATION AND COPYRIGHT

I, **Salum Juma Lidenge**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature……. **Date**……...

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ACKNOWLEDGEMENT

I would like to address special thanks to my supervisor, **Professor Twalib Ngoma** for his, support, advice and endless patience in improving my writing.

I also would like to thank members of Department of Clinical Oncology, specifically **Dr. Khamza Maunda** for their insightful comments and guidance throughout my study period.

My sincere gratitude goes to **Dr Julius Mwaiselage** and **Dr. Patricia Scanlan** for their critical appraisal of this work.

I would like to thank members of Pediatric Oncology Unit for their support and encouragement.

I would like to express my gratitude to Mr. Omary H. Dihani and Ms Mwamvita for their assistance in data collection especially in locating patients' files.

Special thanks to my lovely wife for her understanding, support, and endless prayers that led to the successful completion of this dissertation.

Also I would like to thank my parents Mr and Mrs Juma R. Lidenge, my brothers (Ramadhani & Hassan) and my sisters (Amina & Sihaba) for their continued support throughout my studies.

Finally, I would like to thank the Ministry of Health and Social Welfare for providing funds to support my studies.

DEDICATION

To my lovely wife, Tunu Burhani Kisamo for her love, friendship, patience and dedication to our family.

To our daughters Adiah and Aairah for the joy they bring to our family.

To my parents, Mr & Mrs Juma R. Lidenge, for the values and guidance.

To my brothers (Ramadhani & Hassan) and sisters (Amina & Sihaba) for their love and support.

ABSTRACT

Retinoblastoma (RB) remains to be one of the most common intraocular malignant tumors among children. While survival rates are high (over 90%) in developed countries, little is known about treatment outcomes of this condition in Africa, especially Sub-Saharan Africa. Before 2007, chemotherapy was not part of the routine regimen in the treatment of RB in Tanzania except for palliative basis in advanced recurrent disease.

This study aimed at looking at the socio-demographics, clinical presentation, treatment modalities given and evaluating the outcome of treatment and survival of children with retinoblastoma after introduction of chemotherapy protocols at ORCI.

It was a retrospective study in which hospital data and case notes of all children with a diagnosis of retinoblastoma from Jan 2008 to Dec 2010 were analyzed. This study was done at ORCI, the only tertiary cancer referral center in the country with a paediatric oncology unit of 17 beds capacity seeing about 150-300 children per year with about 10% of the cases being retinoblastoma.

It was found that majority of the patients were female and were aged less than 36 months. It was also found that the overall 3-year survival of the patients was 26%. Chemotherapy courses completeness and stage of the disease were found to have significant relationship with survival. Emphasis should be on early diagnosis by informing the general public and health care providers especially at the primary health facilities.

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ABBREVIATIONS

MUHAS	Muhimbili University of Health and Allied Sciences
ORCI	Ocean Road Cancer Institute
MNH	Muhimbili National Hospital
DSM	Dar es Salaam
INCTR	International Network for Cancer Treatment and Research
UKCCSG	United Kingdom Children's Cancer Study Group
RB	Retinoblastoma
PLONI	Post laminar optic nerve invasion
HIV	Human Immunodeficiency Virus
Hb	Haemoglobin
CR	Complete Remission
PR	Partial Remission
PD	Persistent/Progressive Disease
R	Relapse
SPSS	Statistical Package for Social Science
DFS	Disease free survival
EFS	Event free survival

OS	Overall survival
CCBRT	Comprehensive Community Based Rehabilitation For Tanzania Disability Hospital
CNS	Central Nervous System

BACKGROUND

Retinoblastoma is the most common primary intraocular malignancy in children(1) accounting for about 3% of cancers in children younger than 15 years of age(2). The average age of diagnosis is 18 months and in the vast majority of cases it presents within the first 3 years of life(3). Retinoblastoma can be familial or sporadic. In familial retinoblastoma inheritance is autosomal dominant with 90-95% penetrance. Interestingly only 6% of these have a positive family history and tend to be of early onset and bilateral. They tend to have second non-ocular tumors. Patients with familial retinoblastoma have a 50% risk of transmitting the affected gene to their children.

It can present as unilateral, bilateral and rarely as trilateral when there is brain stem involvement (4). It is a fatal disease uniformly if left untreated(5).

Worldwide, the incidence rates of retinoblastoma on average ranges from 1 in 15,000 to 1 in 20,000 live births. Evidence suggests that retinoblastoma is more common in some regions such as Latin America, India and Africa. In these regions, retinoblastoma is one of the most frequent tumours seen in paediatric oncology units. In Africa, the annual incidence of retinoblastoma is largely unknown but there is evidence suggesting an increased incidence for unknown reasons(6),(7).

In developed countries, the survival rate has increased from 30% in the 1930s to more than 90% in the 1990s, while in developing countries, the majority of patients with retinoblastoma present with advanced disease with the resultant 5 year survival of less than 50%(8),(9). It is estimated that mortality due to retinoblastoma in Africa is close to 70% while that in Europe and North America is less than 10%(9). In Tanzania, with population of around 44.4 million, the mortality pattern due to retinoblastoma is similar to that of other African countries(6). Although there is some improvement in treatment over recent years, data is scarce in Africa and Tanzania is no exception (6).

The introduction of chemotherapy in the treatment of children with retinoblastoma in resource rich regions, although not without challenges, has significantly and positively changed the lives of these unfortunate children(10). Chemotherapy in the form of different drugs and in combination with other treatment modalities like surgery and radiotherapy has led to improved survival of children with retinoblastoma to over 90% in recent years in Europe and north America(11). In Africa, where most cases present late(12), chemotherapy has been introduced recently, there is trend towards improvement. However survival rates remain poor,(8),(13). By late 2007, Tanzania's only tertiary oncology referral centre, the Ocean Road Cancer Institute (ORCI), Dar es Salaam (DSM), a state-run hospital which receives nationwide referrals and provides care free at the point of delivery in collaboration with International Network for Cancer Treatment and Research (INCTR), adopted a modified version of the United Kingdom Children's Cancer Study Group (UKCCSG) chemotherapy protocol for retinoblastoma(14). Before 2007, every child with retinoblastoma attending ORCI, regardless of stage was treated with surgery and external beam radiotherapy(9),(6). Zia et al analyzed the first year experience of chemotherapy in Tanzania and found that only 37 children were referred to ORCI and an overall remission rate of 35% had been achieved(9). It was too early to permit accurate assessment of mortality and survival. After four and a half years of use of the protocol, the current study aimed to complete this work by analyzing the impact of chemotherapy in a resource poor African country where the majority of the children present late.

LITERATURE REVIEW

Retinoblastoma incidence rate is about 1 in 18,000 live births. In Africa, the incidence is thought to be generally higher than elsewhere in the world. There are also regions where the incidence appears to peak even for the African average(6). In Senegal, for example, there are 15 cases of hospital consultations for retinoblastoma out of every 1000 consultations. In Mali, retinoblastoma is the second most common type of cancer among children in the Paediatric Oncology Unit in the Gabriel Touré Hospital in Bamako, Mali. Untreated, retinoblastoma is a deadly disease. In Tanzania, it is estimated that there are 75 new cases of retinoblastoma every year based on incidence of 1 in 18,000 live births and a birth rate of 34 per 1000 but as indicated above this may be an underestimate(9).

In many African countries surgery remains the main modality of treatment and in a few centers external beam radiotherapy is used when available. Very recently chemotherapy protocols have been introduced as part of treatment of retinoblastoma in some countries.

Studies done in Europe and North America have demonstrated the effectiveness and importance of chemotherapy in the treatment of retinoblastoma(15),(16),(17),(18). In a study done by Gallie et al of university of Toronto, USA to establish the effect of combining chemotherapy with focal therapy in curing intraocular retinoblastoma (without the use of radiotherapy) found that retinoblastoma is a curable disease by combining chemotherapy with cyclosporine therapy, laser therapy, and cryotherapy, without requiring external beam radiotherapy(15). Also Murphree et al conducted a study in USA to describe chemotherapy combined with local treatment modalities as an alternative to external beam radiotherapy in intraocular retinoblastoma and found that thermo-chemotherapy is a successful primary treatment modality for early stage retinoblastoma. For larger tumors in the absence of vitreous or extensive sub-retinal seeding, 3 cycles of chemo-reduction followed by sequential aggressive local therapy eradicates residual viable tumor(16).

To further emphasize the importance of chemotherapy in retinoblastoma, Kim et al followed up retrospectively a cohort of children with retinoblastoma who underwent enucleation for intraocular retinoblastoma in New York, USA to see whether it was enough to prevent them from recurrences and found that 60 out of 71 children who recurred developed metastatic disease emphasizing the importance of adjuvant chemotherapy and close follow up(19). Chemo-reduction was also found to shrink the intraocular tumour and allow for treatment with less invasive measures, such as cryotherapy, laser photocoagulation, thermotherapy, or plaque radiotherapy, thereby avoiding enucleation and external beam radiotherapy as reported by Shields et al(20). Brichard et al in Brussels Belgium, assessed the efficacy of chemotherapy (chemo-reduction) plus local treatments as an alternative to external beam and enucleation for intraocular retinoblastoma and found that it may be possible to eradicate viable tumor in all eyes with intraocular retinoblastoma by chemo-reduction followed by local treatments. Although 8 out of 21 eyes (38%) with advanced intraocular retinoblastoma were salvaged after chemo-reduction and local therapies, enucleation remained the treatment of choice in those eyes with total retinal detachment and diffuse vitreous seeding(21). Similar results were reported in Poland by Balwierz et al(22) in a similar study.

Chemotherapy was also found to be effective in children with advanced intraocular RB as reported by Kingston et al in UK in their study to determine survival after combined chemotherapy and whole eye radiotherapy for patients with bilateral advanced retinoblastoma(23). In another study done by Chantada et al in Buenos Aires, Argentina to evaluate the outcome of patients with retinoblastoma and post laminar optic nerve invasion (PLONI), it was found that patients with PLONI and concomitant choroidal and/or sclera invasion (n=22), all received chemotherapy and had a 5 year probability EFS of 0.86. The chemotherapy regimen included standard dose of carboplatin and etoposide alternating with cyclophosphamide and vincristine. (24).

In developing countries extraocular retinoblastoma is a common problem in pediatric oncology. A study in Argentina by Chantanda et al, looked at treatment of overt extraocular retinoblastoma. Forty-one patients were included. Fifteen of them had orbital or pre- auricular disease and had a 5-year event-free survival (pEFS) of 84%. Twenty-six had distant metastatic disease and non survived 5-years. All patients were treated with neoadjuvant chemotherapy. After two or three cycles of chemotherapy, all patients underwent enucleation or resection of residual mass followed by adjuvant chemotherapy. Once chemotherapy was completed, patients underwent radiotherapy to the affected sites. The chemotherapy regimen included cyclophosphamide, doxorubicin and vincristine.

It is obvious that chemotherapy in combination with other local modalities is effective and offers significant survival benefit for children with retinoblastoma even in advanced disease as reported in different parts of the world. We expected chemotherapy to be effective and have an appreciable impact in Africa despite the fact that most of the children present with advanced disease. Although chemotherapy protocols have been adopted in some African countries in the last few years, there is still insufficient data on how these children fare on chemotherapy in the African context. In Africa, few studies analyze outcome measures for retinoblastoma children especially in centers where chemotherapy has been introduced and the few available do not provide long term follow up to give the real picture of how advanced retinoblastoma in Africa fares**.**

Togo et al conducted a 30-month prospective study on the treatment of retinoblastoma in the Gabriel Toure´ Teaching Hospital, Bamako, Mali where chemotherapy had been introduced in the treatment protocols and they found that the survival rate at 30 months was 56% with 18% lost at follow-up. Mortality as a result of retinoblastoma remains high because diagnosis is always late and it is difficult to follow-up the patients. The chemotherapy regimen included two neo-adjuvant chemotherapy courses of cyclophosphamide, adriamycine and oncovin, an enucleation and two courses of adjuvant chemotherapy identical to the neo-adjuvant chemotherapy. (2). In a single institution retrospective study by Ali et al in Gezira, Sudan analyzing clinical presentation and outcome of retinoblastoma among children treated at their

National Cancer Institute, 25 RB cases were identified. Nine patients were lost to follow-up, another 9 were alive at last follow-up, and 7 (28%) died. Of the 7 patients who died, 5 died of disease, and 2 died of infectious causes. Of the 9 patients confirmed to be alive, 7 were in remission, and 2 were alive with disease; the median follow-up for these 9 patients was 15.4 months (range, 9–36 months)(13).

Bowman et al looked at outcome of retinoblastoma in East Africa, specifically Tanzania in a 5 year retrospective study with a cohort of 91 patients. Seven patients died. Thirty-five patients were lost to follow-up. Thirty-three patients were clinically disease-free at the time of their last follow-up and 16 were alive with progressive or recurrent disease. More than 4 months follow-up was available on 44% of patients (overall mean follow-up 8 months). Disease free survival (DFS) probability was 0.23 but the follow up possible was very short. DFS rates for intraocular disease appeared to be poor. Possible reasons for this included absent histopathology or routine ancillary investigations resulting systematically under-staging disease. As chemotherapy was not part of the routine regimen for treatment of retinoblastoma at that time, lack of chemotherapy for patients with histological risk factors such as choroid involvement was regarded as another likely factor for poor outcome.

In addition to encouraging earlier presentation Bowman et al also suggested introducing chemotherapy in the protocol of retinoblastoma treatment(6).

Late in 2007, chemotherapy protocols for treatment of retinoblastoma were introduced in Tanzania, at ORCI, the only referral cancer center. In 2008, Zia et al assessed the first year experience of chemotherapy for advanced retinoblastoma in Tanzania looking at disease profile, outcome and challenges. Among other findings, chemotherapy for retinoblastoma appeared to be associated with remission in the absence of orbital involvement(9).

PROBLEM STATEMENT

Untreated retinoblastoma is a fatal disease worldwide. It is estimated that, Tanzania have 75 new cases of retinoblastoma every year based on incidence of 1 in 18,000 live births and a birth rate of 34 per 1000 but this may be an underestimate(9). Due to unknown and known factors like late case presentation to health care facilities, late case diagnosis at primary health care facilities, delay in referrals and mistreatment and under-treatment in other facilities, ORCI sees about 45 cases per year. Number of cases seen per year has been increasing over the years but majority of cases that manage to reach medical services are at advanced stages of the disease. With the evolution of chemotherapy in combination with other treatment modalities, it is hoped that the survival of children with retinoblastoma over the years has improved significantly even in advanced disease. However until now the impact of chemotherapy protocols in addition to surgery and external beam radiotherapy has not been properly evaluated in Tanzania. This study aimed at evaluating how children with retinoblastoma in Tanzania behave in terms of their socio-demographics, their clinical presentation, modalities of treatment given and the outcome of treatment and survival after 4 years of experience with chemotherapy as part of multimodality treatment approach.

RATIONALE

From January 2008, chemotherapy protocols were introduced as part of retinoblastoma treatment at ORCI, to date no study has analyzed the impact of chemotherapy introduction in terms of survival impact. The one year experience had shown the promise of chemotherapy as assessed by Zia et al. This study hoped to find an improved outcome of these children over the years as several improvements have been made. These include the expertise of a dedicated full time pediatric oncologist, consistent supply of chemotherapeutic drugs, a few awareness campaigns across the country and good communication and strengthening of relationships between various stake holders like the ophthalmology departments of MNH and CCBRT, the oncologists and pathologists. Also the study helped to identify areas of concentration in order to improve the outcome of treatment.

OBJECTIVES

Broad objective: To describe the socio-demographics, clinical presentation, treatment modalities and outcome of children with Retinoblastoma at the paediatric oncology unit of the Ocean Road Cancer Institute, Tanzania.

Specific objectives:

1. To describe the socio-demographic characteristics of children with Retinoblastoma presenting at the paediatric oncology unit of the Ocean Road Cancer Institute, Tanzania.
2. To describe the disease profile including the proportion of bilateral disease in children with Retinoblastoma presenting at the paediatric oncology unit of the Ocean Road Cancer Institute, Tanzania.
3. To describe the treatment modalities of children with Retinoblastoma at the paediatric oncology unit of the Ocean Road Cancer Institute, Tanzania.
4. To describe the outcome of children with Retinoblastoma treated at the paediatric oncology unit of the Ocean Road Cancer Institute, Tanzania.
5. To evaluate the relationship between disease profile and treatment outcome among children with Retinoblastoma treated at the paediatric oncology unit of the Ocean Road Cancer Institute, Tanzania.
6. To evaluate the 3 years survival of children with Retinoblastoma treated at ORCI from 2008 to 2010.

METHODOLOGY

Study Design

A retrospective study of retinoblastoma children treated at ORCI from January 2008 to December 2010. Children with a diagnosis of retinoblastoma were identified from the central hospital register. Entries were cross-checked against a prospectively updated electronic database held by the Paediatric Oncology team. Hospital case-notes were retrieved for each patient. Details pertinent to patient demographics, diagnosis, disease severity and laterality, treatment, and outcome were recorded.

Study Settings

Ocean Road Cancer Institute (ORCI) in Dar es Salaam, Tanzania. The ORCI is located along the Indian Ocean about 200 meters from the beach. This health facility, one of the oldest health institutions in Tanzania was founded in 1895 by the German colonial government(25). At the time of the study it was the only tertiary cancer referral center in the country with a paediatric oncology unit of 17 bed capacity seeing about150-300 (increased over time) children per year(26). The International Network for Cancer Treatment and Research (INCTR) and Children in Crossfire provide one full time paediatric oncologist, drugs and worked with a local hard working team.

Study Participants

Target population: All children with diagnosis of retinoblastoma in Tanzania.

Accessible population: All children referred to ORCI with diagnosis of retinoblastoma

Study population: All children with retinoblastoma who fulfill the eligibility criteria.

ELIGIBILITY CRITERIA

Inclusion criteria

We included all children referred to ORCI with diagnosis of retinoblastoma from January 2008 to December 2010, and whose baseline characteristics were determined before appropriate management was started.

Exclusion criteria

We excluded subjects whose records were not available.

SAMPLING

Sampling procedure

Convenience sampling whereby all children who attended ORCI between 1st January 2008 and 31st December 2010 with a diagnosis of retinoblastoma were identified from the central hospital register. Entries were cross-checked against a prospectively updated electronic database held by the Paediatric Oncology team. Hospital case-notes were retrieved for each patient. Details pertinent to patient demographics, diagnosis, disease severity and laterality, treatment, and outcome were recorded.

Sample size

Due to a number of assumptions involved in sample size calculations in retrospective studies, this study included all children who attended ORCI with diagnosis of retinoblastoma between 1st of January 2008 and 31st of December 2010. A trend towards increase in number of patients with retinoblastoma has been observed over the years of the study. A total of 135 cases were recruited in this study.

STUDY VARIABLES

Exposure

Exposures of interest are the socio-demographic characteristics of the children with retinoblastoma presenting at ORCI, associated co-morbidities like HIV status and anaemia (Hemoglobin levels) at the time of presentation, disease presentation and stage at diagnosis (Intraocular Low Vs High risk and Extra ocular Microscopic Vs Macroscopic), and chemotherapy regimen given to the child under the consultation of the paediatric oncologist, type of surgery given (enucliation or exenteration), local treatment given like cryotherapy/leser or subtenon carboplatin and site, dose and type of radiation therapy given.

Operational definitions

Clinicopathological staging was done due to inadequate histopathology reporting whereby disease stage was categorized as intraocular low risk (disease confined to the retina and posterior chamber with no deep choroidal invasion), intraocular high risk (involvement of anterior chamber and/or deep choroidal invasion), extraocular microscopic (evidence of disease microscopically on cut ends and optic nerve involvement), extraocular macroscopic (gross disease with involvement of periorbital tissue), orbital recurrence, metastatic, bone marrow and CNS disease. Relatively early stage disease was intraocular low risk and intraocular high risk where as the rest was advanced disease.

In this study, chemotherapy refers to cytotoxic anticancer drugs in the form of two main regimens. Regimen 1 included the following cytitoxic anticancer drugs.

Drug: Vincristine

Dosage: 1.5 mg/msq for children >10kg. For children less than 6 months of age: 50% of the calculated dose by body surface area. Six months to 1 year of age: 75% of the calculated dose by body surface area. Over 1 year of age: 100% of the calculated dose by body surface area.

Administration: Intravenous bolus (max. total dose 2mg).

Drug: Carboplatin

Dosage: 600 mg/msq for children >10kg. For children less than 6 months of age: 50% of the calculated dose by body surface area. Six months to 1 year of age: 75% of the calculated dose by body surface area. Over 1 year of age: 100% of the calculated dose by body surface area.

Administration: Dilute to not less than 500 micrograms/ml according to the child's fluid requirement and infuse over 1 hour.

Hydration: The etoposide infusion may act as post carboplatin hydration insuring an infusion rate of at least 2.51/msq/hour for a minimum of 4 hours.

Drug: Etoposide

Dosage: 300 mg/msq for children >10kg. For children less than 6 months of age: 50% of the calculated dose by body surface area. Six months to 1 year of age: 75% of the calculated dose by body surface area. Over 1 year of age: 100% of the calculated dose by body surface area.

Administration: Dilute with 0.9% saline to a maximum concentration of 0.4mg/ml and infuse over 4 hours.

Regimen 1 included the following cytitoxic anticancer drugs.

Drug: Cyclophosphamide

Dosage: 600 mg/msq for children >10kg. For children less than 6 months of age: 50% of the calculated dose by body surface area. Six months to 1 year of age: 75% of the calculated dose by body surface area. Over 1 year of age: 100% of the calculated dose by body surface area.

Administration: Intravenous infusion reconstituted in 5% dextrose or 0.9% Sodium chloride to get concentration of 2mg/ml.

Drug: Vincristine

Dosage: 1.5 mg/msq for children >10kg. For children less than 6 months of age: 50% of the calculated dose by body surface area. Six months to 1 year of age: 75% of the calculated dose by body surface area. Over 1 year of age: 100% of the calculated dose by body surface area.

Administration: Intravenous bolus (max. total dose 2mg).

Drug: Doxorubicin

Dosage: 60 mg/msq for children >10kg. For children less than 6 months of age: 50% of the calculated dose by body surface area. Six months to 1 year of age: 75% of the calculated dose by body surface area. Over 1 year of age: 100% of the calculated dose by body surface area.

Administration: Slow intravenous infusion in 5% dextrose.

Each course given at approximately 21 day intervals. Also intrathecal Cytarabine is given on separate day to IV Vincristine.

Advanced cases retinoblastoma were given alternating courses of the two chemotherapy regimens.

Outcome

The outcome variables assessed include remission status after treatment (complete, partial, persistent/progressive disease, relapse and death) and survival status at the last follow up (dead, alive or lost to follow up).

- Complete Remission; CR- Absence of disease clinically (no signs and symptoms of the disease after clinical and othalmological examination. Bone marrow aspiration, CT brain and CSF cytospin were not routinely done)

- Partial Remission; PR- Reduction of the tumour (size) and/or signs and symptoms of disease clinically.
- Persistent/Progressive Disease; PD- The signs and symptoms of the disease have either reduced very little, remained constant or increased clinically over time.
- Relapse; R- After being in complete remission for some time, signs and symptoms of the disease have occurred again clinically.
- Lost to follow up; Those who do not have complete follow up data due to several reasons at the time of the study.

DATA COLLECTION

Research assistants under the supervision of the principal investigator used data extraction forms to retrieve data from patients records stored in manual files and or files on computer. The data extraction forms captured demographic characteristics, severity of disease and outcome of treatment and other variables of interest.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data Management

The data extraction forms were carefully reviewed for completeness and consistency. In case of missing or inconsistent data patient periodical records or medical registers were checked while ensuring utmost confidentiality of patient records and identity.

Statistical analysis

Proportions and Chi square test were performed. SPSS version 21.0 for windows was used for analysis. Overall survival (OS) was calculated from the date of starting treatment to the date of death or censored at last follow up. Kaplan-Meier curves were used to estimate the survival probabilities of OS.

Quality control

The data obtained were coded, edited and cleaned before any statistical analysis was carried out on the data. Study research assistants were trained before the start of the study. Data capture sheet were pre-tested to improve consistency and double entry was done to control for errors.

ETHICAL CONSIDERATION

Permission to do this research was sought from the university review board, the ORCI and the Paediatric cancer unit.

DISSEMINATION

The findings will be disseminated to appropriate bodies which include school of medicine MUHAS, ORCI, Paediatric unit and regional and international journals.

RESULTS

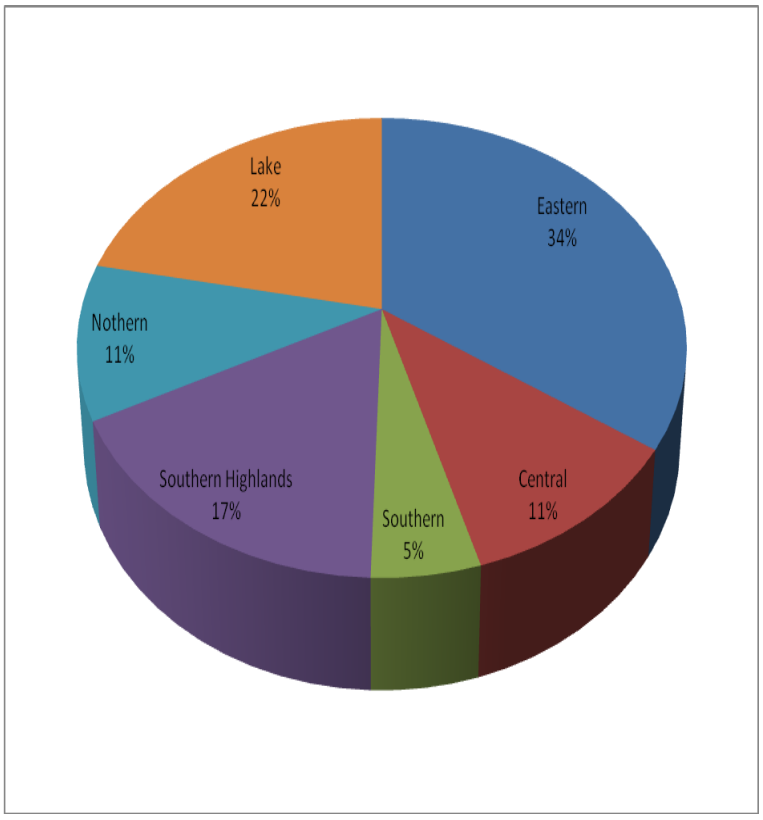
A total of 143 patients with Retinoblastoma attended at the ORCI between January 2008 and December 2010. However 10 patients had incomplete information and were excluded from the study. Thus a total of 133 patients were available for final analysis.

Table 1: The socio-demographic characteristics of the 133 study subjects.

Variables	Frequency (n=133)	Percentage
Sex		
• Male	59	44.4
• Female	74	55.6
Age categories (months)		
• ≤ 36	88	66.2
• 36 >	45	33.8

Table 1 shows the socio-demographic characteristics of the study population. It shows that the majority of the study subjects were females (55.6%). The mean (SD) age of the patients at presentation was 34(22) months. Sixty six percent of the patients were in the age category of 36 months and below (Table 1).

Figure 1 Distribution of retinoblastoma patients by zones of the country (n=133)



The Fig.1 pie chart shows that majority of the patients came from eastern zone (34%) followed by the lake zone (22%). Only 5% of the patients came from the Southern zone comprising of Lindi and Mtwara regions. (Figure 1).

Table 2: The disease profile of retinoblastoma patients included in the study.

Variables	Frequency (n=133)	Percent
Stage of the disease		
• Intraocular Low risk	3	2.2
• Intraocular High risk	28	21.0
• Extra ocular Microscopic	13	9.8
• Extra ocular Macroscopic	54	40.6
• Orbital recurrence	17	12.8
• CNS disease	18	13.5
Affected eye/site		
• Right eye	38	28.6
• Left eye	50	37.6
• Bilateral	43	32.3
• Trilateral	2	1.5
Presenting Symptom at primary health facility		
• White pupil	106	79.7
• Red eye	6	4.5
• Squint	2	1.5
• Swollen eye	19	14.3
Time from start of symptoms to arrival at ORCI		
• < 6 months	48	36.1
• 6-12 months	66	49.6
• 12 > months >	19	14.3

Correct diagnosis of RB at initial health facility		
• Yes	32	24.1
• No	101	75.9
Hemoglobin levels		
• 0-7.9	8	6.0
• 8.0-10.0	46	34.6
• 10.0 >	79	59.4
HIV status		
• Positive	2	1.5
• Negative	120	90.2
• Unknown	11	8.3

Majority of the patients presented with the RB disease at extra ocular macroscopic stage (40.6%) followed by intraocular high risk stage (Table 2). Thirty seven percent of the patients had the disease on the left eye and 32% of the children had bilateral disease (Table 2). It was found that 49.6% of the children presented at least 6 to 12 months after initial presence of the symptoms and the main presenting symptom was a white pupil 79.7% (Table 2).

It was also found that majority of the patient (75.9%) were not correctly diagnosed with RB at the initial health facility at first presentation. Those who were correctly diagnosed at initial health facility, majority of them (60%) presented at ORCI within 6 months of initial presentation. In our study we found that most children were HIV negative 90.2% (Table 2). However there were about 8.3% of the participants with unknown HIV status. Majority of the patients with RB had normal hemoglobin level at presentation (Table 2).

Table 3 shows distribution of bilateral retinoblastoma patients by age groups.

	Age groups in months		Total	
	≤ 36	36 >		
Sex				Fisher's exact
• Male	17 (89.47)	2 (10.53)	19 (100)	0.648
• Female	20 (83.33)	4 (16.67)	24 (100)	
Total	37	6	43	

Majority of the patients with bilateral retinoblastoma were younger children below 36 months of age (Table 3).

Table 4 Modalities of treatment offered at different stages of the RB.

Modality	Yes (%)	No (%)	Total (%)
Surgery	125 (93.9)	8 (6.0)	133 (100)
Chemotherapy	109 (81.9)	24 (18.0)	133 (100)
Radiotherapy	54 (40.6)	79 (59.3)	133 (100)
Laser/cryo/subtenon	6 (4.5)	127 (95.5)	133 (100)

Nearly the entire study population had surgical procedure performed as part of the treatment (Table 4). The surgical procedures which were done were either enucliation or exenteration. However 6% of the patients presented with too advanced disease for surgery to be performed. Only six patients received local treatment in the form of laser, cryotherapy or subtenon carboplatin. Surgery was mainly performed at MNH and CCBRT.

Majority of the patients (82%) also received chemotherapy, and this was mainly given at ORCI (Table 4). Twenty four (18%) patients did not get chemotherapy due to either early stage disease which did not require adjuvant chemotherapy or too advanced disease for chemotherapy to have any benefit. In the study we found that there were two main chemotherapy regimens used depending on the stage of the disease. The regimens were combination of Carboplatin, Oncovin and Etoposide (JOE) or Cyclophosphamide, Oncovin and Doxorubicin. . Intrathecal Cytarabin was used for CNS prophylaxis. The subjects who received chemotherapy as part of their treatment, a total of 61 (55.9%) had complete courses of the chemotherapy prescribed.

Table 5: The outcome of treatment and survival status of the study population.

Variables	Frequency (n=133)	Percent
Treatment outcome		
• Complete remission	59	44.4
• Partial remission	8	6.0
• Persistent/progressive	61	45.9
• Death	5	3.7
Survival		
• Dead	69	51.9
• Alive	49	36.8
• Loss to f/up	15	11.3

At the end of treatment, 44.4% of the patients had complete remission while 6.0% had partial remission (Table 5). The median duration period of the study was 4 months. During the follow-up period of the study, a total of 49 (36.8%) patients were alive up to the end of the study period (Table 5).

Table 6: The association between treatment outcome and stage of the disease as well as chemotherapy courses.

Variables	**Outcome of treatment**				**Chi2-value**	**P-value**
Chemo course completion	CR (%)	PR (%)	PD (%)	DEATH (%)		
Complete cycles	54 (88.5)	2 (3.2)	5 (8.1)	0 (0)		
Incomplete cycles	3 (6.2)	6 (12.5)	36 (75.0)	3 (6.2)	90.04	0.000
Stage of the disease						
• Intraocular Low risk	3 (100)	0 (0)	0 (0)	0 (0)		
• Intraocular High risk	22 (78.5)	2 (7.1)	4 (14.2)	0 (0)		
• Extraocular Microscopic	10 (76.9)	0 (0)	2 (15.3)	1 (7.6)		0.000
• ExtraocularMacroscopic	18 (33.3)	3 (5.5)	31 (57.4)	2 (3.7)	52.179	
• Orbital recurrence	6 (35.2)	3 (17.6)	8 (47.0)	0 (0)		
• CNS disease	0 (0)	0 (0)	16 (88.8)	2 (11.1)		

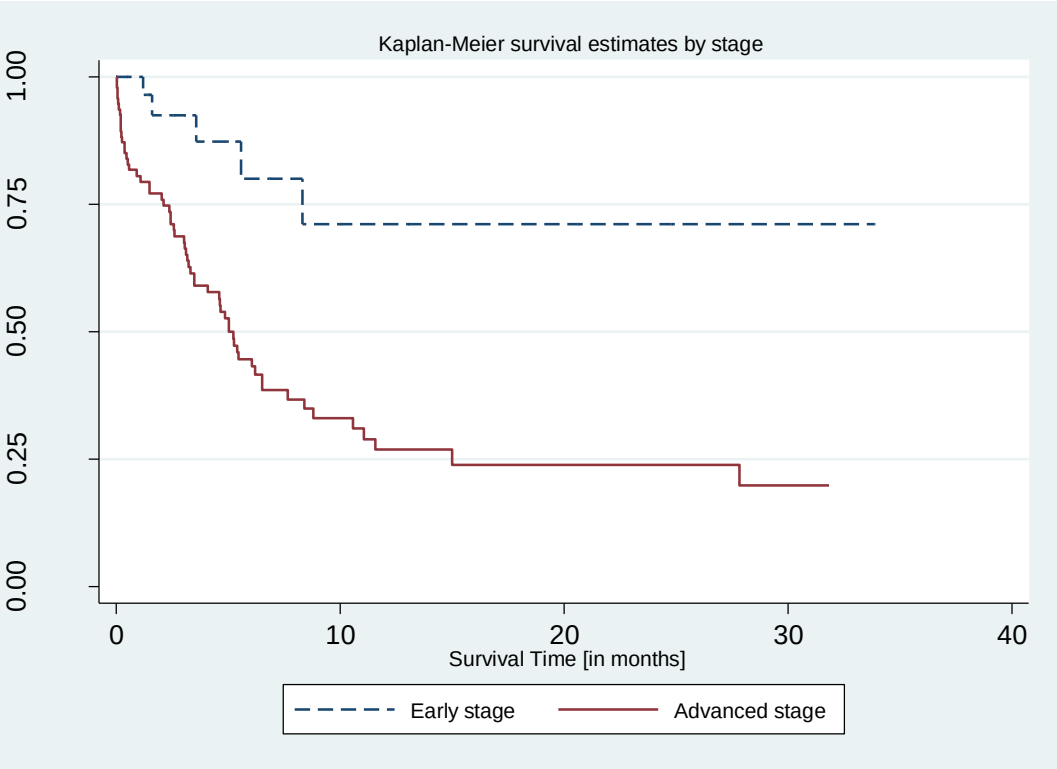
Patients who had completed chemotherapy courses had a significantly higher complete remission rate compared to the patients who did not complete their chemotherapy courses (88.5% versus 6.2%; $p < 0.0001$) It was also found that stage of the RB disease was significantly associated with treatment outcome (Table 6).

Table 7: Relationship between clinical factors and survival of retinoblastoma patients

	Univariate Analysis		**Multivariate Analysis**	
Variables	**OR(95% CI)**	**P value**	**OR(95% CI)**	**P value**
Age	0.99(0.98-1.01)	0.82	1.00(0.98-1.01)	0.70
Radiotherapy given	**1.70(0.95-3.05)**	**0.07**	**5.74(1.17-28.13)**	**0.03**
Stage of the disease	0.62(0.35-1.10)	0.10	4.31(0.83-22.36)	0.08
Duration of symptoms	0.97(0.92-1.02)	0.32	0.99(0.93-1.04)	0.76
Chemo completion	1.12(0.36-3.49)	0.84	0.75(0.17-3.24)	0.70
Diagnosis at initial facility	0.59(0.32-1.08)	0.09	0.62(0.32-1.20)	0.16

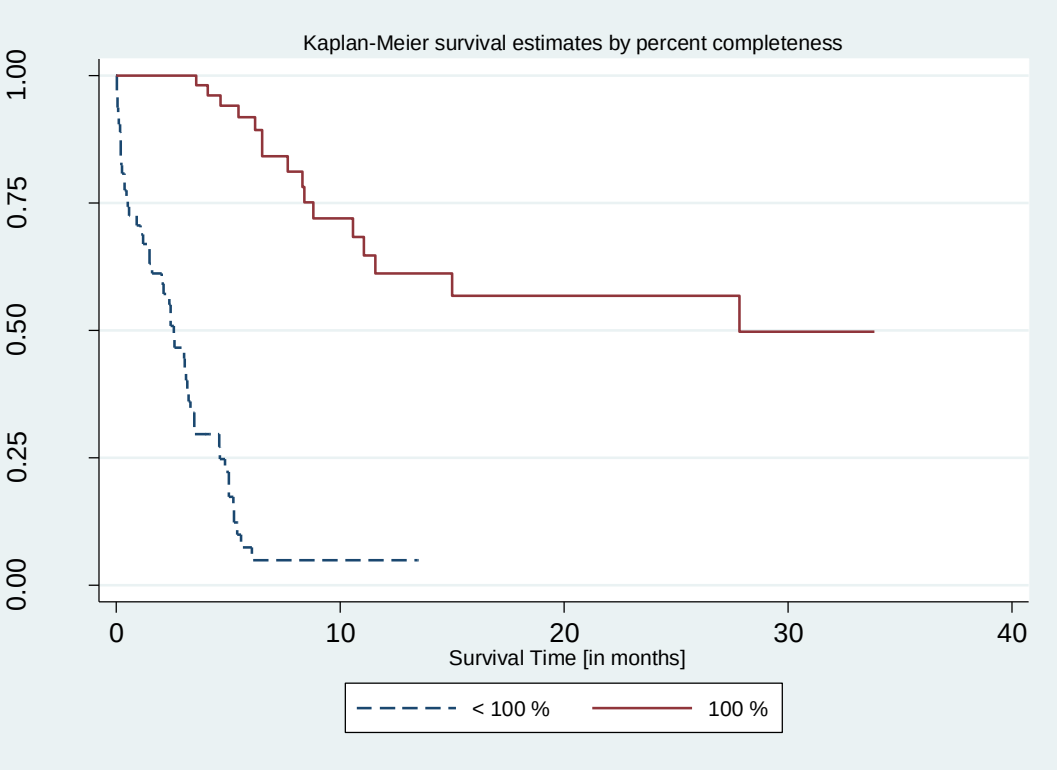
In cox regression analysis there no factors found to be significantly associated with survival of retinoblastoma patients at univariate analysis. However after control for other factors at multivariate analysis, radiotherapy has been shown to be significantly associated with survival of the patients (Table 7).

Figure 2: Comparison of the 3 year overall survival by stage of the disease.



The overall 3 year survival of the children who presented with relatively early stages was significantly higher than those with advanced stages. ($P < 0.001$)

Figure 3: Comparison of the 3 year overall survival by percentage chemotherapy course completion.



The overall 3 year survival of patients who had completed the prescribed chemotherapy courses was significantly higher than those who did not complete chemotherapy courses. ($P < 0.001$).

DISCUSSION

Early presentation to the right health facility remains a corner stone in the management of children with retinoblastoma in Tanzania. When different modalities of treatment are combined, the chances of curing retinoblastoma increase significantly. At an early stage, retinoblastoma can not only be cured but vision can be spared. Systemic and local chemotherapy is an important component in the management of this disease. This study aimed at evaluating socio-demographic characteristics, clinical presentation and modalities of treatment and outcome of children with retinoblastoma referred to ORCI after 4 years of experience with chemotherapy as part of multimodality treatment approach.

Based on incidence of 1 in 18,000 live births and a birth rate of 34 per 1000, it is estimated that, Tanzania have 75 new cases of retinoblastoma (9). It has been reported that some parts of Africa the incidence of retinoblastoma is much higher for unknown reasons (6), (7). The estimated number of new cases in Tanzania could be an underestimate.

In this study a total of 143 patients were referred to ORCI. The male-female ratio was 1:1.2. Many studies report similar ratio (4), (27), (28), (29), (30) but some authors report a male to female ratio of 2:1 (31), (32). Since about half of the patients could not manage to reach this institute, the ratio could be the same as reported elsewhere.

Majority of the patients came from Eastern zone, 34% followed by the lake zone 22%. Presence of big referral hospitals like Bugando Medical Center, MNH, CCBRT and ORCI where diagnosis of retinoblastoma can be made could be the reason for high number of referrals. Southern zone had the least number of patients 5%. Poor economic conditions in this zone, infrastructural challenges and lack of quality health facilities could be the reason for low referrals.

The mean age at presentation was 34 months and about 91% of the children were below the age of 5 years. Many studies in developing countries report age at presentation between 24 and 36 months (8), (9), (32), (31), (33). This is contrary to developed countries where mean age at presentation is 18 months and majority of the patients are diagnosed below the age of 3 years (4), (34), (5). Poor socio economic conditions, lack of information and infrastructural

challenges lead to delay of about 10 to 12 months from initial symptoms in developing countries.

As reported in other studies in developing countries (8), (9), (32), (31), this study found that mean duration of presentation from first symptom to arrival to ORCI was 8.5 months. About 64% of all patients presented at least 6 to 12 months from initial symptoms. It was also found that only 32 (24.1%) patients were correctly diagnosed and channeled to the appropriate facility after presenting for the first time at the initial health facilities. Majority of the patients 75.9% were at first treated as non retinoblastoma for several visits before finally being referred to higher centers. In villages and districts in Africa, majority of health care workers are non physicians. There are no pediatricians or ophthalmologists to make right diagnosis at the right time. While in most African countries children first present to non physicians, it was reported in Argentina that the pediatrician underestimated the complaints in half of the patients while the diagnosis was suspected by the ophthalmologist on the first visit (12). The difference in presentation observed between Africa and developed countries can be explained by financial and infrastructural challenges and low level of knowledge of the presenting symptoms of retinoblastoma both to the general public and some of the health care providers.

One of the major obstacles in the successful management of retinoblastoma in Africa is late presentation of the patients. In this study, it was found that 102 (76.7%) patients presented with advanced extra ocular disease. Similar findings were reported by many authors in Africa (35), (7), (8), (9), (33). In developed countries, the opposite has been reported where majority of the patients present with early stage disease. The difference in the health seeking behaviors, socio economic status, and level of education and knowledge of diseases could be the main reason for this difference in presentation. Retinoblastoma at an early stage is a painless, asymptomatic disease apart from white pupil with normal vision in majority of cases. Without proper knowledge it is difficult for most African families to seek proper medical advice. Cultural beliefs and ignorance in some situations causes children with retinoblastoma to be taken to traditional healers and prayer houses instead of hospitals (36), (37).

In this study, majority of the patients (66%) had unilateral disease as reported in literature (4), (38),(32). The frequency of bilateral disease of retinoblastoma was 32% and majority of these

patients were young children below the age of 36 months. The reported frequency of bilateral disease varies from 10 to 50% in different studies (5), (38), (33). Many children did not manage to reach the institute and those lost to follow up could have been lost too early for the second eye to be involved, hence misclassified as unilateral.

Majority of the patients had normal hemoglobin level at presentation and were HIV negative. The main symptom that was first noticed by parents was white pupil (79.7%) as reported by different authors (4), (6), (39), (40) but at tertiary hospital, these patients presented with advanced disease in 76.7%. Delays in seeking medical help, misdiagnosis and treatment and poor referral systems could be the reason for this major gap in stages between primary and tertiary health facilities.

Management of retinoblastoma is multidisciplinary. Depending on the stage of the disease surgery, chemotherapy, radiotherapy and local therapy in the form of laser or cryotherapy can be used alone or in combination (4). In this study majority of the patients had either enucliation or exenteration. External beam radiotherapy was used in 54 patients to the orbit and lymph nodes with average dose of 36Gy. Only six patients (4.5%) had local therapy.

In many studies in developing countries, surgery in the form of enucliation or exenteration forms the backbone of treatment (4). This is mainly because patients present with advanced disease making sight and eye sparing therapy not possible in most cases. In developed countries patients present with small disease making local therapy possible with resultant preservation of sight (5). In most African countries, radiotherapy to the orbit is given infrequently depending on the availability of the service (32), (41). In this study, the average dose of external beam radiotherapy using Co-60 machine was 36Gy ranging from 24 to 70Gy in 1.5 to 2Gy fractions to the orbit and periauricular lymph nodes. Similar average dose was reported by other authors (42),(32). This wide range of dose prescription could be attributed to the palliative nature of the treatment intent in most cases. Although majority of the patients presented with advanced disease but only 54 patients were given radiotherapy. Defaulting treatment, machine break down and under staging of the disease could be among the reasons.

As reported in some studies in Europe and North America, chemotherapy in advanced retinoblastoma had appreciable impact in outcome of treatment (43), (44). In this study it was found that chemotherapy was given to 109 (81.9%) patients. However 61 (55.96%) patients managed to complete the planned chemotherapy courses. Chemotherapy had to be stopped to some patients due to disease progression and others defaulted. Several studies in developing countries report disease progression, defaulting treatment and sometimes parents could not afford the cost chemotherapy (31), (45). In other patients chemotherapy was not offered at all due to too advanced disease at presentation. Those who had completed the planned chemotherapy courses, 54 (89%) had complete remission at the end of treatment. Furthermore, 95% of all patients who had complete remission were those who had completed the planned chemotherapy courses.

A number of studies done in developing countries reported poor treatment outcome of retinoblastoma patients (13),(45), (31), (32). In this study, at the end of treatment 59 patients (44.36%) attained complete remission clinically. Another 61 (45.86%) patients had progressive disease and 5 died. This is different from findings of studies in developed countries were majority of the patients attain complete remission (4), (34). It has been observed that histopathology reporting was poor and there is a significant delay in sending the report to the pediatric oncologist. This could be the reason for under staging the disease leading to giving chemotherapy to those who did not need it according to their true stage.

When remission status was analyzed against stage of the disease, it was found that majority of the patients with intraocular disease 25 (80.6%) attained complete remission while 68 (66.7%) of those with advanced disease had residual or progressive disease. This was found to be statistically highly significant (P = 0.000). As documented by several studies, early stage disease correlates well with the complete remission (4), (34). In this study, 20% of those with intra ocular disease failed to attain complete remission. This could be due to under staging of the disease following inadequate investigations and poor reporting. Investigations like CT scans were not done routinely. Bone marrow aspiration or biopsy and cerebral spinal fluid cytospin results were not well documented.

In contrast to most of the European and North American countries, survival of children with retinoblastoma in Africa remains poor (31). Several studies in Africa report 5 year survival of retinoblastoma to be less than 50% (8), (9), (32). In this study, those who presented with intraocular disease had overall 3 year survival of about 75%, significantly higher compared to those with extra-ocular and metastatic disease, 25%. The major breakthrough leading to the success in management of retinoblastoma in developed countries came when patients started presenting early (34). If emphasis is put on educating the general public and health care workers on the importance of early presentation to the right health facilities, there is hope for these children in the future.

In this study, the impact chemotherapy had on overall survival was analyzed in terms of those who had complete courses and those who did not. It was found that chemotherapy as part of treatment had appreciable 3 year survival benefit compared to those who got incomplete courses, (50% versus 5%). Studies done in developed countries found that 5 year survival of above 90% (5), (34). This difference in survival between most African countries and developed countries lies in a number of factors including late presentation and absence or inconsistent use of the right chemotherapy. Although majority of the patients presented with advanced stages of the disease, it is clear that complete chemotherapy courses have a positive impact on the outcome of treatment and survival of children with retinoblastoma. More efforts should be put forward in order to get these patients at an early stage so as to appreciate the great benefit of chemotherapy in the management of retinoblastoma in Tanzania.

STUDY LIMITATIONS

A combination of clinical and pathological staging was done but in most cases histopathological reports were late and inadequate. Treatment decisions were made on clinical stage, only to be revised when histopathology report arrived.

Poor documentation of the patient's progress and follow up information. Some patients did not go to the oncology unit for follow up instead attended CCBRT for ophthalmologist review.

Bone marrow aspiration and cerebral spinal fluid cytospin results were not clearly documented except for a few patients.

Findings reported in this study are in regards to retinoblastoma patients who attended ORCI with convenient sampling, thus extrapolation to the general population may be limited.

CONCLUSION

This study found that the majority of the patients were aged less than 36 months. Chemotherapy courses completeness and stage of the disease were found to have significant relationship with survival. The benefit of chemotherapy could have been higher had the patients presented early. The overall survival remains poor although for those with intra ocular disease it can be up to 75% in 3 years. Emphasis should be on early diagnosis by informing the general public and health care providers especially at the primary health facilities.

RECOMMENDATIONS

A large prospective study should be done properly to assess treatment outcome and survival of patients with retinoblastoma.

Proper records keeping and documentation of all important findings should be encouraged.

Public awareness campaigns on early signs and symptoms of retinoblastoma are needed to improve health seeking behavior and discourage non healthy cultural beliefs.

Early case detection and referral to the appropriate facility is important in order to catch early stage disease.

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APPENDIX I DATA EXTRACTION FORM

Patient identification	1. Patient study No.	[ ]
	2. Patient Reg. No.	[ ]
	3. Patient Initials	[ ]
Demographic characteristics	4. Age	[ ]
	5. Sex	[ ]
	6. Region	[ ]
Comorbidities	7. Hb level at presentation	[ ]
	8. HIV status	[ ]
Clinical characteristics	9. Time from first symptom to arrival at ORCI (Lag time)	[ ]
	10. Diagnosis of RB made at initial health facility?	[ ]
	11. Was the patient treated as a non RB case?	[ ]
	12. Was the patient referred to higher health facility?	[ ]
	13. Presenting symptom	[ ]

	14. Laterality	[ ]
	15. Stage	[ ]
	16. BMA	POS NEG
	17. Cytospin	POS NEG
	18. Histology	YES NO
	19. Date of arrival at ORCI	[ ]
	20. Date of starting treatment	[ ]
	21. Date of final assessment/ last seen	[ ]
Treatment given	22. Surgery	1. Yes 2. No [ ] 2. Exenteration/enucleation
	23. Type of chemo given	[ ]
	24. No. of chemo cycles completed/intended	[ ]
	25. Local treatment given	1. YES 2. NO

cryo/laser/subtenon carbo

		1.YES 2.NO [ ]
	26. Radiotherapy	Dose [ ]
Outcome	27. Remission	1. CR 2. PR 3. PD 4. R [ ]
	26.Survival	1.Dead 2.Alive 3.Loss to follow up [ ]