# A 5 year's retrospective case series on the clinical profile and management of retinoblastoma at Maputo Central Hospital, Mozambique

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## ABSTRACT

**Background:** Retinoblastoma is the commonest intraocular malignancy in childhood. The national epidemiological characteristics of retinoblastoma in Mozambique are not clearly known. Early diagnosis and appropriate treatment leads to a favourable outcome while a delayed diagnosis and inappropriate treatment can be fatal.
**Objective:** To determine the pattern of presentation and management of retinoblastoma patients at Maputo Central Hospital during a 5 year period (1st January 2010 to 31st December 2014).
**Methodology:** The study was a retrospective case series carried out at Maputo Central Hospital (Ophthalmology and Paediatric Oncology Services). Records of all retinoblastoma patients were retrieved with the help of the specific file number. Demographic characteristics, clinical presentation, investigations and management modalities of retinoblastoma patients were retrieved. Data was extracted and entered into a structured questionnaire and analysed.
**Results:** A total of 57 patients from 7 different provinces of Mozambique had clinical, histological or both clinical and histological diagnosis of retinoblastoma. The overall mean age at presentation was 30.5 months (CI 24.65 - 36.05) (SD 21.5); 82.4% of cases had unilateral retinoblastoma while 12.3% of cases had bilateral (mean age at presentation was 30.2 months and 26.4 months respectively). The female: male ratio was 1.2:1. The main presenting complaint was white reflex (62.5%) followed by eye swelling (50%), eye redness (40%) and poor vision (32.5%) while the main clinical signs were leukocoria (55%) followed by proptosis (50%) and eye redness (27.5%). Out of the 51 eyes who had surgery: 96% did not have documentation of the choroid and 98% of the scleral, but 54.9% of the eyes had optic nerve involovement, 33.3% had resection margin involvement and 31.4% had periocular tissue involvement. The main modalities of management were enucleation (93.9%), chemotherapy (24.5%) and exenteration (18%). The eligible patients for chemotherapy were 67.7% but only 35.3% of the patients received chemotherapy.
**Conclusion**: Many patients presented at older ages (with a mean age at presentation of 30.5 months) and many presented late with advanced orbital disease. Majority of the patients had unilateral retinoblastoma. Significant number of patients had optic nerve, resection margin and periocular tissue involvement noted on histology. The main modalities of management were enucleation, exenteration and chemotherapy, although there were no clear eligibility criteria for chemotherapy in retinoblastoma patients.

**Key words:** Retinoblastoma, Maputo Central Hospital (MCH), Modalities of management, Eligible

## INTRODUCTION

Retinoblastoma accounts for about 3% of all childhood cancers and is the commonest primary intraocular malignancy in childhood affecting children less than 5 years with over 90% being diagnosed before 3 years, while uveal melanoma is the commonest intraocular malignant tumour in adults and overall. There is no racial or gender predisposition in the incidence of retinoblastoma[1]. Untreated retinoblastoma is almost uniformly fatal, therefore, early diagnosis and treatment is critical in saving lives and preserving the visual function.

With availability of resources for early detection and improvements of treatment modalities, the management of retinoblastoma has been changing over the years and the prognosis for vision and life in patients with retinoblastoma has improved significantly in the last 20 years especially in developed countries[2]. Many studies have been done in African

countries looking at the pattern of retinoblastoma including in South Africa, Kenya, Nigeria, Tanzania, Uganda, Ghana, Malawi and Congo. However a similar study has never been done in Mozambique. In studies in Africa, the survival rate has been found to be poor due to multiple factors including the age at presentation, late presentation, proptosis, recurrent disease, metastatic disease and extraocular disease on histology[3, 4].

## MATERIALS AND METHODS

This was a descriptive retrospective case series of retinoblastoma patients, who presented at MCH, Mozambique including all patients admitted during a 5 year period (1st January 2010 to 31st December 2014). Maputo Central Hospital is the biggest referral hospital of Mozambique serving a population of about 21 million. It is located in Maputo (Capital) which had a population of 1,766,184 and an area of 346 km$^2$ and the primary official language is Portuguese.

Approval was obtained from the Kenyatta National Hospital-University of Nairobi Ethics Board and Maputo Central Hospital Scientific/ Ethics and Research Committee. The IP number was identified from the registration books and respective files were retrieved. Demographic characteristics, clinical presentation, investigations and modalities of management of retinoblastoma patients from eye/paediatric clinic that were referred from Maputo regional hospitals and different provinces of Mozambique were extracted and entered into a structured questionnaire and the data obtained was analysed using the Statistical Package for Social Scientists (SPSS) version 21.0. Patients who had clinical, histological or both clinical and histological diagnosis of retinoblastoma were included.

## RESULTS

All the patient records with an initial diagnosis of retinoblastoma, globe tumor, orbit tumor, orbital cellulitis and endophthalmitis were searched over the study period and a total of 91 patients records were identified. Out of these, a total of 45 patients had an initial clinical diagnosis of retinoblastoma while 46 patients had any of the other diagnoses. Out of the 46 patients with other diagnosis only 12 patients had histological confirmation of retinoblastoma (34 were excluded by histology). Therefore a total of 57 patients with a diagnosis of retinoblastoma either clinically (8), or by histology (12) or by both histological and clinical diagnosis (37).

Out of the 57 retinoblastoma patients found, it was only possible to retrieve 34 files from the hospital records. These were the only records that received a complete analysis in the study. The remaining 24 patients received a partial analysis mainly on the information that could be extracted from the registration book and the histopathology records. The cases found resided in 7 different provinces of Mozambique (Out of a total of 11 provinces). Most of the patients presented between the ages of 13 to 24 months (31.6%) and the mean age of presentation were: 30.5 months, (CI 24.65 - 36.05), (SD 21.5), median 24.00, range 1-96 months.

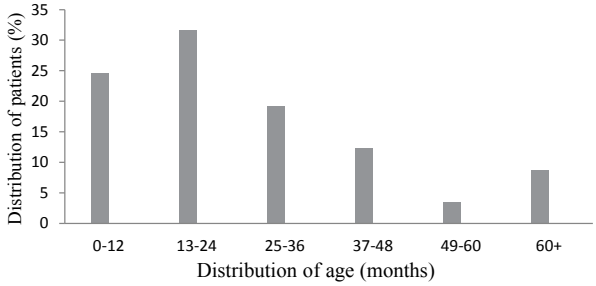


**Figure 1**: Distribution of cases by age of presentation (n= 57)

The mean age at presentation in bilateral cases was 26.4 months (SD 24.8), median: 18.0 while for unilateral cases it was 30.2 months (SD 20.9), median: 24.0. There was no statistical significant difference between them (p -value of 0.599) (Figure 1).

**Table 1:** Distribution by age at presentation vs. laterality (n= 57)

| Age (Month) | Bilateral | Unilateral | Unknown laterality |
|---|---|---|---|
| 0-12 | 3 | 11 | 0 |
| 13-24 | 2 | 15 | 1 |
| 25-36 | 0 | 11 | 0 |
| 37-48 | 1 | 5 | 1 |
| 49-60 | 0 | 2 | 0 |
| >60 | 1 | 3 | 1 |
| Total | 7 (12.3%) | 47(82.4%) | 3(5.3%) |

Sex was almost equally represented among the patients with an F: M ratio of 1.2:1 and family history was not recorded in majority of the patients (94.1%) attributed to a poor recording of family history data. We only noted a positive family history in 1 patient (2.9%).

Out of 34 patients with complete records, a total of 40 eyes were affected (28 unilateral + 6 bilateral), there was an overlap of symptoms because patients presented with more than one complaint and the main presenting complaint was white reflex (62.5%) followed by eye swelling (50%), eye redness (40%) and poor vision ( 32.5%) (Figure 2).


**Figure 2:** Clinical signs of retinoblastoma

The main clinical signs found were leukocoria (55%) followed by proptosis (50%) and eye redness (27.5%). Three patients (8.8%) were found to have recurrent orbital disease documented. Other signs documented: Corneal opacity, mydriasis, shallow anterior chamber, fungating mass, phthysical eye (Figure 3).

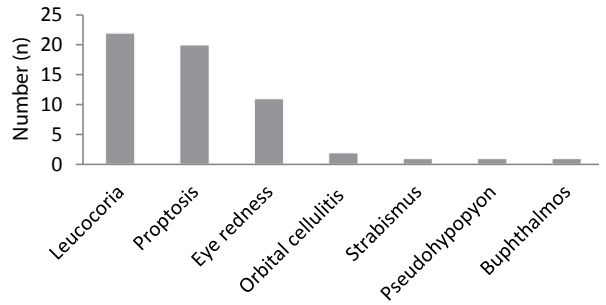


**Figure 3:** Clinical signs of retinoblastoma

Only 1 patient had EUA records of the fellow eye, having normal findings and only 5 patients (14.7%) had ocular ultrasound done, the rest (85.3%) did not have documentation of the ocular ultrasound findings (Table 2).

**Table 2:** Patients who had EUA and ocular ultrasound (n = 34)

| Findings | EUA other eye Frequency (%) n= 34 | Ocular ultrasound Frequency (%) |
|---|---|---|
| Undocumented | 33 (97.1) | 29 (85.3) |
| Yes | 1 (2.9) | 5 (14.7) |
| Total | 34 (100.0) | 34 (100.0) |

Only 5 patients (14.7%) had MRI done, where 4 patients had extraocular mass extension (3 had optic nerve invasion by histology and 1 patient did not have surgery done because parents declined) and intracranial extension was found in 1 patient (This was a 4 year old child that underwent enucleation and tumor was noted at the resection margin) (Table 3).

**Table 3:** Other investigations (CTscan /MRI) (n=34)

| Investigation | Frequency (n= 34) | |
|---|---|---|
| | CT-scan (%) | MRI (%) |
| No | 31(91.2) | 20 (58.8) |
| Requested (awaiting to be done) | 3 (8.8) | 9 (26.5) |
| Yes | 0 | 5 (14.7) |
| Total | 34(100.0) | 34 (100.0) |

Out of the 57 patients only 49 had surgery done (47 patients had one enucleated and 2 patients had bilateral enucleation, therefore a total of 51 eyes had surgical intervention) (Table 4).

**Table 4:** Interventions (n= 49)

| Procedures | Frequency | (%) |
|---|---|---|
| Enucleation | 45 | 93.9 |
| Exenteration | 9 | 18.0 |
| Chemotherapy | 12 | 24.5 |
| Laser photocoagulation | 0 | 0 |
| Cryotherapy | 0 | 0 |
| Radiotherapy | 0 | 0 |

Three patients who had enucleation also underwent exenteration due to tumor recurrence.

The most common histopathologic high risk factors found were optic nerve involvement (54.9%) and resection margin involvement (33.3%), although they were not documented in a significant number of eyes (Optic nerve not documented in 11.7% and resection margin in 39.2%). The optic nerve was not involved in 21.6% of cases but in 9.8% of cases the optic nerve was recorded as "Optic nerve difficult to recognize or not identifiable".

Majority of the patients did not have documentation of choroid and sclera (96% and 98% respectively), although 33.3% of cases had periocular tissues involvement, guiding to a high possibility of extraocular involvement (Table 5).

We identified 2 patients who died: One had resection margin involvement (associated with abdominal mass, severe anemia with blood dyscrasia), while in the other patient the optic nerve was difficult

to identify on histology but an MRI confirmed involvement of the optic nerve.

**Table 5:** Histology report based on the invasion and extension of ocular and periocular structures

| Histology: spread | Frequency n=51 eyes | (%) |
|---|---|---|
| (a) Choroidal involvement | | |
| Undocumented | 49 | 96.0 |
| Yes | 1 | 2.0 |
| Histology not available | 1 | 2.0 |
| (b) Scleral involvement | | |
| Undocumented | 50 | 98.0 |
| Histology not available | 1 | 2.0 |
| (c) Periocular tissues infiltration | | |
| Undocumented | 26 | 51.0 |
| Yes | 17 | 33.3 |
| No | 7 | 13.7 |
| Histology not available | 1 | 2.0 |
| (d) Optic nerve involvement | | |
| Involved | 28 | 54.9 |
| Not involved | 11 | 21.6 |
| Undocumented | 6 | 11.7 |
| Difficult to recognize ON (Not identifiable) | 5 | 9.8 |
| Histology not available | 1 | 2.0 |
| (e) Resection margin involvement | | |
| Undocumented | 20 | 39.2 |
| Involved | 17 | 33.3 |
| Not involved | 13 | 25.5 |
| Histology not available | 1 | 2.0 |

Out the total of 57 patients found only 34 patients had the file to analyze the proportion of patients who received chemotherapy, among them only 35.3% of patients received chemotherapy (Table 6).

**Table 6:** Number of patients who received chemotherapy (n=34)

| Chemotherapy given? | Frequency n=34 | (%) |
|---|---|---|
| Yes | 12 | 35.3 |
| No | 22 | 64.7 |
| Total | 34 | 100.0 |

**Table 7:** Eligible patients for chemotherapy (n= 34)

| Eligible | Clinical / Histological criteria for chemotherapy * | Received chemotherapy Frequency n=34 | | |
|---|---|---|---|---|
| | | Yes (%) n=12 | No (%) n=22 | Total (%) |
| Yes | Clinical criteria (Proptosis) | 1 | 3 | 4 |
| | Histological criteria (ON involvement, periocular tissues) | 3 | 2 | 5 |
| | Clinical and histological criteria | 8 | 6 | 14 |
| | Total patients eligible (%) | 12 (35.3) | 11(32.4) | 23 (67.7) |
| Unknown** | | | | 8 (23.5) |
| Not eligible | | | | 3 (8.8) |

*Eligibility criteria for chemotherapy: Treatment of intraocular bilateral retinoblastoma (for globe salvage)[5-13] extraocular extension (orbital disease -proptosis) and the histopathologic high-risk factors (Massive choroidal involvement, scleral or extrascleral involvement and optic nerve involvement beyond the lamina cribrosa with or without involvement of the resection margin)[4, 14, 15].

Out of the 34 patients with available file noted that 23(67.7%) were eligible for chemotherapy based on clinical and histological criteria. No patient was in globe salvage therapy.

** Unknown eligibility for chemotherapy in 8 patients (23.5%):

- Six patients did not have any surgery done because: In 5 patients the parents declined surgery and 1 patient was sick
- The optic nerve was not documented in 2 patients

**Table 8:** Reasons of no chemotherapy in the 22 patients with available file

| Reasons of no chemotherapy | Frequency (n = 22) | Eligibility for chemotherapy |
|---|---|---|
| Unknown reasons | 6 | Eligible 11 |
| Died | 2 | |
| Awaiting results | 2 | |
| Was to start | 1 | |
| No surgery | 6 | Unknown ** 8 |
| ON undocumented | 2 | |
| Optic nerve no involvement | 3 | Not eligible 3 |
| Total | 22 | |

**Table 9:** Chemotherapy regimen (n=12)

| Regimen (Drugs) | Frequency (n=12) |
|---|---|
| Vincristine, Etoposide, Carboplatine (VEC) | 8 |
| Vincristine, Etoposide, Carboplatine (VEC), Cisplastine (added) | 2 |
| Vincristine, Adriamicine, Ciclophosphamide (VAC) | 1 |
| Vincristine, Adriamicine, Ciclophosphamide (VAC) Actinomicine(added) | 1 |
| Total | 12 |

The patients that had cisplastine (2) added in the previous regimen underwent exenteration and histology showed resection margin involvement.

## DISCUSSION

The cases found resided in 7 different provinces of Mozambique. No cases were found in Beira and Nampula most likely because there are referral central hospitals with ophthalmologists in the regions. Majority of the patients (54.4%) were referred from other provinces (Gaza, Inhambane, Zambezia, Tete, Niassa and Cabo Delgado) to MCH, probably due to unavailability of tertiary care like chemotherapy in these regions.

In Mozambique, this study has showed an overall mean age at presentation of 30.5 months (CI 24.6 - 36.0, SD 21.5) being comparable with what was found in developing countries.

The mean age at presentation in bilateral cases was 26.4 months (SD 24.8), median: 18.0 while in unilateral cases it was 30.2 months (SD 20.9), median: 24.0. We noted that bilateral cases presented younger than unilateral cases, although both groups presented at older ages compared with developed countries, with an average delay from onset of symptoms to presentation of 6.9 months. The older age at presentation found in this study is in keeping with other African studies done which had also shown an older age at presentation (for bilateral and unilateral cases) [3,16, 17] been attributed to late presentation with advanced disease, older age at presentation, seeking of alternative means of healing before coming to hospital, delay from diagnosis to management[3, 18]. Other factors for poor prognosis found included proptosis, tumor recurrences, extraocular disease on histology and metastatic disease; lack of disease awareness among the population and healthcare professionals, difficulty accessing healthcare, fear of enucleation, lack of resources in the health facilities (lack of well-established tertiary care centers) and high costs of hospital care are correlated factors[3, 17, 19-21].

Based on the laterality, in this study most of the patients had unilateral retinoblastoma (47, 82.4%) while only 7 patients (12.3%) had bilateral retinoblastoma. We did not find any patient with trilateral retinoblastoma. Few patients were found to have bilateral retinoblastoma probably due to poor screening of fellow eyes and this may have missed some bilateral retinoblastoma, only 1 patient was noted to have the EUA done on the fellow eye as part of the patients work-up. The findings for bilateral retinoblastoma is less than what is generally found in different studies over the world where bilateral cases usually occur in 30-40% and unilateral cases in 60% -70% of cases[1]. Another study that also found less proportion of patients with bilateral retinoblastoma was by Nyaka *et al*[22], in Malawi; in this study bilateral retinoblastoma was found in 17.6% of patients and unilateral retinoblastoma in 82.4%. In Kenya the studies done had figures almost closer to what is generally found in developed countries, where Nyamori *et al*[16] found that most cases had unilateral retinoblastoma (74.2%) and bilateral retinoblastoma was found in 25.8%, also Nyawira *et al*[3] found unilateral retinoblastoma in 72% of cases and bilateral retinoblastoma in 28% of cases, as well as in Uganda where Waddell *et al*[23] found bilateral retinoblastoma in 26% of cases.

Sex ratio was almost equally represented among the patients with an F:M ratio of 1.2:1 with no statistical significant difference between females and males (p- value of 0.570). Overall, many studies in developed and developing countries show that there is no difference in the distribution between males and females[2, 3, 16, 22, 24, 25].

Generally family history is present in only 5% of retinoblastoma patients[1]. In our study the family history was not recorded in majority of the patients (94.1%) attributed to a poor recording of family history data. We only noted a positive family history in 1 patient (2.9%). Nyaka *et al* [22] also found only 1 patient with positive family history but other studies found family history to be reported in more cases: Nyamori *et al*[16](4.5%), Makite *et al*[18] (6.3%) and Nyawira *et al*[3](8.5%).

Majority of the patients presented with white reflex (62.5%), but half of the patients presented also with advanced disease (proptosis, 50%) and three patients (8.8%) had recurrent orbital disease. This was more than what was reported in other studies in the region, who also found advanced disease at presentation, example in Malawi by Nyaka *et al*[22] (30.9%) and Kenya by Nyamori *et al*[16](21.1%) and Nyawira *et al*[3] (20%). The main factors we found to be associated with proptosis at presentation were: Old age at presentation, patients been coming from other provinces, time delay from initial symptoms to diagnosis.

Ultrasonography is a cost effective diagnostic modality in retinoblastoma with high sensitivity in detecting intraocular calcifications of retinoblastomas[26-28], although few patients in the study (14.7%) had ocular ultrasound done with findings suggestive of retinoblastoma. The MRI was also done in a few patients (14.7%) where 4 patients had extraocular mass extension (3 had optic nerve invasion by histology and 1 did not have surgery done because parents declined) and intracranial extension was found in 1 patient (This was a 4 year old child that underwent enucleation and tumor was noted at the resection margin). Nyaka *et al*[22] found 4 patients with extraocular mass and 1 patient with intracranial extension on the CT scan and Nyawira *et al*[3] found around 4 patients had evidence of intracranial extension on the CT scan.

The most common histopathologic high risk factors reported in this study were optic nerve involvement (54.9%) and resection margin involvement (33.3%). The optic nerve was recorded as "Optic nerve difficult to recognize or not identifiable" in 9.8% of the eyes, possibly pointing to poor specimen handling, preservation (not put in formalin immediately such that it undergoes decomposition before it reaches a pathologist) as well as poor processing and identification of the eye structures during histopathologic analysis. We also found periocular tissues involvement in 33.3% of the eyes, guiding to a high possibility of extraocular involvement. On the other hand, majority of the patients did not have documentation of choroid and sclera (96% and 98% respectively). Also none of the patients had documentation of the Cerebrospinal Fluid (CSF) and Bone Marrow Aspirate (BMA) cytology.

In Kenya, Nyawira *et al*[3] also found a significant but less proportion of patients with optic nerve involvement (24%) and resection margin involvement (21%). They also found retrolaminar with resection margin free in 3%, choroid extension in 10.4% and extraocular disease in 37% of the patients; the extension of the tumor was not indicated on the histology of 13.3% patients. While in Uganda, Waddell *et al*[23], found more proportion of cases (45%) had extraocular tumour.

In USA, Uusitalo *et al*[15], found a higher number of cases (63.5%) with optic nerve involvement, 13.4% had tumor extension beyond the lamina cribrosa, but fewer patients (4.8%) had involvement of the resection margin. They also found choroid involvement in 33.3% of patients and 2.3% of cases had tumor invading the sclera. One patient with tumor extending to the surgical margin of the optic nerve died of metastatic disease[15].

Histology results have an important role in the management of retinoblastoma patients and in predicting the prognosis. The major histopathologic prognostic factors to take in consideration for the disease dissemination are usually patients with massive choroidal involvement, scleral or extrascleral involvement and optic nerve involvement beyond the lamina cribrosa (retrolaminar). Involvement of the resection margin is the major prognostic factor with a mortality rate of 50-81%. Anterior chamber or uveal structures infiltration are also important histopathologic high-risk factors for metastasis[4, 15, 19, 29, 30].

During the study period we identified 2 patients who died: One had resection margin involvement (associated with abdominal mass, severe anemia with blood dyscrasia) and in the other patient the optic nerve was difficult to identify on histology, with an MRI confirming involvement of optic nerve. Nyawira *et al*[3] also found a high number of patients who died (77) where (34; 44.2%) had extraocular disease; choroid invasion was found in 6 patients without sclera involvement and out of them 5 patients died after 3 years. Therefore they found a very low survival rate (26.6%) in the 3 year study period.

In this study, out of a total of 57 patients, 49 (86%) patients had surgery of which 45 (93.9%) patients had enucleation and 9 (18%) patients had exenteration. Three of the patients who had enucleation also underwent exenteration due to tumor recurrence.

A total of 8 patients (14%) did not have any intervention because the parents of five patients declined surgery and requested to be discharged probably to consult family members, two patients had advanced disease (No file available) and one patient was not ready because of severe anemia and respiratory infection. The number of patients who declined surgery was high showing the need of counseling of parents to understand the consequences, complications and prognosis of the disease.

According to various studies done all over the world, different indications for chemotherapy in retinoblastoma patients should include: Treatment of intraocular bilateral retinoblastoma (for globe salvage) [1,5,8-13,19], extraocular extension (orbital disease -proptosis) and the histopathology high-risk factors (massive choroidal involvement, scleral or extrascleral involvement and optic nerve involvement beyond the lamina cribrosa with or without involvement of the resection margin) [4, 14,15]. In this study only 34 patients had their files available to analyze the proportion of patients who received chemotherapy, out of which 23 patients (67.7%) were eligible for chemotherapy, but only 12 patients (35.3%) received chemotherapy, lower than what was found in other African countries: Uganda found 70 children had chemotherapy[23]. The other eligible patients for chemotherapy (11; 32.4%) based on the clinical and histological criteria did not received chemotherapy (due to unknown reasons, died, awaiting histology at that time). The other 11 patients with available files did not receive chemotherapy because 5 patients had no intervention (declined), 2 had no documentation of the optic nerve spread, 1 was sick and 3 did not have clinical and histological criteria for chemotherapy.

The criteria used in those patients who received chemotherapy were: Big orbital tumors with difficult surgical intervention, histological confirmation of optic nerve or resection margin involvement. But we noted that some other retinoblastoma patients with "proptosis" were awaiting surgery for histological confirmation of the disease before chemoreduction. Therefore there were no clear eligibility criteria for chemotherapy.

Also with the inadequate histology reporting in some of the patients (11.7%) and lack of EUAs in the other eye, it was difficult to determine who should have received chemotherapy or not, and is also possible that some deserving patients missed chemotherapy with fatal consequences. There was no patient on salvage therapy for the other eye (like: laser therapy, cryotherapy, laser hypothermia or brachytherapy), could be because they were never picked early by routine EUAs.

In the study out of the 12 patients who were on chemotherapy, 8 patients received Vincristine, Etoposide and Carboplatine (VEC). Two patients had cisplastine added to the regime of VEC; these were patients who underwent exenteration and histology had shown resection margin involvement. The other two patients received adriamicine, ciclophosphamide, actinomicine; therefore there was no clear standard chemotherapy protocol.

There are no randomized clinical trials on the proper regimes in the management of retinoblastoma. However most centers (like in USA, Canada and India) use the VEC regime with a good success, having a high success: On enucleated eyes with high risk features on histopathology[4,14,15] and adjuvant chemotherapy treatment for intraocular retinoblastoma[4,11,13,31]. Honovar *et al*[4], for example has a protocol in the management of retinoblastoma where patients with high histopathology risk factors should do a baseline systemic evaluation for metastasis and standard 6 cycle of adjuvant chemotherapy. In patients with extraocular extension, scleral infiltration, and optic nerve extension on the resection margin should be given a high dose adjuvant chemotherapy and orbital external beam radiotherapy.

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