INTRODUCTION

Retinoblastoma is the most common primary ocular malignancy of childhood. It is the most common paediatric ocular tumour in Pakistan as well.\(^1\) Worldwide, about one case of retinoblastoma (Rb) is recorded per 15,000 – 20,000 live births.\(^2\) With the advent of new and better diagnostic and treatment modalities, the outcome of retinoblastoma has improved tremendously in developed countries. In contrast to the previous management protocols, where enucleation and external beam radiation was considered pivotal in management of Rb, more emphasis is now being paid to focal therapies and chemotherapy. This has led to improved outcomes in terms of globe survival and patient survival. Over the last decade, the documented survival rate of Rb patients has reached to above 87 – 99% in developed countries.\(^3\)

In this era of improvised therapies, the underdeveloped countries are still facing many challenges in the management of retinoblastoma. Data on pattern of presentation and metastasis,\(^4,5\) epidemiological aspects\(^6,8\) and Rb among histopathological audits are available in literature from Pakistan. However, the assessment of results of current therapeutic methods in the Pakistani population has not been presented earlier.

METHODOLOGY

This study was conducted prospectively at a tertiary care eye hospital in Pakistan. Consecutive patients, diagnosed with retinoblastoma were enrolled between January 2006 and December 2009. All demographic details including age at presentation, gender, age at the onset of symptoms, laterality, presenting symptoms and family history of retinoblastoma were recorded. Following initial ocular examination in the clinic, complete ophthalmic examination under anaesthesia including fundus photography by Ret Cam (Massie Labs) was done. Ophthalmic ultrasound and computerized tomography of the brain and orbit was done for every patient.

The aim of this study was, therefore, to determine the clinical presentation and outcome of prevalent management for retinoblastoma at the tertiary care eye hospital in Rawalpindi, Pakistan.
thecia every month. External beam radiotherapy (EBRT) was given in the cases where after maximum chemotherapy and focal treatment the tumour did not fully regress or there was optic nerve involvement or extrascleral extension of the tumour.

In the eyes with ICRB group-A and B cryotherapy or indirect laser photocoagulation was performed, depending on the tumour location. In patients having bilateral involvement, Group-A tumours also received chemotherapy along with focal treatment in specific cases having worse ICRB staging in the fellow eye. Group-B eyes with macular retinoblastoma also received chemotherapy in addition to focal treatment.

All group-E eyes were offered primary enucleation. In the presence of adverse histopathological features like invasion of anterior segment, retrolaminar invasion of optic nerve, invasion of choroid greater than 2 mm, scleral or orbital invasion, 6 cycles of chemotherapy were continued postoperatively to prevent metastasis. Exenteration was done in the cases where there was extra ocular extension of the tumour.

Data was analysed with the help of Statistical Package for Social Sciences (SPSS) for windows software. Descriptive statistics were obtained as mean ±SD for time in months and age, frequencies in percentages were presented for sex, unilateral or bilateral disease, number of case per year, mode of presentation, number of eyes having different classification of retinoblastoma, mode of treatment used for each involved eye and the outcome of treatment described in terms of globe survival and patient survival. Globe survival was defined as globe salvaged compared to enucleation or exenteration of the globe. Kaplan-Meier test was applied for globe survival analysis across different ICRB groups. Patient survival was taken as a minimum of one year of tumour-free survival.

RESULTS

One hundred and seventy-seven eyes of 139 patients were enrolled in this study. The number of eyes with Rb that presented in each year were 57 (32.2%) in 2006, 48 (27.1%) in 2007, 37 (20.9%) in 2008 and 35 (19.8%) in 2009. There were an average 34.75 new cases with Rb each year (2.9 cases per month).

One hundred and one (72.7%) cases had unilateral involvement and the remaining 38 (27.3%) patients had bilateral tumours. Among the patients with bilateral disease, 24 (63.2%) were males and 14 (36.8%) were females, while among unilateral cases, there were 44 (43.6%) males and 57 (56.4%) females. The mean age of presentation was 24.05 ± 10.74 months (ranging from 6 to 50 months). It was 25.78 ± 10.66 months (ranging from 9 to 50 months) in unilateral cases and 19.47 ± 9.67 months (ranging from 6 to 45 months) for bilateral cases.

Family history for retinoblastoma was positive in 7 (5%) patients. Among these 5 (13.15%) children had bilateral Rb and 2 patients (1.98%) had unilateral tumours. In addition, parents of 3 patients with bilateral Rb were diagnosed with retinomas. The mean follow-up duration was 18.96 ± 18.40 months.

Leucocoria was the most common presenting sign in 78 (44.1%) eyes, followed by fungating mass, enlarged or ruptured globe seen in 38 (21.5%). Strabismus was seen in 22 (12.4%), uveitis in 18 (10.2%) and buphthalmos in 8 (4.5%) eyes. Eight (4.5%) eyes presented with decreased vision and 5 (2.8%) eyes with phthisis bulbi.

Group-A tumour was diagnosed in 6 eyes of patients with bilateral involvement, group-B in 14 eyes of patients with bilateral tumours, group-C in 2 unilateral cases and 10 eyes of patients with bilateral lesions, group-D in 8 unilateral cases and 2 eyes of cases with bilateral Rb, while group-E tumours were seen in 91 unilaterally involved eyes and 44 eyes of patients with bilateral involvement.

Different treatment modalities were used in 160 eyes (Table I). Among 17 eyes that did not receive treatment for different reasons, one belonged to ICRB group-A, 2 to group-C and 14 were group-E eyes. Enucleation was done in 112 (70%) of the treated 160 eyes. Among them in 19 (16.96%) eyes only enucleation without adjuvant therapy was performed. Exenteration was carried out in 12 (7.5%) of the 160 eyes that received treatment. All of them were given adjuvant chemotherapy, while 2 (16.66%) of the post-exenteration orbital sockets also received radiotherapy.

The patient survival was 66.2% (n = 92) who were tumour-free for at least one year after completion of treatment. Out of the 92 surviving patients, 64 (69.57%) had unilateral and 28 (30.43%) had bilateral retinoblastoma. Twenty four patients died during the study.

<table>
<thead>
<tr>
<th>ICRB group</th>
<th>Focal</th>
<th>Focal + chemotherapy</th>
<th>Enucleation</th>
<th>Enucleation + adjuvant therapy</th>
<th>Exenteration + adjuvant therapy</th>
<th>Total No. of eyes</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4</td>
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<td>0</td>
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<td>C</td>
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<td>10</td>
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<td>0</td>
<td>0</td>
<td>10</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>9</td>
<td>0</td>
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</tr>
<tr>
<td>E</td>
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<td>7</td>
<td>19</td>
<td>84</td>
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</tr>
<tr>
<td>Total</td>
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<td>35</td>
<td>19</td>
<td>93</td>
<td>12</td>
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</table>
period and 23 patients were lost before one year of follow-up.

Seventeen (70.8%) out of the 24 cases that died had advanced retinoblastoma with optic nerve and or anterior segment involvement and extensive metastasis at initial presentation. Four (16.7%) patients initially presented with small tumours but soon defaulted and went for alternative medicines or visited quacks. They later came back with fungating mass and extensive metastasis with eventual fatal outcome. Two (8.3%) of the patients died during chemotherapy due to disseminated intravascular coagulation or other chemotherapy related complications. One (4.2%) patient of unilateral retinoblastoma presented with orbital tumour in the enucleated socket 3 months after the completion of chemotherapy and died shortly because of metastasis.

The mean time lag between the age of presentation and the time when parents first noticed the symptoms was 5.63 ± 3.79 months in those who eventually showed tumour-free survival. It was 13.79 ± 6.91 months in those who eventually died during the study duration.

Two eyes of 2 patients developed retinal detachment after completion of treatment for which vitrectomy with silicon oil was done. One patient remained well with ambulatory vision while the other developed repeated retinal detachment due to tumour progression, for which secondary enucleation was done. At the end of study period, the globe was salvaged in 36 (22.5%) of the 160 eyes that received treatment, mostly belonging to group-A and B. Among the 36 salvaged globes, 28 (77.8%) were the other eye of the bilateral Rb cases and 8 (22.2%) eyes had unilateral retinoblastoma. Kaplan-Meier curve showing globe survival in different ICRB groups as shown in Figure 1.

DISCUSSION

Although retinoblastoma has been mentioned in studies analyzing histopathology data,9-11 This study reports the outcome of current treatment, which has not been documented before from our part of the world. The mean age of presentation in these patients was 24.05 ± 10.74 months. This is comparable to that reported by Naseripour et al.12 In this study, it was 25.78±10.66 months in unilateral cases and 19.47 ± 9.67 months for bilateral cases. Another report by Lee et al. mentions19.65 months as age at presentation which is less than that noted in the present study.13 The mean lag time between first noticing the symptoms and initiation of treatment was much greater in these patients and this might be the reason for lesser globe survival and patient survival in this study. Twenty three (16.5%) patients who were lost to follow-up before one year of age, may also have contributed to the lesser patient survival. The diagnostic delay is associated with greater risk of local tumour spread.14 In this study, patients born to educated parents and those having a positive family history reported early. This reflects the need for better health education in our community.

In this study, the number of new cases of retinoblastoma, who presented each year in a single institute, was greater than many of previous studies. It was 9.33 according to Bonanomi et al.,15 Naseripour et al. reported 16.57, Chantada et al. documented 31.67,12,16 while Shanmugam et al.17 recorded 25.36 new cases each year compared to 34.75 new cases each year according to this study.

The most common presenting symptom in this study was leucocoria. Frequency of leucocoria as the commonest presenting feature is much less in a published report where proptosis is the second commonest sign.17 Badhu et al. reported proptosis to be most common mode of presentation in Nepal (90.70%).19 According to Menon et al. it was the second most common presentation in Malaysian (22%) children.20

Among the 101 unilateral cases, 91 eyes (90.1%) presented with advanced stage of disease (ICRB-E) while 44 (57.9%) eyes of bilateral cases presented with advanced disease in at least one eye and variable stage tumour in the other eye. This is consistent with reports from other developing countries.21

The news of cancer itself brings in great stress for parents of children with retinoblastoma, be it a developed or underdeveloped country. To avoid the physical and cosmetic deformity of enucleation, parents in underdeveloped countries revert to quacks. When they finally come back to the hospital, the patients have advanced disease that greatly increases the morbidity and mortality associated with it. Enucleation or exenteration and subsequent chemotherapy require repeated inpatient stays with consequent disruption to
normal domestic and working life. This problem has also been narrated by other researchers.13,22

In developed countries, there is an increased trend towards globe salvaging treatments of retinoblastoma, as reported by Dondey et al.23 Lee et al.13 and Shields et al.24 In underdeveloped countries, the globe survival rates are considerably lower. In this study, the globe survival rate was only 22.5% at the end of study duration. Globe survival was 44.2% in an Iranian study,12 and 32% in a Malaysian study.20 This again is attributable to late presentation and poor health education in developing countries. One patient in the present study was diagnosed with a new retinoblastoma lesion in the fellow eye, 9 years after one eye was enucleated in infancy.25 The need for strict adherence to follow-up should be highlighted to detect such rare cases of late bilateralization. Most of the patients in this study were from the north and central parts of the country.

We believe that incidence of Rb in this area of Pakistan is much higher than reported worldwide but due to lack of good health services and referral system, it is impossible to know the true scenario. The need of the hour is to work in a cooperative group and develop an intensified national early detection program as well as a treatment protocol. Educating parents and physicians is required to improve clinical outcome with less morbidity and mortality as survival in retinoblastoma patients will be increased only by earlier diagnosis and better treatment adherence.26

CONCLUSION

Most children with retinoblastoma showed an advanced stage of tumour at the time of diagnosis in this study. Although they were treated with an updated therapeutic approach, the rate of globe preservation did not reach that of developed countries.

REFERENCES
