

EXTENDED REPORT

A multicentre report from the Mexican Retinoblastoma Group

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Background: Retinoblastoma (RB) is a relatively uncommon tumour in childhood. The incidence of retinoblastoma in Mexico is probably higher than the incidence reported worldwide, however there is not enough information about the characteristics of this illness in Mexico. This report aims to present the results of a multicentre clinical survey of RB in Mexico.

Methods: A retrospective study was carried out on all RB cases treated in 16 institutions during the last six years. The variables analysed were age at diagnosis, sex, affected eyes, treatment modalities, and pathological staging. Overall survival was obtained.

Results: The authors analysed 500 cases; age range was 0–182 months. There were 364 unilateral cases (72.8%). Enucleation was performed in 84.9% of the patients. The St Jude's staging was: 7.4% stage I, 52.8% stage II, 18.0% stage III, 11.4% stage IV, 7.2% not evaluated, and 3.2% missing data. Chemotherapy was used in 74.4% of the patients. Disease free survival was 89% at 73 months follow up.

Conclusions: The paper presents a great number of cases and pioneers multicentre studies in paediatric ophthalmology and oncology in this country. Given the great number of patients in advanced stages and the variability on treatment schemes, it is evident that it is mandatory to work in a cooperative group and develop a national early detection programme as well as a treatment protocol which include all specialists involved in the care of patients with RB.

Retinoblastoma (RB) is the most common malignant ocular tumour in childhood.¹ In the United States the incidence is 11 new cases of RB per million population under 5 years of age.² In developing countries, most of the cases are detected at advanced stages.^{3–5} At the present time, nearly all patients diagnosed during the early stages can achieve a prolonged disease free survival,⁶ and at least 50% of the affected eyes can be preserved.⁷ In Mexico, RB may represent the second most frequent malignant solid tumour in paediatrics.⁸ However, there is no accurate information regarding the frequency and clinical characteristics of RB in the country. In a previous study we reported a series of 552 patients from a single institution.⁹ The study included patients diagnosed over a period of 15 years, with a minimum follow up of 4 years. The institution studied was a national reference hospital; most of those patients were from the southeast and central parts of the country, so the results presented in that report may not represent the clinical characteristics of retinoblastoma in Mexico.

The purpose of this paper is to present the results of a multicentre study on the frequency and clinical characteristics of RB in Mexican children around the country.

MATERIALS AND METHODS

A multicentre, retrospective, and descriptive study was carried out. Sixteen Mexican centres provided information on patients with RB diagnosed between 1 January 1997 and 31 December 2002. The contributing centres were as follows (number of patients shown in brackets): Centro Estatal de Cancerología de Jalapa (4); Centro Médico de Occidente, IMSS Jalisco (13); Centro Médico La Raza (41); Centro Médico Nacional SXXI (43); Hospital Civil de Durango (2); Hospital Civil de Guadalajara (24); Hospital del Niño

Morelense (10); Hospital del Niño Oaxaqueño (13); Hospital General de México (21); Hospital Pediátrico de Sinaloa (12); Hospital Infantil de México Federico Gómez (54); Hospital Central Universitario de San Luis Potosí (12); Hospital del Niño de Villahermosa (9); Instituto Nacional de Pediatría (229); Instituto Materno Infantil de Estado de México (7), and Hospital O'Horan de Mérida (6).

Recorded data included age at diagnosis, date of diagnosis, ocular affection (unilateral or bilateral) at diagnosis, stage at diagnosis according to St Jude's staging system,¹⁰ treatment modalities used (radiotherapy, surgery, and chemotherapy), and date of last visit. The survey did not consider information regarding second malignancies and treatment related deaths. The status of the patient evaluated by clinical examination and/or radiological studies at last visit was considered to be: alive with no evidence of disease; alive with active disease (patients with neoadjuvancy were considered in this group); dead with no evidence of disease, and dead with active disease.

Statistical analyses were performed using the SPSS system (SPSS for Windows 10.0; SPSS Inc, Chicago, IL, USA). Descriptive statistics for each variable were obtained. The Kaplan-Meier method with log rank test was used to determine overall survival. Differences between groups were considered significant when two sided p value was <0.5.

RESULTS

Between January 1997 and December 2002, a total of 500 patients were diagnosed with RB in the participating centres (mean 83.3 new cases per year). Figure 1 presents the number of patients per year; 262 were male and 238 female

Abbreviations: RB, retinoblastoma.

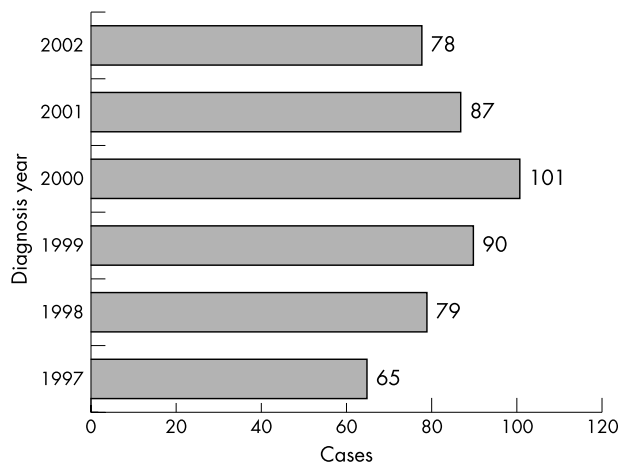


Figure 1 Frequency of new patients per year.

(M:F ratio 1.1:1.0). The age at diagnosis ranged from 1 day to 182 months, with a mean of 27.68 months (median 24). Initial ocular presentation was unilateral disease in 364 (72.8%) and bilateral disease in 136 (27.20%) patients. Mean age at diagnosis for unilateral cases was 30.96 months (median 28), whereas mean age for bilateral cases was 18.87 (median 14).

Most of the centres did not provide information concerning the ocular stage at diagnosis (Reese-Elsworth staging system); therefore this data is not included in the report. Stage at diagnosis (St Jude's staging system) is presented in table 1, showing that almost 30% of the patients were diagnosed at advanced stages. Approximately 13% of the cases could not be staged due to multiple causes such as neoadjuvancy, incorrect management of the enucleated eye, or insufficient material of the optic nerve.

Treatment

The treatment modalities were mainly surgery, chemotherapy, and radiotherapy. Enucleation was performed in 87.62% of the patients (table 2). External radiotherapy was used in 131 patients (26.2%); the indications for this treatment modality were adjuvant therapy in orbital or metastatic disease and eye rescue for bilateral disease when vitreous seedlings were present. The stage at diagnosis for radiated patients is presented in table 3. Among radiated patients 57 were bilateral. Seventy nine patients with bilateral disease were not radiated because the preserved eye had an early ocular stage and did not need this modality.

Chemotherapy was applied in 372 (74.4%) patients. The indications for chemotherapy were: in 37 patients neoadjuvancy for eye preservation; adjuvant chemotherapy in 147

Table 1 Stage at diagnosis

St Jude's stage	Unilateral		Bilateral		Total	
	Frequency	%	Frequency	%	Frequency	%
I Limited to retina	22	6.0	15	11.0	37	7.4
II Limited to the eye	194	53.3	70	51.5	264	52.8
III Limited to the orbit	75	20.6	15	11.0	90	18.0
IV Metastatic disease	44	12.1	13	9.6	57	11.4
Not classifiable	19	5.2	17	12.5	36	7.2
Missing data	10	2.8	6	4.4	16	3.2
Total	364	100.0	136	100.0	500	100.0

Table 2 Surgery modalities used

	Unilateral	%	Bilateral	%
No surgery				
Rejects surgery	5	1.4	9	6.6
Eye preservation	9	2.5	14	10.3
Unilateral enucleation	330	90.6	97	71.3
Bilateral enucleation	0	0.0	11	8.1
Unilateral exenteration	17	4.7	5	3.7
Missing data	3	0.8	0	0.0
Total	364	100.0	136	100.0

patients in advanced stages (orbital and metastatic disease), and 188 patients with ocular disease (in many centres their chemotherapy protocol still considers its use necessary). More than 15 different regimens were used by the participating centres (table 4). Twenty one per cent (106) of the patients received chemotherapy based on cyclophosphamide and doxorubicin, 50.6% (253) received chemotherapy based on cisplatin or carboplatin plus other drugs, and 2.6% (13) received treatment based on research/new drugs protocols or miscellaneous schemas. Twenty three per cent of the patients did not receive chemotherapy agents.

The calculated overall survival was 85% at 73 months of follow up; the mean survival time was 23.1 months (median 19.4). Figure 2 presents the overall survival by stage.

DISCUSSION

In Mexico, retinoblastoma is the second most frequent solid malignancy in paediatric patients, the most frequent being central nervous system tumours.¹¹ Several centres that treat RB in Mexico did not participate in this survey so the number of cases of RB in Mexico could be higher than reported here. Hurwitz has suggested that the number of new cases per year could be higher in developing countries than in developed.¹² However, with the data collected thus far we could not support this hypothesis.

As mentioned above, 45.8% of the patients were treated in a single institution (Instituto Nacional de Pediatría). This situation could be related to many factors: firstly, it is a national reference centre; secondly, for many years it was one of the few centres in the country for the treatment of retinoblastoma, and even now that other centres are working, ophthalmologists and general practitioners do not refer patients to other centres; finally, because many non-profit organisations support treatment in this centre but not in others. One of the aims of the retinoblastoma group is to create a national reference programme to better distribute the medical attention for RB patients, and reduce the risk of lost follow up by minimising the costs of transportation to the treatment centres.

The mean age at diagnosis was similar to what we reported in our previous study,⁹ and higher than that reported in other series from developed countries.¹³ Diagnosis at older ages seems to be a common finding in developing countries.¹⁴ In

Table 3 Radiated patients: stage at diagnosis

St Jude's stage	Frequency	%
I Limited to retina	4	3.05
II Limited to the eye	31	23.67
III Limited to the orbit	47	35.88
IV Metastatic disease	25	19.08
Not classifiable	17	12.98
Missing data	7	5.34
Total	131	100.0

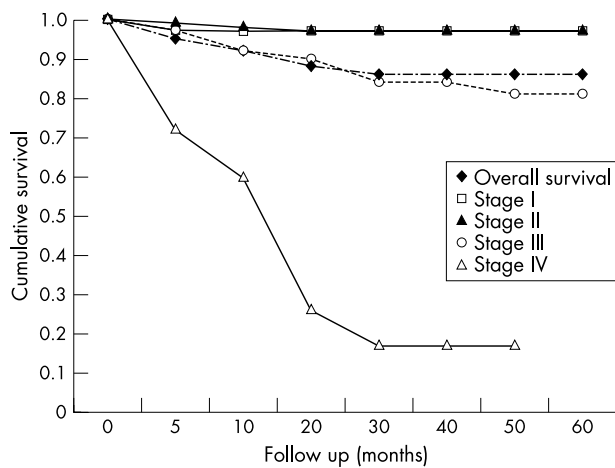


Figure 2 Overall survival by St Jude's stage (log rank 188.9, df=4, significance 0.00001).

our previous study about 47% of the patients presented in advanced stages; in contrast, in the present report only one third of the patients were diagnosed at advanced stages (St Jude's stages III and IV). In any case, these data suggest the need to develop a national early detection programme. Such a programme would permit us to decrease the number of patients with advanced extra ocular disease and offer less aggressive treatments at lower costs.

The distribution by affected eye is similar to our previous report and other international reports.¹⁴ Unfortunately, we do not have reliable data concerning the kind of community (rural or urban) where the patients come from, but this issue should be evaluated in a prospective study as there are reports of a higher prevalence of the disease in rural communities.¹⁵

Chemotherapy regimens used reflect the evolution of treatment of RB. Some centres are still using the regimens proposed by the Paediatric Oncology Group in 1972^{10, 16}; other centres have modified their treatments to include drugs such as carboplatin plus VP 16, and in a few centres new drugs such as taxol, irinotecan, and other new agents are being tested in metastatic disease. Even the indications for chemotherapy vary among centres; in some of them chemotherapy is still used for patients in stage II. One of the aims of the Mexican Retinoblastoma Group is the

development of a national treatment protocol, which would enhance the medical care of these patients and would open the possibility to perform controlled clinical trials.

The survival of this series of patients is similar to other large series reported before,^{13, 16} nevertheless the follow up is still short. In comparison with our previous report, this series presents higher survival rates for stages II and III. Schwartzman *et al*¹⁶ from Buenos Aires, reported similar overall survival rates (84%). Antoneli *et al*¹⁷ from Sao Paulo, and Chantada *et al*¹⁸ from Buenos Aires, report similar survival rates for orbital and metastatic disease. The common finding in all these series is the low survival rates for metastatic disease. As described above, the survival of our patients is similar to other series from Latin America; however the comparison between them is difficult as our follow up period is still short and the reports mentioned are from single institutions with more standardised treatments, whereas our report is a multicentre national study with a great diversity of chemotherapeutic regimens.

Given the number of new cases per year registered in this survey, RB is a frequent neoplasia in Mexico. It is necessary to create a national registry to understand the actual impact of RB in our country. The late diagnosis is a common problem in developing countries, and should be controlled to enhance prognosis and quality of life for these patients. In the same way, treatments need to be standardised so that every centre can offer the best available treatments at the lowest cost for patients. There is a lot of work to be done; nevertheless survival for RB patients in Mexico is similar to what has been reported in other series.¹⁶⁻²⁴

This survey is relevant not just because of the data obtained, but because is the first attempt to work in a cooperative multicentre group in paediatric oncology in Mexico.

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Table 4 Chemotherapy: drugs schema used

	Frequency	%
VCR-CFX	28	5.6
VCR-ADR	4	0.8
VCR-CFX+ADR	72	14.4
VP16+CFX	2	0.4
CDDP+VP16+CFX	7	1.4
Carboplatin+VP16+CFX	54	10.8
Carboplatin+VP16+VCR	20	4.0
Carboplatin+VP16	129	25.8
CDDP+VP16	10	2.0
Carboplatin	16	3.2
Carboplatin+VCR	5	1.0
Carboplatin+VP16 Altering VCR-CFX	9	1.8
ICE	3	0.6
Taxol	2	0.4
Irinotecan	3	0.6
Miscellaneous	8	1.6
No chemotherapy	116	23.2
Missing data	12	2.4
Total	500	100.0

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