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The aim of this study was to look at the visual outcome and treatment complications of children diagnosed with Retinoblastoma during the years 1985-2003 inclusive. A retrospective review of all patients records was performed. Patient characteristics, treatment methods and complications were recorded. Twenty eight children presented to Temple street Hospital between 1985-2003. Six of these infants had bilateral tumours. The mean age at presentation was 23.7 months. Sixty-nine percent presented with Leucocoria, of these 33% also had a squint. The mean duration of symptoms was only known in 58% and this gure was approximately 19.8 months. Enucleation was performed in 24 eyes of 24 patients. Three patients required adjuvant chemotherapy post enucleation. Two eyes was treated with external beam radiation and one eye with plaque radiotherapy. One eye (second eye) was treated with systemic chemotherapy and radiation. Five eyes of three patients were treated with systemic chemotherapy followed by adjuvant Arg

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Introduction

Retinoblastoma is the most common orbital malignant tumour of childhood with an incidence worldwide that ranges from 1 in 14,000 live births to 1 in 34,0001. The tumour is typically diagnosed during the rst year of life in familial and bilateral cases and between 1-3 years in sporadic unilateral cases. As survival now approaches 90-95% the recent emphasis has been on treatment strategies that preserve vision in place of the traditional treatment of enucleation for all patients with retinoblastoma. Tumour reduction by rst line chemotherapy followed by local treatments is now accepted as a means of avoiding enucleation +/- ext beam radiation. Our study, which spans two decades, is a retrospective review of visual outcome and complications of treatment of Retinoblastoma in Ireland.

Methods

A retrospective review was performed using the records of the ophthalmology department in Temple Street Hospital, Dublin. Included were children treated for retinoblastoma from 1985-2003 inclusive. The sex, age, mode of presentation, inheritance pattern and histology of tumour was recorded for all patients (Table 2 and 3). The visual outcome in the salvaged eye and the fellow eye of the enucleated group was also noted.

Table 1 Histological Grade of tumour in Retinoblastoma patients

Differentiation	No. of Patients
Well Diff.	3
Mod. Diff	4
Poorly Diff.	4
Undiff.	1
Unknown	1

The chemotherapeutic regime involved a combination of carboplatin, vincristine, etoposide and cyclosporin for an average of six cycles. The outcome of treatment in terms of mortality, complications and recurrence rate was recorded.

Table 2 Histological findings of prognostic significance in study population.

Differentiation	No. of Patients
Vitreous Seeding	9 Patients
Choroidal+Subretinal invasion	8 Patients
Glaucoma/Rubreosis	6 Patients
Invasion at Lamina Cribrosa	4 Patients
Invasion at resection margin	0 Patients

Results

Twenty eight children presented between 1985-2003.Ten females, eighteen males. Six of these infants had bilateral tumours- Four were diagnosed with bilateral tumours simultaneously and two patients had their second tumour diagnosed after the rst tumour had been treated. The mean age at presentation was 23.7 months. The age range was ve weeks to four years eight months. Sixty-nine percent presented with Leucocoria (gure 1), of these 33% also had a squint. Seventy-one percent of tumours were initially picked up by the parent of the affected infant having noticed a gross abnormality in the eye. Seven percent of tumours were diagnosed in hospital during an unrelated admission and a further 7% were diagnosed during screening. The majority of our patients were at an advanced stage at presentation. Eighteen patients were at stage ve and a further three patients were at stage four at time of presentation. The histological grade was not stated in a further six patients. The mean duration of symptoms was only known in 58% and this gure was approximately 19.8 months.

The epidemiology of the patients showed no regional predominance. The majority of patients were of non-germline inheritance , seven patients had a germline inheritance pattern. One patient had 13q delation (gure 2). CT brain and orbits was performed in all patients prior to surgery. We do not perform follow up orbital CT scans routinely. Prior to chemotherapy all patients had cerebrospinal uid analysis, total body

scan and bone marrow aspirate. We do not perform bone marrow examinations routinely in our patients.

Enucleation was performed in 24 eyes of 24 patients. Three patients required adjuvant chemotherapy post enucleation. The latter three children had invasion of tumour at the lamina cribrosa on histology. One eye of a bilateral case and one unilateral tumour was treated with external beam radiation alone. One eye (second eye) was treated with systemic chemotherapy and external beam radiation. One eye (salvaged) was treated with plaque radiotherapy in another centre.One eye of a bilateral case was salvaged in an American centre, the details of his treatment are unknown. Five eyes of three patients were treated with systemic chemotherapy followed by adjuvant Argon laser, cryotherapy and diode laser to each eye.

The complications of each treatment modality were recorded. The follow up ranged from 4 to 170 months. In the enucleated group(n=24) the following complications were recorded. Recurrent infection de ned as positive culture of organism from the wound and necessitating antibiotic treatment occurred in 45 %(n=11). Conjunctival dehiscence occurred in seven patients(29%).Most occurred in the short term (n=4) (mean;17 days); one medium term (mean;56 days) and two late term(mean; > 6 months). Four patients required a scleral patch graft and three patients required conjunctival resuturing. The implant was replaced by the same implant or another type of implant in 16%(n=4). Prosthesis became displaced recurrently in one patient (4%) and this patient required a mucous membrane graft to the inferior fornix. Orbital Haematoma occurred post enucleation in one patient. This same patient went on to develop Post enucleation syndrome requiring reconstructive surgery of the socket and a hard palate mucosal graft into the lower lid tract. Ptosis developed in one patient and this patient required a frontalis sling procedure.

In the group treated with eye conservation modalities, a cataract developed in two patients post radiation which subsequently required extraction. Growth retardation and recurrent sepsis was noted in one patient secondary to chemotherapy. A recurrence of tumour was noted in one eye of the group treated with chemotherapy and adjuvant laser/cryotherapy. This recurrence was treated with intensive laser and cryotherapy and is currently in remission(gure 3 and 4)
The visual outcome in the salvaged eyes was recorded.The most recent visual acuity of a child who had plaque radiotherapy was 6/5. Two children who had EBR had a recent visual acuity of 6/9 and 6/6 respectively. Of the three children who underwent the chemoreduction regime with focal treatment one child has good vision (6/7.5)in one eye and poor vision in the second eye. The visual acuity in the other two children was described as Poor and unassessable. The visual acuity in the fellow eye of the enucleated group was recorded also. Eleven patients had a visual acuity of 6/6 or better. Three patients had a visual acuity of 6/9. Two patients had a visual acuity of 6/12. One patient had a visual acuity of 6/18. The visual acuity was unknown in three patients. The number of examinations under anaesthetic performed varied widely depending on whether the tumour was unilateral or bilateral, the method of treatment and the complications of treatment. The mean number of EUAs performed on the unilateral enucleated group was 3.5. In comparison, the salvaged eyes treated with chemotherapy and local treatment required extensive follow up having a mean number of EUAs of 20.

There were no deaths in this series. There were no metastases outside the orbit and there was no occurrence of tumours secondary to treatment.

Discussion
The management of Retinoblastoma has evolved over the past decade through advances in new treatments such as chemotherapy and diode laser therapy. Timely diagnosis and treatment have contributed to a marked improvement in survival.[1] The retrospective nature of our study which spans two decades re ects this change.

Enucleation still remains an accepted therapeutic modality. Due to the advanced stage at presentation of the majority of the patients in this study enucleation was performed in 71% of the total number of eyes. Dividing our patients into those with a unilateral and a bilateral presentation we nd that our enucleation rate for unilateral cases was 91% but only 33% of eyes from the latter group. Looking at gures recently published from larger series the rate of enucleation in unilateral cases has been cited at 75% and 64% in bilateral cases.[2] According to this study these rates have stabilized in the past decade. However, more advanced tumours have maintained a higher enucleation rate of 79%(RE IV-V).[2]

The management of bilateral cases has generally been more conservative than the unilateral cases. Our study included six children with bilateral tumours(12 eyes). Eight eyes were salvaged to date. Four eyes had chemoreductive treatment and adjuvant local treatment. One eye had external beam radiotherapy. One eye had plaque radiotherapy. One eye had systemic chemotherapy and external beam radiotherapy.One eye had an unknown salvage treatment. Enucleation was performed for four eyes in four patients(33% of eyes). There was no case of bilateral enucleation. Cases with both eyes enucleated has been shown to have decreased from 24%(1974-1978) to 10% (1984-88) to 2% (1999-2001).[2] Bilateral cases that avoided enucleation in either eye increased from 4%(1974-1978) to 25%(1984-88) to 36%(1989-2001).Overall, the enucleation rate for bilateral tumours has generally stabilized at 64%.[2]

Twenty patients (71%) were referred to us having been noted to have an abnormality of the appearance of their eye by a parent. Two children(7%) were noted to have leucocoria during an unrelated hospital admission. Two patients were diagnosed following screening of the eye due to an identi ed genetic abnormality at birth.

Considering such a late presentation at an advanced stage, the role of screening at birth for any fundal abnormality may be valuable in the salvation of some eyes with Retinoblastoma. In California, eye screening has become a mandatory part of the paediatric examination.

Chemotherapy has resulted in excellent salvage rates in our series. Combined with local treatments such as laser and cryotherapy we have currently maintained an eye salvage rate of 100%. There was one recurrence within one year of treatment and this child is currently in remission following intensive treatment (Figure 3 and 4). All children treated with chemotherapy were treated according to The Toronto Regime. This regime involves a combination of carboplatin, vincristine,etoposide and cyclosporin. An average of six cycles are administered. This aggressive regime has seen excellent results in terms of tumour response and salvage rates even in the advanced tumours.

Despite nearly uniform agreement that newer protocols of chemoreduction are effective for intraocular retinoblastoma, there is still uncertainty regarding the number of chemotherapeutic drugs,[3-7] the number of cycles[4,6], the necessity of adjuvant cyclosporin to the protocols[9,10] and the long term effect of chemotherapy.[11]

Shields et al reported 100% and 78% ocular salvage rates when a chemotherapeutic regime consisting of carboplatin, vincristine and etoposide with adjuvant treatment was used in stages iv and v retinoblastomas respectively.[7]

Signi cant retinoblastoma volume reduction is vital for the effective application of local treatment. In a recent study chemotherapy was found to exhibit an earlier reduction in tumour volume than that of external beam radiotherapy.[12] Faster reduction in tumour volume and partial reduction in foveal involvement may allow for improved visual acuity outcomes and decreased amblyopia and strabismus.[12]

Systemic chemotherapy is not free of complications. Myelosuppression,febrile episodes, subsequent infections, gastrointestinal toxicity, dehydration and growth retardation are all serious side effects that can impact on the life of the child.[3,5,11] Secondary malignancy is also a potentially devastating side effect which may, as yet , be underestimated.

No treatment modality is without its side effects and complications. Our rate on conjunctival dehisence post enucleation has been of particular interest. An hydroxyapatite implant was used in all but one of the enucleations. We have uncovered a dehisence rate of 36.8% with this implant which is higher than previously published dehisence rates with this implant.[15] Four patients required scleral patching and three patients required resuturing of the conjunctiva.

Recurrent infection of the socket occurred in 45% of patients which led to hospital admission in some cases due to the development of preseptal cellulitis.
The other major complications such as ptosis and post enucleation syndrome though affecting just one patient each led to signi cant morbidity in terms of repeated hospital admissions and surgery.

Three eyes in our study were treated with external beam radiotherapy.This treatment modality has been associated with severe comlications such as cataracts, retinopathy,vasculopathy, facial deformities and neuropathy.[13,14] There were two documented cataracts in our series.

Though external beam radiotherapy has been shown to have good results in terms of eye conservation rates ,100% in one series[12] ,its associated complications has led to its loss of favour in recent times

In spite of the advanced stage at presentation of the majority of children in this series our results are encouraging. We had no deaths, no metastasis and no secondary tumours to date. Our total eye salvage rate was 29% with an enucleation rate of 90% in unilateral cases and 33% of bilateral cases. Two-thirds (66%) of eyes with bilateral tumours were salvaged. Though the salvage rate for RE stage 1-3 tumours has improved dramatically enucleation still plays a vital role in the treatment of advanced tumours. The use of Retcam imaging and Telemedicine in consultation with The Hospital For Sick Children, Toronto has allowed us to maintain a high standard of care in the treatment of this rare tumour and has allowed Irish children to be treated in Ireland.

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