



Nina Mikhailenko. *Fall Day*. Oil on canvas, 16" x 20".

*The clinical features, current methods of diagnosis, and trends in management for retinoblastoma in children are reviewed.*

# Diagnosis and Management of Retinoblastoma

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**Background:** *Retinoblastoma is a highly malignant tumor of the eye that manifests most often in the first 3 years of life.*

**Methods:** *Published articles were reviewed to evaluate the clinical features and current methods of diagnosis and to assess the trends in management.*

**Results:** *This malignancy leads to metastatic disease and death in 50% of children worldwide but in less than 5% of children in the United States and other developed nations with advanced medical care. Over the past decade, there has been a trend away from enucleation and external beam radiotherapy and toward chemoreduction followed by focal therapies. This is largely due to more effective chemotherapeutic regimens, improved focal treatment modalities, and the desire to avoid loss of the globe and/or exposure to radiotherapy. Chemoreduction and focal therapies are most successful for eyes with minimal to moderate retinoblastoma, with enucleation needed in less than 15% of cases. Eyes with very advanced retinoblastoma require enucleation in approximately 50% of cases.*

**Conclusions:** *Progress in the clinical recognition and management of retinoblastoma has led to high survival rates. Improved methods of treatment using chemoreduction and focal treatments without the need for external beam radiotherapy allow preservation of the eye in some cases, often with visual function.*

## Introduction

Retinoblastoma is the most common intraocular cancer of childhood.<sup>1,2</sup> It represents approximately 4% of all pediatric malignancies. It is estimated that 250 to 300 new cases of retinoblastoma are diagnosed in the United States each year, and 5,000 cases are diagnosed worldwide. Over 95% of

children with retinoblastoma in the United States and other medically developed nations survive their malignancy, whereas approximately 50% survive worldwide. This discrepancy is largely due to earlier detection in the United States and developed nations when the tumor is contained to the eye, whereas in underdeveloped regions, retinoblastoma is often detected after it has invaded the orbit or brain.

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## Genetics: Basic Facts

Retinoblastoma affects approximately 1 infant in 15,000 to 20,000 live births in the United States each year.<sup>1-3</sup> Most studies indicate that the incidence of retinoblastoma among the various geographic populations is relatively constant. The role of environmental influences in the development of this malignant intraocular tumor remains unclear. Prior to the 1860s, before the role of enucleation in the management of retinoblastoma was known, most cases of retinoblastoma proved fatal. At that time little was suspected about the inheritance patterns of this tumor because few patients, if any, survived to reproductive age. Later, as more patients survived and had children of their own, more evidence arose suggesting the hereditary nature of retinoblastoma.<sup>4,5</sup> It is now known that retinoblastoma can be inherited as a familial tumor in which the affected child has a positive family history of retinoblastoma or as a nonfamilial (sporadic) tumor in which the family history is negative for retinoblastoma. Approximately 6% of newly diagnosed retinoblastoma cases are familial and 94% are sporadic. All patients with familial retinoblastoma are at risk to pass the predisposition for the development of the tumor to their offspring, but the manifestations are only 80% penetrant.

Retinoblastoma is generally classified in three different ways: familial or sporadic, bilateral or unilateral, and heritable or nonheritable.<sup>6</sup> Clinically, we tend to use the first two classification schemes.<sup>7</sup> Thus, a case may be classified as unilateral sporadic, bilateral sporadic, unilateral familial, or bilateral familial. About two thirds of all cases are unilateral and one third are bilateral. Genetically it is simpler to discuss retinoblastoma with the latter classification of heritable or nonheritable. The three classification schemes, however, are interrelated. It is recognized that bilateral and familial retinoblastoma are caused by a germline mutation and are thus a heritable tumor. Unilateral sporadic retinoblastoma is usually not heritable. However, it is estimated that approximately 10% to 15% of children with unilateral sporadic retinoblastoma have a germline mutation. Genetic testing using DNA analysis of the patient's tumor and peripheral blood can help to identify those patients with germline mutation.<sup>8,9</sup> The retinoblastoma gene is located on the long arm of chromosome 13 (13q14). It is a large 4.73 kilobase message. An intact gene protects against expression of retinoblastoma. It is believed that the gene is a recessive suppressor gene and may play a role in cell growth and development. In order for retinoblastoma to develop, both copies of the gene at the 13q14 locus must be lost, deleted, mutated, or inactivated. If either the maternal or paternal copy of the gene that is inherited by an individual is defective, then that individual is heterozygous for the mutant allele. Tumor formation requires both alleles of the gene to be mutant or inactive. These two mutations correlate to the two "hits" theorized by Knudson<sup>10</sup> In 1971, he proposed the "two

hit" hypothesis to explain the events that are necessary for both heritable and nonheritable retinoblastoma. His theory was based on a comparative analysis of unilateral and bilateral retinoblastoma cases. He proposed that the development of any retinoblastoma was caused by two complementary chromosomal mutations. Each of these genetic events could occur randomly with a frequency of  $2 \times 10^{-7}$  per year. In the case of familial retinoblastoma, the initial event or "hit" was a germinal mutation that was inherited and found in all cells of the offspring. The second "hit" occurred sometime during development, and if it occurred in a somatic cell, such as a retinal cell, then retinoblastoma would develop. Therefore, in familial cases of retinoblastoma, all cells in the body are predisposed to possible tumor development since germline mutation ("first hit") has been inherited in all cells of the body, including the ovaries and testes. This may help to explain the high incidence of second nonocular tumors, such as osteosarcoma, seen in patients with familial retinoblastoma or bilateral sporadic retinoblastoma. The offspring in cases of familial retinoblastoma will likewise be predisposed because their germline mutation will be passed on. By contrast, in most cases of unilateral sporadic retinoblastoma, the "two hits" occur during development of the retina and both "hits" are somatic mutations. The rest of the body theoretically carries no higher risk to develop other tumors because these patients presumably have normal chromosomal structure elsewhere in the body.

## Genetics: 13q Deletion Syndrome

The retinoblastoma gene is located on the long arm of chromosome 13 (13q). The 13q deletion syndrome can manifest by several phenotypic abnormalities.<sup>6,8,9</sup> Many patients have minimal or no visible abnormality.<sup>10</sup> The characteristic findings include some degree of the following dysmorphic features: microcephaly, broad prominent nasal bridge, hypertelorism, microphthalmos, epicanthus, ptosis, protruding upper incisors, micrognathia, short neck with lateral folds, large, prominent, low-set ears, facial asymmetry, imperforate anus, genital malformations, perineal fistula, hypoplastic or absent thumbs, toe abnormalities, and psychomotor and mental retardation.<sup>11,12</sup> The midface of patients with 13q deletion is notable for prominent eyebrows, broad nasal bridge, bulbous tipped nose, large mouth, and thin upper lip (Fig 1). We reported a case of severe midline facial and central nervous system abnormalities in a child with 13q abnormalities that manifested retinoblastoma and holoprosencephaly.<sup>9</sup>

Karyotype analysis of children with these or other dysmorphic features may allow earlier detection of retinoblastoma. We have seen several cases of retinoblastoma that were initially suspected based on the recognition of the above dysmorphic features that prompted a karyotype analysis revealing a deletion in chromosome 13.

This finding subsequently prompted a retinal examination that revealed unilateral multifocal tumors in both cases.<sup>12</sup>

## Life-Threatening Problems

Children with retinoblastoma are at risk for three important, life-threatening problems including metastasis from retinoblastoma, intracranial neuroblastic malignancy (trilateral retinoblastoma), and second primary tumors.

### At Risk for Metastasis

Retinoblastoma metastasis, when it occurs, generally develops within 1 year of the diagnosis of the intraocular tumor. Those at greatest risk for metastasis show features of retinoblastoma invasion beyond the lamina cribrosa in the optic nerve, in the choroid (>2 mm dimension), sclera, orbit, or anterior chamber.<sup>13</sup> Eyes with invasion of the optic nerve or choroid generally demonstrate large retinoblastoma over 15 mm greatest dimension along with elevated intraocular pressure and total retinal detachment.<sup>14,15</sup> Patients with evidence of invasive retinoblastoma should be treated with chemotherapy for 4 to 6 months to prevent metastases; however, criteria for regarding the need for adjuvant chemotherapy remain unclear. In an analysis from our department, metastases were reduced from 24% in those without preventive chemotherapy to 4% in those with chemotherapy.<sup>13</sup>

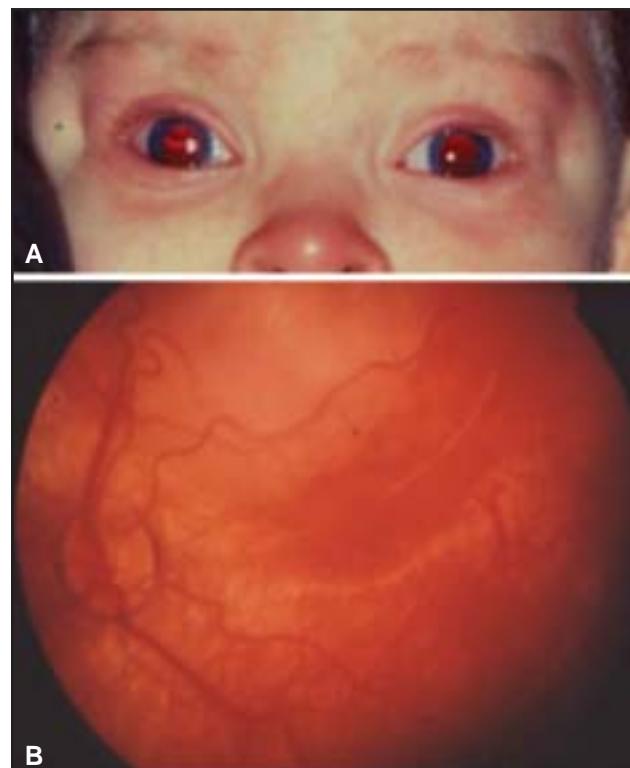


Fig 1. — Child with 13q syndrome. (A) Sixteen-month-old child with manifested developmental delay and characteristic facies of 13q deletion syndrome. (B) Unilateral retinoblastoma was later discovered in this patient. The tumor was successfully treated with plaque radiotherapy.

### At Risk for Neuroblastic Intracranial Malignancy (Trilateral Retinoblastoma)

There is an association of neuroblastic intracranial malignancy in patients with the hereditary form of retinoblastoma, most often manifesting as pineoblastoma or other parasellar tumors.<sup>16</sup> The pineoblastoma is identical to retinoblastoma from an embryologic and pathologic standpoint.<sup>16-19</sup> This association of midline intracranial pineal tumors and suprasellar/parasellar neuroblastic tumors with bilateral retinoblastoma has been termed *trilateral retinoblastoma*.<sup>20</sup> Loss of function of the retinoblastoma gene is believed to confer an increased susceptibility to developing these intracranial tumors. Trilateral retinoblastoma is found in approximately 3% of all children with retinoblastoma.<sup>18,19</sup> Those patients with bilateral or familial disease are at greatest risk, with 5% to 15% developing this finding.<sup>18,19</sup> Hence, patients with bilateral or familial retinoblastoma are advised to have screening for pineoblastoma using computed tomography or magnetic resonance imaging of the brain twice yearly for the first 5 years of life. In some cases, the intracranial tumor preceded the diagnosis of retinoblastoma.<sup>18</sup> It is possible that many cases of pineoblastoma were previously misinterpreted as metastatic retinoblastoma to the brain. Unlike other second tumors, the pineoblastoma usually occurs during the first 5 years of life,<sup>19</sup> whereas second tumors often take many decades to develop. Unfortunately, pineoblastoma is usually fatal. The possibility of pineoblastoma should be included in the genetic counseling of patients with hereditary retinoblastoma. Newer evidence suggests that recent treatment methods of systemic chemoreduction for retinoblastoma may prevent trilateral retinoblastoma.<sup>21</sup> In a study of 100 patients with hereditary retinoblastoma, trilateral retinoblastoma was found in no patient who received chemoreduction and it would have been expected in 5 to 15 patients. Thus, prevention of trilateral retinoblastoma may be possible with neoadjuvant chemotherapy.

### At Risk for Second Primary Tumors

Another important aspect of genetic counseling concerns the development of new genetically related cancers in survivors of bilateral or heritable retinoblastoma. It is now recognized that a child with retinoblastoma has approximately a 5% chance of developing another malignancy during the first 10 years of follow-up, 18% during the first 20 years, and 26% within 30 years.<sup>22</sup> The 30-year cumulative incidence is approximately 35% or even higher for those patients who received radiation therapy (external beam therapy) compared with an incidence rate of 6% for those patients who avoided radiation. Therefore, patients with bilateral retinoblastoma have an increased incidence of second tumors, and this rate is further increased in those treated with external radiation therapy.<sup>22</sup> Osteogenic sarcoma, often involving the femur, is most common, but other tumors such as spindle cell sarcoma,



Fig 2.—Leukocoria in a child with advanced unilateral sporadic retinoblastoma.

chondrosarcoma, rhabdomyosarcoma, neuroblastoma, glioma, leukemia, sebaceous cell carcinoma, squamous cell carcinoma, and malignant melanoma have also been recognized. The mean latency period for the appearance of the second primary is approximately 13 years.<sup>22</sup> Patients who survive a second tumor are at risk for a third, fourth, and even fifth nonocular tumor.<sup>23</sup>

## Clinical Features of Retinoblastoma

The clinical manifestations of retinoblastoma vary with the stage of the disease at the time of recognition. In its earliest clinical stage, a small retinoblastoma, ie, less than 2 mm in basal dimension, appears ophthalmoscopically as a subtle, transparent or slightly translucent lesion in the sensory retina.<sup>1,2</sup> Slightly larger tumors lead to dilated retinal blood vessels that feed and drain the tumor. Some larger tumors show foci of chalk-like calcification that resemble cottage cheese. Any retinoblastoma of any size can produce leukocoria. The larger tumors more often present with this leukocoria (Fig 2). This white pupillary reflex is a result of reflection of light from the white mass in the retrobulbar area.

Retinoblastoma growth patterns are subdivided into intraretinal, endophytic, and exophytic (Fig 3). Intraretinal tumors are those listed above, limited to the substance of the retina. Endophytic retinoblastoma is one that grows from the retina inward toward the vitreous cavity. Hence, it is characterized by a white, hazy mass with obscuration of the retinal blood vessels. Because of its friable nature, an endophytic tumor can seed the vitreous cavity and anterior chamber and simulate endophthalmitis, especially toxocariasis, a parasitic disease found in young children.

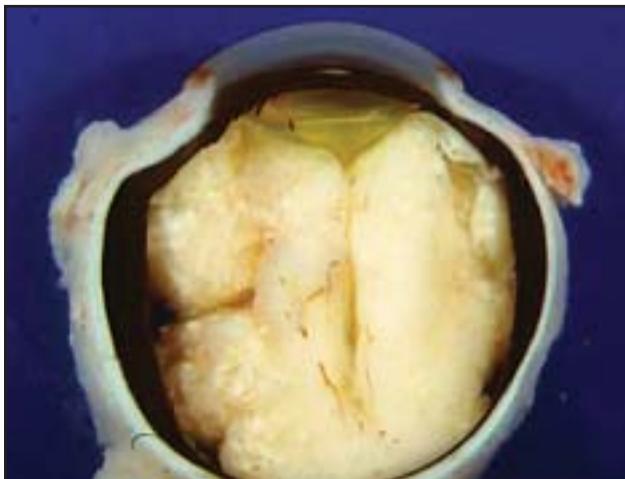


Fig 4.—Enucleated globe with large retinoblastoma filling the vitreous cavity.

An exophytic retinoblastoma is one that grows from the retina outward into the subretinal space. Such tumors produce a progressive retinal detachment, with the retina often displaced anteriorly behind a clear lens (Fig 4). An exophytic retinoblastoma can clinically resemble Coats' disease or other forms of exudative retinal detachment. Occasionally, a retinoblastoma can assume a diffuse infiltrating pattern, characterized by a relatively flat infiltration of the retina by tumor cells without an obvious mass. In such cases, the diagnosis may be more difficult, and this pattern can simulate uveitis or endophthalmitis. Less frequently, the presenting feature can be pseudohypopyon due to tumor seeding in the anterior chamber, hyphema secondary to iris neovascularization, vitreous hemorrhage, or signs of orbital cellulitis.

## Classification of Retinoblastoma

Several classifications of retinoblastoma have been developed to assist in prediction of globe salvage. The most popular grouping is the Reese-Ellsworth classification (Table 1).<sup>24</sup> A new International Classification of Retinoblastoma is currently being developed to simplify the grouping scheme and allow a more practical approach to judging results of chemoreduction.<sup>25</sup>



Fig 3.—Variations in the appearance of retinoblastoma. (A) Intraretinal retinoblastoma. (B) Endophytic retinoblastoma. (C) Exophytic retinoblastoma.

**Table 1. — Reese-Ellsworth Classification for Conservative Treatment of Retinoblastoma\***

Group I: Very favorable
(a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator
(b) Multiple tumors, none over 4 disc diameters in size, all at or behind the equator
Group II: Favorable
(a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator
(b) Multiple tumors, 4 to 10 disc diameters in size, behind the equator
Group III: Doubtful
(a) Any lesion anterior to the equator
(b) Solitary tumors larger than 10 disc diameters behind the equator
Group IV: Unfavorable
(a) Multiple tumors, some larger than 10 disc diameters
(b) Any lesion extending anteriorly to the ora serrata
Group V: Very unfavorable
(a) Massive tumors involving over half the retina
(b) Vitreous seeding

\* Refers to chances of salvaging the affected eye and not systemic prognosis.

## Differential Diagnosis

A number of ocular disorders in infants and children can clinically resemble retinoblastoma.<sup>26</sup> Despite the classic appearance of retinoblastoma, nearly 50% of patients diagnosed initially with possible retinoblastoma prove, on referral to ocular oncologists, to have simulating conditions and not retinoblastoma.<sup>27</sup> The most common pseudoretinoblastomas include persistent hyperplastic primary vitreous, Coats' disease, and ocular toxocariasis (Table 2). Therefore, it is important that the diagnosis of retinoblastoma be established without question prior to beginning treatment. Consultation with ocular oncologists experienced with retinoblastoma may be helpful in confirming the clinical diagnosis of retinoblastoma and assisting in designing a management plan for this potentially fatal disease.

## Diagnostic Testing

Accurate diagnosis in a child with suspected retinoblastoma is accomplished by taking a detailed history, physical evaluation, external ocular examination, slit lamp biomicroscopy, and binocular indirect ophthalmoscopy with scleral indentation. This is generally performed either in the office or under anesthesia in order to determine precisely the number and location of all tumors. The diagnosis is established by the classic appearance of the retinal tumors by an experienced examiner. Needle biopsy confirmation is rarely, if ever, necessary. Ancillary diagnostic studies can be helpful in confirming the diagnosis of retinoblastoma. Fluorescein angiography shows early vascularity and late hyperfluorescence of the tumor. Ultrasonography and computed tomography can demonstrate

the intraocular tumor and possibly detect calcium within the mass. Approximately 5% to 10% of retinoblastomas show no intrinsic calcification. Magnetic resonance imaging does not usually detect calcium but may be of value in the assessment of the optic nerve, orbit, and brain. Optic coherence tomography has been found useful in the detection of cystic retinoblastoma that might show less dramatic response to chemotherapy, and it is also helpful in the follow-up of patients to assess macular anatomy.<sup>27</sup>

If a clinician who is not entirely familiar with retinoblastoma is contemplating use of chemoreduction for a child with possible retinoblastoma, or even a needle biopsy or diagnostic vitrectomy, we recommend that the clinician consult with an experienced ocular oncologist before continuing with the procedure.

## Management of Retinoblastoma

The most important objective in the management of a child with retinoblastoma is survival of the patient, and the second most important goal is preservation of the globe. The focus on visual acuity comes later, after safety of the patient and globe is established. Therapy is tailored to each individual case and based on the overall situation, including threat of metastatic disease, risks for second cancers, systemic status, laterality of the disease, size and loca-

**Table 2. — Conditions Closely Simulating Retinoblastoma in an Analysis of 212 Pseudoretinoblastomas**

Condition	Percentage of Other Diagnoses
Persistent hyperplastic primary vitreous	28
Coats' disease	16
Ocular toxocariasis	16
Retinopathy of prematurity	5
Combined hamartoma	4
Coloboma	4
Vitreous hemorrhage	4
Astrocytic hamartoma	3
Familial exudative vitreoretinopathy	2
Bilateral retinal vascular hypoplasia with persistent primary vitreous	2
Rhegmatogenous retinal detachment	2
X-linked retinoschisis	2
Medulloepithelioma	2
Congenital cataract	2
Retinal capillary hemangioma	1
Circumscribed choroidal hemangioma	1
Diffuse choroidal hemangioma	1
Peripheral uveoretinitis	1
Toxoplasmic retinitis	1
Idiopathic endophthalmitis	1
Norrie's disease	<1
Incontinentia pigmenti	<1
Morning glory disc anomaly	<1

Adapted from Shields JA, Parsons HM, Shields CL, et al. Lesions simulating retinoblastoma. *J Pediatr Ophthalmol Strabismus*. 1991;28:338-340. Reprinted with permission by Slack, Inc.

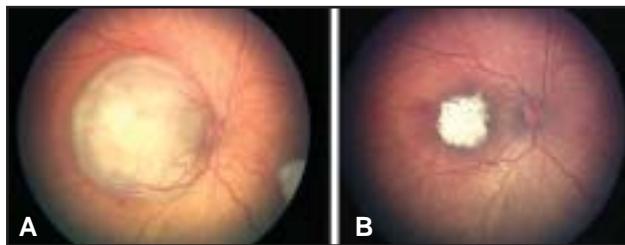
**Table 3. — Chemoreduction Regimen for Intraocular Retinoblastoma Given for a Total of 6 Monthly Cycles**

Day	Vincristine	Etoposide	Carboplatin
0	×	×	×
1		×	
Vincristine: 0.05 mg/kg			
Etoposide: 5 mg/kg			
Carboplatin: 18.6 mg/kg			

tion of the tumor(s), and estimated visual prognosis. There are several options for treatment of retinoblastoma, and the ocular oncologist should be thoroughly familiar with the indications, technique, and expected results of all treatment methods as well as the expected systemic and visual problems. The currently available treatment methods for retinoblastoma include intravenous chemoreduction (sometimes combined with subconjunctival chemoreduction), thermotherapy, cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, enucleation, orbital exenteration, and systemic chemotherapy for metastatic disease.<sup>1,2,7,28</sup> In recent years, eyes with unilateral retinoblastoma are generally managed with enucleation if the eye is classified as Reese-Ellsworth group V; for those eyes in groups I to IV, chemoreduction or focal measures are used. For bilateral retinoblastoma, chemoreduction is utilized in most cases unless there is extreme asymmetric involvement, with one eye having advanced disease necessitating enucleation while the other eye has minimal disease, treatable with focal methods. Most children with bilateral retinoblastoma are treated with chemoreduction for at least one of their two involved eyes.

### Chemoreduction

Chemoreduction is a method of reducing tumor volume to allow for therapeutic measures that are more focused and less damaging.<sup>29</sup> It has evolved to be an important measure in the initial management of retinoblastoma.<sup>30-34</sup> The chemotherapeutic agents vary depending on the preference of the pediatric oncologist. We presently use carboplatin, etoposide, and vincristine (Table 3). Other oncologists include only one agent (carboplatin) or two agents (vincristine, carboplatin) in their protocol. The chemotherapy regimen is generally given for 6 cycles to allow for adequate tumor reduction. Focal therapy to the individual tumors is delivered at cycle 2 after achieving adequate tumor reduction and subretinal fluid resolution. The objective of chemoreduction is to reduce tumor size so that focal treatments can be applied to a smaller tumor volume in order to preserve more vision and possibly avoid enucleation and external beam radiotherapy (Fig 5). We



**Fig 5. — Regression of macular retinoblastoma following chemoreduction and focal foveal-sparing thermotherapy. (A) Before treatment. (B) After treatment, the tumor has remained regressed without recurrence at 4 years.**

reported that the retinoblastomas decreased a mean of 35% in tumor base and nearly 50% in tumor thickness after 2 cycles of chemoreduction.<sup>34</sup> Subretinal fluid resolved in 76% of cases and both vitreous and subretinal seeds showed regression with the treatment.<sup>35</sup> Thus, it is apparent that retinoblastoma is sensitive to current chemoreduction regimens.

Ocular salvage rates have improved with the addition of chemoreduction to treatment regimens (Table 4).<sup>36-38</sup> Following the initial observations on the usefulness of chemoreduction by Kingston et al,<sup>31</sup> we found that chemoreduction permitted globe salvage in 85% of eyes classified as Reese-Ellsworth groups I to IV and 47% of those classified as group V, but some of the advanced eyes required external radiotherapy for salvage (Table 5).<sup>38</sup>

The main problem with chemoreduction is recurrence of related vitreous or subretinal seeds, usually remote from the main tumors (Table 6).<sup>39,40</sup> These seeds generally respond to initial chemoreduction but later they can recur. Recurrent seeds are generally detected within the first 2 years after chemoreduction. Active subretinal and vitreous seeds require treatment, and it is important to recognize them early as treatment modalities are limited. Additionally, it should also be realized that 24% of patients develop new retinoblastomas during or after chemoreduction, mostly in those who present as infants and with family history of retinoblastoma.<sup>41</sup>

**Table 4. — Comparison of Globe Salvage Rate Using External Beam Radiotherapy Alone, External Beam Radiotherapy Plus Salvage Treatment, and Chemoreduction Plus Focal Adjuvant Treatment**

Reese-Ellsworth Group	Globe Salvage		
	EBRT Alone Ellsworth et al <sup>36</sup> 1965-1972	EBRT + Salvage Treatment Hungerford et al <sup>37</sup> 1970-1985	CRD + AT Shields et al <sup>38</sup> 1994-2001
I	91%	100%	100%
II	83%	84%	93%
III	82%	82%	100%
IV	62%	43%	74%
V	29%	66%	47%

EBRT - external beam radiotherapy  
CRD - chemoreduction using vincristine, etoposide, and carboplatin  
AT - adjuvant treatment (laser photocoagulation, cryotherapy, thermotherapy, plaque radiotherapy, external beam radiotherapy)

**Table 5. — Chemoreduction Plus Focal Therapy for Retinoblastoma (N = 158 Eyes) in 103 Consecutive Patients: Overview of Treatment Failure and Need for Enucleation**

Reese-Ellsworth Group	Kaplan-Meier Estimates of Probability of Enucleation		
	At 1 year (probability $\pm$ SE)	At 3 years (probability $\pm$ SE)	At 5 years (probability $\pm$ SE)
I (n = 0 of 9 eyes)	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00
II (n = 1 of 26 eyes)	0.00 $\pm$ 0.00	0.07 $\pm$ 0.06	0.07 $\pm$ 0.06
III (n = 0 of 16 eyes)	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00
IV (n = 4 of 32 eyes)	0.07 $\pm$ 0.05	0.15 $\pm$ 0.09	0.26 $\pm$ 0.13
I-IV (n = 5 of 83 eyes)	0.03 $\pm$ 0.02	0.08 $\pm$ 0.04	0.15 $\pm$ 0.08
V* (n = 32 of 75 eyes)	0.23 $\pm$ 0.05	0.49 $\pm$ 0.07	0.53 $\pm$ 0.07
Total groups I-V (n = 37 of 158 eyes)	0.13 $\pm$ 0.03	0.29 $\pm$ 0.04	0.34 $\pm$ 0.05

\* Chemotherapy included vincristine, etoposide, carboplatin for 6 cycles  
SE = standard error  
Adapted from Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: Factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol*. 2002;133:657-664. Reprinted with permission by Elsevier.

Only a few reports have addressed tumor control following specific chemoreduction regimens for retinoblastoma. Wilson et al<sup>39</sup> used chemotherapy alone (vincristine and carboplatin) without tumor consolidation for 36 eyes with retinoblastoma for eight cycles over 6 months. Complete tumor control was found in only 8% of eyes, whereas 92% showed recurrence of retinal tumor, subretinal seeds, or vitreous seeds. We later evaluated individual control of retinal tumor, subretinal seeds, and vitreous seeds per treated eye.<sup>40</sup> We treated 158 eyes with retinoblastoma using vincristine, etoposide, and carboplatin for 6 cycles over 6 months. All retinoblastomas, subretinal seeds, and vitreous seeds showed initial regression. Tumor consolidation with thermotherapy or cryotherapy following chemoreduction was provided for each retinal tumor, but the vitreous and subretinal seeds were treated with chemoreduction alone without consolidation. The 5-year Kaplan-Meier results showed that approximately 50% of the eyes with vitreous seeds at presentation showed at least one vitreous seed recurrence, 62% of the eyes with subretinal seeds at presentation showed at least one subretinal seed recurrence, and at least one retinal tumor recurrence per eye was found in 51% of the eyes (Table 6).<sup>40</sup> A more recent analysis of 457 consecutive retinoblastomas by our group has focused on individual tumor control with chemoreduction with or without focal tumor consolidation.<sup>42</sup> Those tumors treated with chemoreduction alone showed recurrence in 45% by 7 years of follow-up, whereas

those treated with chemoreduction plus thermotherapy, cryotherapy, or both showed recurrence in only 22% by 7 years (Table 7). This suggests that tumor consolidation following chemoreduction is the best approach to prevent ultimate recurrence. However, this is not always possible as some tumors are located in the central fovea, and consolidation would compromise visual acuity. In these cases, we make every effort to avoid consolidation or provide foveal-sparing thermotherapy.<sup>43,44</sup>

Overall, chemoreduction is an effective initial measure for selected children with retinoblastoma. Definitive focal therapy is important once tumor reduction is achieved from the chemotherapy. The 6-cycle regimen that we employ might cause transient bone marrow suppression and a risk for infection.<sup>45</sup> The risk for induction of second cancers exists and is not known, but it is predicted to be minimal due to the short-term treatment period. Secondary leukemia is a concern in children who receive high doses of etoposide. Other problems include ototoxicity and nephrotoxicity. By using our chemotherapy protocol in over 200 children with retinoblastoma, we have not experienced any of these serious side effects in our patients.

### **Subconjunctival Chemoreduction for Retinoblastoma**

Children with advanced retinoblastoma in both eyes or in their only remaining eye are generally treated with systemic chemoreduction and a local periocular boost of subconjunctival carboplatin. Animal models have shown that carboplatin penetrates the sclera into the vitreous cavity, allowing for effective higher dosages at that site.<sup>46-49</sup> Initially, subconjunctival carboplatin alone

**Table 6. — Chemoreduction and Focal Treatment for Retinoblastoma in 158 Eyes of 102 Patients: Kaplan-Meier Estimates of Recurrence Per Eye of Retinal Tumor, Vitreous Seeds, and Subretinal Seeds**

Feature	Kaplan-Meier Estimates of Probability of an Event		
	At 1 year (probability $\pm$ SE)	At 3 years (probability $\pm$ SE)	At 5 years (probability $\pm$ SE)
Retinal tumor recurrence (n = 69 of 158 eyes)	0.37 $\pm$ 0.04	0.51 $\pm$ 0.05	0.51 $\pm$ 0.05
Vitreous seed recurrence (n = 21 of 54 eyes)	0.26 $\pm$ 0.06	0.46 $\pm$ 0.08	0.50 $\pm$ 0.08
Subretinal seed recurrence (n = 40 of 71 eyes)	0.53 $\pm$ 0.06	0.62 $\pm$ 0.06	0.62 $\pm$ 0.06

SE = standard error  
From Shields CL, Honavar SG, Shields JA, et al. Factors predictive of recurrence of retinal tumor, vitreous seeds, and subretinal seeds following chemoreduction for retinoblastoma. *Arch Ophthalmol*. 2002;120:460-464. Copyright 2002, American Medical Association. All rights reserved.

Table 7. — Chemoreduction for 457 Retinoblastomas in 193 Eyes of 125 Patients: Kaplan-Meier Estimates of Recurrence per Tumor

Kaplan-Meier Estimates Recurrence of Retinoblastoma	Chemoreduction Strategy			Total Chemoreduction With or Without Adjuvant Therapy n = 457 tumors % failed*
	Chemoreduction Alone n = 63 tumors	Chemoreduction Plus Thermotherapy n = 256 tumors	Chemoreduction Plus Adjuvant Therapy n = 394 tumors	
	% failed*	% failed*	% failed*	
at 1 year	39% [24 / 37]	18% [43 / 188]	13% [50 / 309]	17% [73 / 347]
at 2 years	45% [27 / 18]	20% [49 / 163]	17% [61 / 258]	20% [88 / 276]
at 3 years	45% [27 / 15]	21% [50 / 122]	17% [62 / 191]	21% [89 / 202]
at 4 years	45% [27 / 10]	22% [51 / 101]	18% [64 / 153]	22% [91 / 164]
at 5 years	45% [27 / 10]	22% [51 / 72]	18% [64 / 99]	22% [91 / 105]
at 6 years	45% [27 / 10]	22% [51 / 39]	18% [64 / 57]	22% [91 / 66]
at 7 years	45% [27 / 8]	22% [51 / 16]	18% [64 / 31]	22% [91 / 40]

\* [# events / # still in risk set]

Adapted from Shields CL, Mashayekhi A, Cater J, et al. Chemoreduction for retinoblastoma. Analysis of tumor control and risks for recurrence in 457 tumors. In press. Reprinted with permission by Elsevier.

was tested for retinoblastoma control. However, retinoblastoma recurrence was inevitable, so currently the subconjunctival approach is combined with systemic chemotherapy for best results. Toxicities include localized subconjunctival hemorrhage and pain, loss of limbal stem cells with conjunctival overgrowth onto the cornea, and orbital fibrosis with limited ocular motility.<sup>50</sup>

### Focal Therapies

Focal therapies include laser photocoagulation, thermotherapy, cryotherapy, and plaque radiotherapy. Most of these therapies are employed for small tumors, especially those that have been reduced by chemoreduction. Commonly, focal therapies are applied to an eye while the child is receiving chemoreduction, and they are repeated to each tumor at each chemotherapy session. Plaque radiotherapy is generally reserved for tumors that fail other focal therapies, even those that reach a moderate size, up to 8 or 10 mm in thickness. The remainder of the focal therapies are reserved for small tumors, generally those under 3 mm in greatest dimension.

Laser photocoagulation is usually employed for small retinoblastomas posterior to the equator of the eye. In this era of chemoreduction, laser photocoagulation is rarely employed as its success depends on vascular coagulation and tumor ischemia, whereas the opposite applies to chemoreduction. Thus, it is not employed in eyes receiving chemoreduction. Laser photocoagulation is performed using the indirect ophthalmoscopic argon or green diode laser with two rows of photocoagulation surrounding the tumor base and special effort to avoid direct treatment to the tumor, which could lead to vitreous seeding.<sup>51</sup> Commonly, it is repeated at 1-month intervals for three sessions.

Thermotherapy is a method of tumor heating using a diode infrared laser system. It is usually performed in conjunction with chemoreduction or carboplatin alone so that

the two techniques work in synergy to affect the tumor. The goal is to deliver a temperature of 42°C to 60°C, a temperature that is below the coagulative threshold and thus sparing the retinal vessels of photocoagulation. The combination of heat and chemotherapy is termed *chemothermotherapy*, and the combination of heat and radiation is termed *thermoradiotherapy*. Heat has been found to have a synergistic effect with both chemotherapy and radiation therapy for the treatment of systemic and ocular cancers.<sup>52</sup> We employ thermotherapy as the main focal treatment to tumors following chemoreduction. The goal of this treatment is to heat the tumor to a gray-white scar. In general, small tumors require approximately 300 mW of power for 10 minutes or less, and large tumors require up to 800 mW of power for 10 minutes, each delivered over three sessions at 1-month intervals.<sup>52</sup>

Thermotherapy coupled with chemoreduction is especially suited for tumors adjacent to the fovea and optic nerve where radiation or laser photocoagulation would possibly induce more visual loss. It is a time-consuming, tedious process that requires careful observations, recordings, judgments, and treatment of subtle tumor findings. In addition, the cooperation of experienced facilities with pediatric oncologists, radiation oncologists, ocular oncologists, and patient counselors is essential for such a program.

Cryotherapy is useful in the treatment of equatorial and peripheral small retinoblastomas.<sup>53</sup> Tumor destruction is usually achieved with one or two sessions of triple freeze-thaw cryotherapy delivered at 1-month intervals. It is important to recognize that cryotherapy will usually fail if there is overlying vitreous seeds. In these failed cases, plaque radiotherapy is usually employed. Cryotherapy remains an important method for tumor consolidation following chemoreduction. It is a critical modality for management of recurrent subretinal seeds near the ora serrata.

Plaque radiotherapy is a method of brachytherapy in which a radioactive implant is placed on the sclera over the base of a retinoblastoma to irradiate the tumor transsclerally. Generally, it is limited to tumors less than 16 mm in base and 8 mm in thickness. It requires an average of 2 to 4 days of treatment time to deliver the total dose of 40 Gy to the apex of the tumor. Plaque radiotherapy can be used as a primary or secondary treatment.<sup>54,55</sup> In fact, in 70% of cases, plaque radiotherapy is used as a secondary treatment to salvage a globe after prior failed treatment, usually failed external beam radiotherapy or chemotherapy.<sup>54</sup>

Overall, using Kaplan-Meier estimates, there is approximately an 80% tumor control rate at 4 years with one application of plaque radiotherapy.<sup>55</sup> Carefully selected retinoblastoma, even juxtapapillary and macular tumors, can be successfully treated with plaque radiotherapy. Retinoblastomas that are treated with plaque as a primary treatment show tumor control in 88%, and control is similar (92%) following plaque of previously failed chemoreduction.<sup>55</sup> Tumor control is poorer following plaque of previous failed external beam radiotherapy (75%). The visual outcome varies with tumor size and location as well as radiation problems of retinopathy and papillopathy. The visual outcome has been reported to be good in 62%, and the measured vision was 20/20 to 20/30 in over half of the cases.<sup>55</sup> Radiation maculopathy is found in 25% of treated eyes and papillopathy in 26% of eyes by 5 years.<sup>55</sup>

Innovations with custom design of plaques, especially those for small tumor recurrences, have also assisted in avoiding radiation retinopathy. Plaque radiotherapy has not been associated with induction of second cancers, likely due to its focal, shielded radiation field.

### **External Beam Radiotherapy**

Retinoblastoma is generally a radiosensitive tumor. External beam radiotherapy is a method of delivering whole eye irradiation to treat advanced retinoblastoma, particularly when there is diffuse vitreous seeding. Various treatment plans have been employed. The whole eye technique and lens-sparing technique were recently reviewed by the group at St. Bartholomew's Hospital in London.<sup>37,56</sup> They found that the eye preservation rate had improved markedly from reported older series, and the rate of ocular salvage depended on not only the stage of the disease (Reese-Ellsworth stage) at the time of treatment, but also the availability of focal therapy for limited recurrences. Recurrence of retinoblastoma after external beam radiotherapy continues to be a problem that can develop within the first 1 to 4 years after treatment. Tumor recurrence has also been found to be related to the stage of the disease and largest tumor size at the time of treatment.

Little has been written on the visual outcome after external beam radiotherapy for retinoblastoma. Radiation damage to the retina, optic nerve, and lens can be challenging to manage.<sup>57</sup> In patients with macular retinoblastoma, the visual outcome has been found to be dependent

on the size of the tumor and the degree of involvement of the fovea.<sup>57</sup> Superimposed amblyopia can pose a problem, and patching therapy should be employed when there is hope for vision.

External beam radiotherapy may induce a second cancer in the field of irradiation.<sup>58-60</sup> The 30-year cumulative incidence for second cancers in bilateral retinoblastoma has been reported at 35% for patients who received radiation therapy compared with 6% for those who did not receive radiation.<sup>59</sup> Abramson and Frank<sup>61</sup> found that external beam radiotherapy increased the incidence of second cancers in the field of radiation but did not stimulate second cancers outside the field of irradiation. Importantly, the risk for radiation-induced cancers has been found to be dependent on patient age at the time of irradiation as well as other factors. Patients treated with external beam radiotherapy who are younger than 12 months of age have a greater risk for second cancers than patients over 12 months of age.<sup>61</sup>

### **Enucleation**

Enucleation is a frequently used and important method for managing retinoblastoma. If there is advanced disease with no hope for useful vision in the affected eye or if there is a concern of invasion of the tumor into the optic nerve, choroid, or orbit, then enucleation is appropriate. Those eyes with secondary glaucoma, pars plana seeding, or anterior chamber invasion are also generally best managed with enucleation.

In a review of 324 consecutive cases of retinoblastoma managed on the Oncology Service at Wills Eye Hospital from 1974 to 1988, we found that unilateral retinoblastoma was managed with enucleation in 96% cases from 1974 to 1978, in 86% cases from 1979 to 1983, and in 75% cases from 1984 to 1988.<sup>62</sup> A similar decreasing trend was found with bilateral retinoblastoma. These trends remain relatively stable today, with approximately 65% to 75% of unilateral sporadic retinoblastoma managed with enucleation.<sup>63</sup>

The technique of enucleation is to gently remove the eye intact without seeding the malignancy into the orbit.<sup>64</sup> After the globe is removed, it is placed on a separate tray and fresh tissue is harvested in the operating room for DNA analysis, using a specific technique.<sup>65</sup> The surgeon must change sterile gloves after this step to avoid the risk of tumor contamination into the child's orbit.

Many years ago, an orbital implant was usually not placed after enucleation for retinoblastoma because it interfered with palpation of the socket and clinical detection of orbital tumor recurrence. More recently, with improved knowledge of the behavior of retinoblastoma and its low risks for local orbital recurrence, there is less hesitation for placing an orbital implant. In addition, available orbital imaging modalities of computed tomography and magnetic resonance imaging allow detailed orbital evaluation, despite the presence of an implant. The orbital implant provides a

more natural cosmetic appearance of the patient's artificial eye, minimizing sinking of the prosthesis and enabling motility to the prosthesis. There are several available orbital implants, including polymethylmethacrylate sphere, coralline hydroxyapatite, and polyethylene.

## Conclusions

Retinoblastoma continues to be a challenge both diagnostically and therapeutically. It is important to first clearly establish the correct diagnosis before embarking on therapy. Many factors enter into management decisions such as patient age, tumor laterality, size, location, and extent, and anticipated visual prognosis. Methods of chemotherapy have changed the approach to retinoblastoma in recent years and have permitted many children to maintain their eye(s) and avoid external beam radiotherapy. Enucleation still proves to be useful for advanced tumor.

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