

# Risk definition and management strategies in retinoblastoma: current perspectives

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**Abstract:** This manuscript focuses on high-risk factors of metastatic disease in retinoblastoma and evaluation of the current treatments of retinoblastoma. Presence of histopathologic high-risk factors is associated with a higher risk of local recurrence and systemic metastasis. Currently, globe-sparing therapies, including systemic chemotherapy, intra-arterial chemoreduction, intravitreal chemotherapy, focal consolidation, and combination therapies, are being used and investigated actively. Major advances are being made in the diagnosis and management of retinoblastoma that will lead to improved morbidity and mortality rates in patients with retinoblastoma. By saving the globes, fronting with some high-risk factors for metastasis would be inevitable. International multi-institutional prospective studies could resolve current uncertainties regarding the main tumor treatment regimens for each patient and indications for chemoprophylaxis for high-risk-factor-bearing retinoblastoma cases.

**Keywords:** retinoblastoma, intra-arterial chemotherapy, systemic chemotherapy

## Introduction

Retinoblastoma, a curable cancer of childhood, accounts for 2%–4% of all childhood malignancies.<sup>1,2</sup> Its prevalence is approximately 1:15,000–1:20,000 and can occur unilaterally or bilaterally, with single or multiple foci per eye.<sup>3,4</sup> Retinoblastoma can occur sporadically (60%) or be inherited (40%) in an autosomal dominant mode.<sup>4</sup> Since the past century, prognosis has substantially improved, as only 30% of affected patients survived in the 1930s, 80% in the 1960s, and 95% in the 1990s.<sup>5</sup> The clinical management of retinoblastoma requires multidisciplinary teamwork and treatment, affecting not only visual outcomes but also ocular retention and morbidity.

Inactivation of both *RBI* alleles is the rate-limiting step in retinoblastoma tumorigenesis, but how this tumor acquires the additional changes that constitute a malignant phenotype remains to be determined.<sup>6</sup> Molecular genetic studies with identification of germ-line mutations have made a tremendous impact on the management of siblings and offspring of affected individuals.<sup>7,8</sup> They can obviate the need for prolonged clinical screening under anesthesia for many unaffected children and unnecessary need for lifetime follow-up for nonhereditary cases. These workups enable the possibility of preimplantation genetic diagnosis, an option that is likely to be considered by affected individuals.<sup>9</sup>

Invasive retinoblastoma with higher recurrence rate, termed “high-risk” factors, ranges from 0% to 81% of all retinoblastoma tumors in the literature.<sup>10–15</sup> There have been numerous retrospective studies attempting to identify which patients are at highest risk for metastatic disease after enucleation.<sup>16–21</sup> Considering the high-risk factors, the benefit of adjuvant therapy in preventing relapses after enucleation is addressed in the literature, although there are no prospective, randomized studies.

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This review focuses on the main clinical and pathologic risk factors of invasive retinoblastoma and the current treatment options and then will briefly comment on choosing the treatment protocol.

## High risks in retinoblastoma Histopathologic and clinical high-risk factors

Defining high-risk factor either clinically or histopathologically is of utmost importance for the discussion on retinoblastoma patients. There are three major events causing death in patients with retinoblastoma: second malignant neoplasm, pinealoblastoma, and metastasis.<sup>11,12</sup> Presence of histopathologic high-risk factors is associated with a higher risk of local recurrence and systemic metastasis. Early recognition of the risk factors, followed by prompt treatment, may reduce the incidence of metastatic death.

Metastatic retinoblastoma is reported to develop in less than 10% of patients in developed countries.<sup>13–16</sup> High-risk retinoblastoma leads to metastasis in 24% of patients if not treated with systemic chemotherapy, compared with 4% of those who receive it.<sup>17</sup> However, it is a significant contributor to retinoblastoma-related mortality in developing nations.<sup>22,23</sup> Clinical, genetic, and histopathologic features have been already identified and appreciated as risk factors for metastatic disease.<sup>24</sup> The main histopathologic high-risk factors have been already defined, including anterior chamber seeding, iris and ciliary body infiltration, tumor invasion beyond the lamina cribrosa (in the neural parenchyma, cerebrospinal fluid, and neural blood vessels), involved optic nerve transection site, massive choroidal infiltration (>3 mm), scleral infiltration, and extrascleral extension.<sup>25–27</sup>

There are still controversies about the cell type, degree of differentiation, and necrosis in retinoblastoma as risk factors for metastasis.<sup>28–30</sup> Increasing grade of anaplasia, as defined by increasing cellular pleomorphism, number of mitoses, nuclear size, nuclear hyperchromatism, and necrosis, was associated with decreased overall survival and increased risk of metastasis.<sup>31,32</sup> Karcioğlu et al<sup>32</sup> concluded that the number of tumor vessels in the enucleated eye may be a useful predictor for metastasis in retinoblastoma.

The International Classification of Retinoblastoma can predict those eyes with high-risk retinoblastoma. Groups A, B, and C eyes rarely come to enucleation for histopathologic inspection. In an assessment of 519 enucleated eyes, Kaliki et al<sup>26</sup> found that 17% of Group D and 24% of Group E eyes displayed high-risk features for metastatic disease. There was no metastasis in any patient classified with no high-risk retinoblastoma.<sup>26</sup>

Reported clinical predictors of high-risk histopathology in retinoblastoma include older age, longer lag period before diagnosis and treatment, hyphema, pseudohypopyon, staphylococci, and orbital cellulitis.<sup>33–39</sup> Messmer<sup>40</sup> quantified and found delays of  $\geq 120$  days to be statistically significant for the development of metastatic retinoblastoma. Patients presenting with glaucoma and/or buphthalmia have significantly elevated pathologic risk factors, including those resulting in microscopic residual disease and optic nerve invasion.<sup>33,41,42</sup>

Genetically, non-germ-line tumors had higher tumor stages, more local invasion, more bone marrow involvement and cerebrospinal fluid invasion, higher rates of enucleation, and poorer histologic differentiation. However, germ-line tumors had a greater risk of mortality, phthisis bulbi, and orbital involvement despite earlier diagnosis and lower tumor stage at the time of diagnosis.<sup>24</sup> Kopelman et al<sup>27</sup> in a multivariate analysis focusing on laterality of retinoblastoma found that if patients with concurrent optic nerve and orbital extension were removed from the analysis, patients with bilateral retinoblastoma were more likely to develop metastatic disease ( $P=0.0029$ ). This could be due to a genetic difference between these tumors or it could simply be due to the fact that bilateral retinoblastoma patients have more tumors (larger tumor volumes).<sup>27</sup>

The standard intravenous chemotherapy protocol using vincristine, etoposide, and carboplatin (VEC) resulted in complete tumor control in all (100%) high-risk cases with no evident metastasis.<sup>25,43</sup>

## Nonocular tumor risk

The high risk of secondary nonocular tumors in survivors of retinoblastoma has been recognized for some decades.<sup>44–51</sup> Patients with hereditary retinoblastoma carry a significant risk of secondary nonocular tumors.<sup>44</sup> External beam radiation therapy administered before the age of 12 months is known to increase this risk.<sup>52,53</sup>

Levene<sup>45</sup> and Reese et al<sup>46</sup> reported secondary tumors following treatment in cases of bilateral retinoblastoma. Sagerman et al<sup>47</sup> reported cases of osteosarcoma following retinoblastoma and subsequently raised the possibility that there was an increased susceptibility to neoplasia in retinoblastoma cases. Since then, other studies showed a high incidence of nonocular tumor compared with the general population, the risk being largely confined to the heritable group.<sup>54,55</sup>

Current evidence suggests that retinoblastoma survivors, especially hereditary ones and those who received external beam radiation, should be closely monitored for the risk of developing second and third cancers, especially

in adulthood.<sup>50,52,55</sup> Other researchers documented the main observed categories of nonocular tumors in the heritable cases as soft tissue sarcomas (mainly leiomyosarcoma), osteosarcoma, carcinomas, brain and central nervous system tumors, melanoma, leukemia, and others.<sup>49,51,55</sup> More than a single type of tumor can occur in survivors.<sup>55</sup> Osteosarcoma below the age of 50 years was approximately 200 times as high as the population rate for all bone tumors.<sup>52</sup> Carcinomas can occur in breast, gastrointestinal system, respiratory tract, skin, or genitourinary system following retinoblastoma tumors.<sup>50,52,55</sup> Melanoma was reported in the third and fourth decades in heritable cases of retinoblastoma survivors.<sup>52,55</sup> It seems that patients with retinoblastoma, mainly hereditary cases, are at increased risk for secondary acute myelogenous leukemia after systemic chemotherapy.<sup>54-64</sup>

Based on these studies, it would be prudent to develop a screening protocol for survivors of retinoblastoma, taking into consideration the observed timing suspected of second tumors at various locations in the body.

## Classification of retinoblastoma

A clinical staging system is essential to enable proper definition, treatment plan, outcomes assessment of disease, and international communication.<sup>65</sup> Several classifications for retinoblastoma were already presented, including the Reese Ellsworth Classification, the Philadelphia Classification of Retinoblastoma, the International Classification of Retinoblastoma, and classification based on the American Joint Commission on Cancer's *AJCC Staging Manual Seventh Edition*.<sup>66-70</sup> In 1969, the first classification of intraocular retinoblastoma was introduced by Reese and Ellsworth for prediction of the outcome of external beam radiotherapy.<sup>66</sup> In 2003, the International Intraocular Retinoblastoma Classification (IIRC) was accepted for prediction of outcomes for eyes treated with chemotherapy.<sup>65,67</sup> Some difficulties in the definition of higher stages of retinoblastoma tumors (Groups D and E) and changes to the clinical criteria of each stage have made the IIRC inconsistent in some studies.<sup>71,72</sup> These discrepancies affect the prognostic value of the IIRC, leading to both over- and undertreatment.<sup>73</sup>

The need for including the clinical and pathological findings in predicting the final outcome of patients on management has led to the suggestion of TNM clinical classification by The AJCC and the International Union against Cancer.<sup>69,70</sup> The TNM staging system for all solid tumors was devised by Pierre Denoix between 1943 and 1952, using the size and extension of the primary tumor (T), its lymphatic involvement (N), and the presence of metastases (M) to classify the

progression of cancer.<sup>69,70,74</sup> Because of the rarity of extraocular extension at the time of diagnosis and even less common enucleation rate, nowadays, this classification system itself is not very often used.

## Clinical management of retinoblastoma

The management of retinoblastoma involves a multidisciplinary approach requiring careful consideration of treatment efficacy and toxicity for saving the life, globe, and possible vision.<sup>75-78</sup>

## Enucleation

Timely enucleation reduces risk of metastatic spread, morbidity, side effects of chemotherapy and focal laser treatment, and repeated examinations under anesthesia.<sup>73,76,79,80</sup> Enucleation is typically reserved for massive retinoblastoma classified as Group E, some eyes with advanced Group D, and eyes suspected to have extraocular extension (eg, orbital cellulitis, poor view of the inside of the eye, intraocular hemorrhage, neovascular glaucoma, tumor in anterior chamber, suspicious optic nerve involvement, or suspected extraocular disease on imaging). Following enucleation for retinoblastoma, special attention should be paid to the possible tumor spread to determine the possible danger for metastatic disease.

Orbital implants are important for subsequent bone growth and a good cosmetic appearance.<sup>73</sup> Risk of orbital disease is not a reason to avoid an implant because imaging and treatment of orbital recurrence can be treated without interference from the implant.<sup>73</sup>

Families' rejection of enucleation as curative treatment is not uncommon. With appropriate support, even children who lose both eyes to retinoblastoma can go on to lead full and highly productive lives.<sup>73</sup>

In general, primary enucleation is conducted for advanced stage of retinoblastoma (Group E)-bearing eyes with anterior segment involvement.

## Globe-preserving treatments in retinoblastoma

Globe-saving methods of treatment available to the ocular oncologist include systemic or regional chemotherapy,<sup>81,82</sup> laser,<sup>83</sup> and cryotherapy,<sup>84</sup> while external beam radiation<sup>85</sup> or plaque radiotherapy are less commonly used.<sup>86</sup>

## Chemotherapy for retinoblastoma

The management of retinoblastoma with chemotherapy is a complex science. Many problems should be considered after

the diagnosis of the tumor. Choosing the best treatment after diagnosis depends on the intraocular extent of the tumor, laterality of the tumors, and patient's age. The combination of chemotherapeutic agents and the combining of other local adjunctive treatment (thermotherapy, cryotherapy, or plaque radiotherapy) during the chemotherapy and/or after chemotherapy is of particular importance for proper management of disease.

## Intravenous chemotherapy

Presenting of systemic chemotherapy with different protocols was a major advance in retinoblastoma management in recent years. The aim of chemoreduction is to avoid enucleation and external beam radiotherapy and preserve the globe and vision with focal adjunctive treatments. Chemoreduction was introduced as management for retinoblastoma in the mid-1990s following preliminary observations that chemotherapy delivered before external beam radiotherapy increased tumor control with ocular salvage from 30% to 70%.<sup>87</sup> In 1996, some leading studies stated that systemic chemotherapy was efficient in the short-term control of the tumors in various stages of retinoblastoma.<sup>88–91</sup> Later analysis showed 90% tumor control in Reese–Ellsworth Groups I–IV retinoblastoma by six cycles of VEC and focal thermo- or cryotherapy, without need for enucleation or additional external beam radiotherapy.<sup>92</sup>

Systemic chemotherapy generally involves different multidrug regimens delivered intravenously on a monthly basis for 6–9 consecutive months.<sup>81,94,95</sup> The most popular regimen is 6 months chemotherapy with standard-dose VEC on the basis of patient weight for patients <3 years of age.<sup>81,93–95</sup>

According to the international classification of retinoblastoma, in 249 consecutive eyes, globe salvage was achieved in 100% of Group A eyes, 93% of Group B, 90% of Group C, 47% of Group D, and 25% of Group E eyes.<sup>94</sup> Wilson et al<sup>94</sup> used vincristine and carboplatin alone (without tumor consolidation) for 36 eyes with retinoblastoma for eight cycles over a period of 6 months. They found complete tumor control in only 8% of eyes, whereas 92% had failure with progression of retinal tumor, subretinal seeds, or vitreous seeds. It provided a rationale to use tumor adjunctive local treatments and also the importance of triple chemotherapy regimen to improve the tumor control rate. Eyes with extensive retinoblastoma, classified as Group E, are the most difficult eyes to treat with systemic chemotherapy. Historically, these eyes were generally managed with enucleation. However, when both eyes are of Group E, an attempt to save at least one eye with chemoreduction is made. Eyes of Groups D and E can show

improved control with the addition of low-dose radiotherapy, given 2 months after completion of chemoreduction.<sup>95,96</sup>

Systemic toxicity as transient myelosuppression and fever are common in systemic chemoreduction. Rarely, hearing and renal toxicity, as well as leukemia, can be seen.<sup>81,97–100</sup> Even though these adverse events are treatable and do not result in the cessation of therapy, physicians administering the treatment and counseling the families of affected patients should be aware of the potential complications and should communicate the risks to the families.<sup>99,100</sup> In 2000, a dramatic decrease in the incidence of pinealoblastoma in children treated with systemic chemotherapy was noted, and this result was confirmed 13 years later.<sup>101–103</sup> In addition to control of malignancy, systemic chemotherapy offers remarkable visual results with visual acuity at 20/20–20/40 in 37%–50% of patients.<sup>104,105</sup> In general, systemic chemotherapy is administered primarily for patients with bilateral retinoblastoma tumors, familial cases of retinoblastoma, any suspicion of extensive choroidal and optic nerve involvement, and cases younger than 4 months of age.

## Intra-arterial chemotherapy

Recently, local targeted chemotherapy as the direct injection of chemotherapy agents into the ophthalmic artery was popularized. This technique is highly effective in treating higher-stage tumors and saving most eyes otherwise destined for enucleation and, similar to other treatment modalities, can benefit from supplemental focal treatments such as cryotherapy, laser, and brachytherapy. Success with intra-arterial chemotherapy (IAC) requires special skill and high experience. Reports have shown good rates of tumor control and minimal side effects.<sup>106–108</sup> Yamane et al<sup>106</sup> and Suzuki and Kaneko<sup>107</sup> first reported the successful use of intra-arterial melphalan using a microballoon, guiding catheter, and flushing hub.

Abramson et al<sup>108</sup> reported a technique of delivering melphalan directly through a microcatheter into the ostium of the ophthalmic artery without the need for a microballoon. Hence, some groups developed different strategies to improve the results in these high-risk eyes.<sup>109–113</sup>

IAC generally involves a one- to three-drug regimen. The medication is delivered slowly over a period of 30 minutes in a pulsatile manner, with care taken to not occlude the artery and to minimize reflux into the internal carotid artery.<sup>108,109</sup> The IAC is considered primary or secondary treatment in the management of retinoblastoma cases.<sup>110</sup>

In a 4-year perspective, Gobin et al<sup>114</sup> found that IAC was well tolerated and effective for retinoblastoma with globe

salvage at 2 years in 82% of eyes if IAC was the primary treatment and 58% of eyes if it was the secondary treatment. A 5-year experience with IAC by Shields et al<sup>115</sup> revealed IAC success in globe salvage in 100% of Group B, 100% of Group C, 94% of Group D, and 36% of Group E eyes. In that series, complete regression was achieved for solid tumor in 94% of eyes, for subretinal seeds in 95% of eyes, and for vitreous seeds in 87% of eyes.<sup>115</sup> Thampi et al<sup>111</sup> noted 86% response rate in Groups A, B, and C but only 38% response in Groups D and E. Schaiquevich et al<sup>112</sup> found that IAC was more effective than periocular and intravenous topotecan-containing regimen for treatment of relapsed retinoblastoma.

Other researchers showed synergistic activity of combination melphalan and topotecan IAC and cyclophosphamide in their pharmacokinetic study.<sup>116,117</sup> The combination of melphalan and topotecan for IAC of retinoblastoma was effective and well tolerated without increased hematologic toxicity with respect to melphalan administered as a single drug.<sup>117,118</sup> Topotecan showed a preferential passage to the vitreous humor, where it stayed for at least 4 hours more than its calculated IC<sub>50</sub> (50% inhibitory concentration).<sup>119</sup>

Melphalan showed a less-favorable penetration into the vitreous humor but was present at higher levels in the retinal pigment epithelium, which could explain its excellent efficacy for the treatment of eyes with retinal detachment caused by the tumor.<sup>118</sup>

The IAC is a sophisticated technique. Vaso-occlusive disease has been described following IAC as a potentially sight-threatening complication.<sup>116,120–122</sup> Histopathologic examination of a nonhuman primate model for IAC revealed significant toxic effects in the ocular and orbital vasculature.<sup>121</sup> An overall assessment of complications with 5-year experience included vitreous hemorrhage (2%), branch retinal artery obstruction (1%), ophthalmic artery spasm with reperfusion (2%), ophthalmic artery obstruction (2%), partial choroidal ischemia (2%), and optic neuropathy (<1%).<sup>122</sup> Other studies showed eyelid edema, blepharoptosis, cilia loss, and orbital congestion with temporary dysmotility, retinal detachments, cataract, and retinal pigment epithelium damage (47%).<sup>122,123</sup>

Theoretically, this technique may pose a risk for brain vascular events and other operation territory vessels.<sup>124–126</sup> Sarici et al<sup>125</sup> noted the “blue toe” syndrome as a complication. Episodes of adverse cardiorespiratory reactions, such as hypoxia, hypotension, and bradycardia, have been documented in 24% of procedures in a recent report from the UK.<sup>126</sup> Reactions occurred only during the second or subsequent procedures and these can be life threatening.<sup>126</sup> Tsimpida et al<sup>127</sup> studied visual outcome following IAC and

noted that 5 (43%) out of 12 treated eyes had severe visual loss due to choroidal ischemia or retinal detachment. The authors caution regarding visual complications from this therapy due to possible factors of catheterization or high doses of melphalan.

This treatment technique could be performed as the primary option in the following cases: unilateral cases of retinoblastoma, nonheritable cases of unilateral retinoblastomas, and cases older than 4 months of age.

## Periocular chemotherapy

Periocular chemotherapy is usually indicated for bilateral advanced Groups D or E in which a higher local dose of chemotherapy is required and in some patients with recurrent localized tumor. Periocular chemotherapy achieves rapid levels and six to ten times higher level than that achieved by the intravenous route within the vitreous humor in 30 minutes and can last for hours.<sup>128,129</sup> The method of injection can vary from plain liquid injection; injection within a depot such as gels, Lincoff balloon, long-acting fibrin sealant, or nanoparticles; solid polymers; or injection stimulated by iontophoresis.<sup>128–130</sup> Most clinicians use either carboplatin or topotecan. Periocular injection of carboplatin has been used for retinoblastoma control for >2 decades, generally as an adjunct to systemic chemotherapy but occasionally to treat tumor recurrence.<sup>130</sup> Periocular topotecan is injected in a fibrin sealant or as an episcleral implant.<sup>131,132</sup>

Local side effects include inflammation, ptosis, scarring, and loss of sight.<sup>132,133</sup> Yousef et al<sup>134</sup> found that periocular topotecan was effective and led to fewer complications of fibrosis compared to carboplatin with a mean follow-up period of 37 months.

Periocular chemotherapy could be used in advanced tumors (D or E) or recurrences with the need for greater local dosage of the chemotherapeutic agents.

## Intravitreal chemotherapy

Intravitreal chemotherapy (IVIc) for retinoblastoma was tried for the first time in the 1960s using thio-N,N',N'-triethylenethiophosphoramidate (thio-TEPA) and later with methotrexate.<sup>135,136</sup> Inomata and Kaneko<sup>137</sup> found melphalan to be the most effective against retinoblastoma on the basis of *in vitro* testing. Recently, Suzuki et al reported five years results of intravitreal injection of 8–30 mg melphalan combined with ocular hyperthermia for vitreous tumor seeding in 264 eyes of 250 patients. Sixty-eight percent of the treated eyes achieved complete vitreous seed remission.<sup>138</sup>

Munier et al<sup>139</sup> studied IViC in 23 patients with heavily treated retinoblastoma, with recurrent vitreous seeds. They injected 20–30 mg intravitreal melphalan on a weekly basis and found 83% success rate of tumor seeds control at 15 months. Ghassemi and Shields<sup>140</sup> evaluated 12 eyes treated with intravitreal melphalan for recurrent vitreous seeding and defined proper dosing. They identified that low-dose melphalan (8–10 mg) showed 42% control and minimal side effects, whereas high doses, such as a 50-mg dose, were toxic with possible hypotonia and phthisis bulbi.<sup>140</sup> They concluded that melphalan has promising results with 30–50 mg, not more. In another study, they showed that of 25 IViC-treated cases, eight eyes needed enucleation because of phthisis, parent request, or new tumor development. There was no case of needle-site scleral involvement by retinoblastoma cells.<sup>141,142</sup>

Subsequently, Shields et al<sup>143</sup> reviewed an additional 55 injections for recurrent vitreous seeding in 16 retinoblastoma cases, which led to globe salvage in all cases (100%). Ghassemi et al<sup>143</sup> studied the addition of intravitreal topotecan with melphalan in humans and noted that this led to complete vitreous seed control with a single injection (33%) or two or three injections (67%), without the need for the standard six injections.

Reported complications with IViC were mostly minor retinal pigment epithelial mottling at the site of injection and extra-axial cataract. However, more significant side effects such as preretinal hemorrhage, vitreous hemorrhage, subretinal hemorrhage, retinal detachment, iris atrophy, hypotonia, and phthisis could be seen in some patients.<sup>139–141</sup> There was no reported case of extraocular tumor extension so far.

The main point is the time of considering IViC. This includes patients with unresponsive vitreous seeds to standard treatments and recurrent seeds after complete treatment. It is clear that the present drugs and the doses used are not effective for the treatment of residual tumors. Additionally, multiple injections of IViC agent as either a single agent or double agents did not preclude new tumor development.<sup>139,143</sup> The future path should be to develop new and more specific drugs for combating new tumors or even the main tumor by intravitreal injections.

In the Farabi Eye Hospital, we inject the IViC drugs on a biweekly schedule until the vitreous seeds disappear or crystallize. If any viable seeds are visible in any part of the vitreous cavity, despite some crystallization, the injections are continued. We conduct IViC for patients with the following indications: recurrent or residual vitreous seedings after systemic or IAC and monocular patients with any type

of vitreous seedings after completion or during the systemic chemotherapy or IAC.

Theoretically, tumor seeding can occur following IViC. Smith et al<sup>145</sup> in a review of all published cases or series on IViC from 1946 to 2013, found that a total of 1,304 intravitreal injections were given in 315 eyes of 304 patients and that only one patient developed metastatic disease. They concluded that proper technique leads to no increased risk of tumor spread.<sup>145</sup>

In the next few years, by increasing the survival of retinoblastoma patients and preserving greater number of sick globes, systemic metastasis and local recurrences will be plausible, due to the possible persistence of viable cells after complete treatment. An international, multi-institutional prospective study, with access to larger series of patients with retinoblastoma, could resolve current uncertainties.

Regarding the recurrence prophylaxis, development of appropriate chemotherapy agents and doses, the ideal treatment regimen, and new types of adjunctive treatments is expected. Ongoing gene therapy research in cancer may in future reach clinical practice, but numerous technical hurdles remain to be overcome.<sup>146</sup> In the present era, development of both new guidelines for defining the high risks and appropriate guidelines for chemoprophylaxis in patients afflicted with advanced forms of this disease is necessary.

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## Author contributions

Both authors contributed equally to hypothesis creation, intervention application, data collection, and article writing; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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