Advanced intraocular unilateral retinoblastoma: non-conservative management

Short title:

Advanced unilateral retinoblastoma

Version : December 21, 2022

This document has been developed by:
Alexandre Matet
Arnaud Gauthier
Liesbeth Cardoen
Lisa Golmard
Denis Malaise
Eva Biewald
Ida Russo
Marie-Louise Choucair
Maria Genoveva Correa Llano

Proofreading contributors:
François Doz
Petra Ketteler
Livia Lumbroso-Le Rouic
Paul Fréneaux
Guillermo Chantada
Annette Moll
Maja Beck-Popovic
Isabelle Aerts
Hervé Brisse
Nathalie Cassoux

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1. BACKGROUND AND RATIONALE

1.1 Background: retinoblastoma

Retinoblastoma is the most common malignant ocular tumour in childhood. The reported incidence is estimated at 1 case per 16,000-18,000 live births (Kivelä, 2009; Stacey et al., 2021). Typically, retinoblastoma develops in case of biallelic alterations in the tumour suppressor gene RB1, a cell cycle inhibitor, in cone photoreceptor precursor cells of the developing retina (Dimaras et al., 2015). This developmental tumour may be predisposed by inherited or *de novo* alterations in the *RB1* gene. Retinoblastoma is a medical and therapeutic emergency, since early management will increase the chances of preserving the eye and retaining some visual function in small tumours sparing the macula. However, retinoblastoma may also present with advanced stages at diagnosis. In unilateral advanced cases, first-line enucleation may be indicated to obtain tumour control while sparing unnecessary toxicity from chemotherapy and repeated ocular treatments under general anaesthesia, with little or no visual benefit. If left untreated, retinoblastoma will progress to metastatic disease, threatening the life of affected children (Cassoux et al., 2017b). Although retinoblastoma death rate is now less than 2% in industrialized countries (Fabian et al., 2020a, 2020b; Skalet et al., 2018), its prognosis remains poor in developing countries, often due to later diagnosis.

1.2 Ophthalmological presentation of retinoblastoma

Retinoblastoma occurs almost exclusively in children under 5 years of age, and very rarely between 5 and 15 years. The median age at diagnosis is ~24 months for unilateral forms, and ~12 months for bilateral forms in high-income countries. The clinical presentation depends on disease stage at diagnosis, the number of tumours per eye, the uni- or bilateral involvement and

the degree of asymmetry in bilateral forms. The most frequent presenting signs of retinoblastoma are leukocoria (white pupillary reflex) and/or strabismus. Upon ophthalmological examination, tumours appear as white retinal masses, sometimes associated with dilated and tortuous retinal vessels. Intratumoural calcifications may be visible at presentation or appear more clearly as the tumours become fragmented during treatment. Retinoblastoma is described as exophytic when invading the subretinal compartment with retinal detachment, and/or endophytic when extending into the vitreous cavity. Diffuse infiltrative retinoblastoma is a less frequent entity characterized by diffuse retinal infiltration, vitritis and/or hypopyon, that should not be misdiagnosed as panuveitis. Indeed, invasive procedures such as anterior chamber tap or diagnostic vitrectomy, frequently performed to explore intraocular inflammatory/infectious conditions, entail a high risk of orbital and systemic tumour dissemination, with a catastrophic life-threatening impact on the prognosis.

The risk of developing new tumours is highest in the first two years of life. New tumours develop near the posterior pole in neonates, and then more peripherally over the first months of life, probably because of centrifugal migration of retinal stem cells with maturation of ocular tissues. By 18-24 months, new tumours will appear in the extreme retinal periphery, and can only be visualized by indirect ophthalmoscopy under general anaesthesia, with scleral indentation. Regular monitoring under general anaesthesia in specialized centres is therefore critical (Balmer et al., 2006). From the age of four, surveillance can be progressively carried out without general anaesthesia, if the cognitive status allows a good cooperation. Nevertheless, a proportion of children develop retinoblastoma in a context of partial or complete deletion of chromosome 13, where the *RB1* gene is located. These children suffer from mental retardation, which requires examinations under anaesthesia until older ages.

1.3 Classifications of retinoblastoma at diagnosis

Several prognostic classifications have been proposed, none of which is fully satisfactory. Staging systems aim to predict both eye salvage and patient survival. The first classification system was established by Reese and Ellsworth in the 1950's, at the time when enucleation and external beam radiotherapy were the sole therapeutic options, to evaluate the chances of globe conservation after radiotherapy. It is now obsolete since external radiotherapy is no longer performed, because it induces a significant risk of orbito-facial dysmorphia, and secondary skull or soft tissue tumours in *RB1* gene alteration carriers. Initiated by Linn Murphree who proposed a first version in the 2000's in the era of systemic chemotherapy (the *International Intraocular Retinoblastoma Classification*, IIRC), and adapted by Shields and colleagues, the *Intraocular Classification of Retinoblastoma* (ICRB), is now the most widely used. Classifying the disease into five groups, from A to E (Appendix 1), it estimates the probability of globe preservation after systemic chemotherapy combined with local treatments (transpupillary thermotherapy or cryotherapy) (Murphree, 2005; Shields et al., 2006). These classifications coexist, and induce a confusion in the literature, especially regarding eyes with retinoblastoma limited to the posterior segment by occupying > 50% of the vitreous cavity, classified as D in the IIRC and as E in the ICRB (Fabian et al., 2018). For clarity, the present ESCP guidelines will refer to the ICRB (displayed in the Appendix 1).

In parallel, an international group has proposed the International Retinoblastoma Staging System (IRSS) in 2006, aiming at predicting patient survival (Appendix 2) (Chantada et al., 2006). The same international group proposed later the only consensus to date on retinoblastoma pathological evaluation (Sastre et al., 2009).

Recently, the use of the American Joint Committee on Cancer TNMH classification (8th Edition) has increased. It recapitulates the ocular, extraocular, pathological and for the first time

hereditary status (Appendix 3) (Mallipatna, 2017). The widespread use of the TNMH staging system should be encouraged since it was designed to predict both patient survival and eye salvage.

1.4 Imaging of retinoblastoma

High-resolution contrast-enhanced magnetic resonance imaging (MRI) is the technique of choice to evaluate the loco-regional spread in the eye, orbit, and central nervous system. The main parameters explored are: optic nerve invasion, trans-scleral extension, pineal gland status (pinealoblastoma, pineal cyst). Retinoblastoma is slightly hyperintense with respect to the vitreous body on T1-weighted sequences and demonstrates a low signal on T2-weighted sequences. The characteristic intralesional microcalcifications are visualized as small black dot-shaped spots on the high-resolution T2- or T2*-weighted sequences. Enhancement of the tumour varies according to the degree of necrosis. Different growth patterns of local tumour extension are distinguished (exophytic with retinal detachment, endophytic with vitreous seeding or diffuse infiltration) (De Graaf et al., 2012).

Optic nerve invasion and/or trans-scleral tumour spread can be assessed by MRI.

1.5 Histopathology of retinoblastoma

1.5.1 Histopathological risk factors for metastatic disease evaluated in the pathology report

Some patients with advanced retinoblastoma managed by primary enucleation will benefit from adjuvant therapy (systemic chemotherapy, and less frequently radiation therapy, detailed in Section 3). These adjuvant treatments have allowed to reduce the overall risk of metastasis from ~24% to ~4% after primary enucleation (Lu et al., 2019; Shields and Shields, 1999). Over time, several factors of metastatic risk have been identified and can help justify adjuvant

chemotherapy or radiotherapy. However, such factors are difficult to validate rigorously for several reasons, including low incidence of the disease (Kivelä, 2009), the effectiveness of neoadjuvant treatments (Bechrakis et al., 1998; Demirci et al., 2003), and the fact that these risk factors are present in less than 50% of cases without neo-adjuvant treatment (GL Chantada et al., 2004; Kaliki et al., 2013). Nevertheless, a few prognostic features on histopathologic examination have been recognized by the *Consensus Meetings from the International Retinoblastoma Staging Working Group* (Sastre et al., 2009), which subsequently served as basis for the current pTNM classification (Mallipatna, 2017). These pathological criteria are now widely used by European centers participating to the European Retinoblastoma Group (EuRbG), as confirmed by a recent survey (Dittner-Moormann et al., 2021). It is therefore recommended that the following parameters be included in the histopathology report:

1. **Choroidal invasion** (Khelfaoui et al., 1996; Messmer et al., 1991; Sastre et al., 2009)

- Choroidal invasion is often considered an intermediate-risk factor if it shows a "massive" pattern, i.e. when one of the following criteria is met:
  - the maximum diameter (either thickness or width) of the invasive tumour foci within the choroid measures 3 mm or more; or
  - the majority of the invasive tumour focus within the choroid reaches or exceeds the inner fibers of the scleral tissue

- Conversely, choroidal invasion is considered « focal » when the tumour foci measure less than 3 mm in largest diameter (thickness and width) and do not reach the sclera. There is a consensus that focal choroidal invasion is not considered a high-risk histopathological feature, and has been classified as a low-risk feature (Dittner-Moormann et al., 2021).

- The importance of recognizing artifactual tumour seeding in the choroid and in extraocular tissues during fresh tumour retrieval to avoid overdiagnosis of choroidal invasion (Sastre et al., 2009).

2. **Optic nerve invasion** (Aerts et al., 2013; Chantada et al., 2010; Pérez et al., 2018; Shields et al., 1994) is associated with different degrees of metastatic risk depending on the part of the nerve that is involved. When invasion is limited to the pre-laminar or intra-laminar segments, it is considered a low-risk factor. When the tumour extends to the post-laminar segment, but not reaching the posterior surgical margin (cut end section), it is considered an intermediate-risk factor. The length of post-laminar invasion, measured from the lamina cribrosa, should be given. Involvement of the posterior surgical margin of the optical nerve and invasion of optic nerve meningeal sheath are considered high-risk factors, since it corresponds to microscopically residual disease, at high risk of relapse, particularly in CNS (Aerts et al., 2013; Chantada et al., 2010; Dittner-Moormann et al., 2021; Pérez et al., 2018; Sastre et al., 2009). Given the low number of patients with postlaminar optic nerve invasion reported in clinical studies, it has not been established with certainty that the theoretical distinction between low, intermediate and high-risk categories, corresponds to incremental metastatic risk levels. The certainty is that high-risk patients are at high risk of local relapse, which increases the metastatic risk.

3. **Trans-scleral extension**, also termed ‘extra-scleral’ extension (Aerts et al., 2013; Chantada et al., 2010; Dittner-Moormann et al., 2021; Pérez et al., 2018; Sastre et al., 2009), also corresponds to microscopically residual disease and is therefore considered a high-risk factor.

4. **Anterior segment invasion** remains to date a controversial criterion (de Sutter et al., 1987; Haik et al., 1987; Rubin et al., 1985). It proved difficult to validate as a risk factor, because of the lack of a precise definition of this feature, the lack of expert central review, the retrospective nature of the studies, the rarity of this finding, and the frequent confounding association with other risk factors which warrant adjuvant therapy per se (Chévez-Barrios et al., 2019; Sreelakshmi et al., 2017). One could distinguish anterior chamber seeding (recognized clinically and upon aqueous humour cytology) and anterior segment invasion (defined as massive ciliary body or trabecular meshwork invasion). Recent reports of intracameral chemotherapy contributing to control primary or secondary aqueous seedings support the notion that isolated anterior seeding is likely a low-risk factor, whereas ciliary body or trabecular meshwork invasion is likely an intermediate risk. Consequently, most but not all European centres consider isolated seeding in the anterior chamber as an indication for adjuvant treatment to decrease metastatic risk (Baroni et al., 2014; Dittner-Moormann et al., 2021; Khelfaoui et al., 1996; Sreelakshmi et al., 2017).

There is a consensus that patients with enucleated eyes presenting focal choroidal invasion, pre- or intra-laminar infiltration of the optic nerve are considered low-risk histopathological features do not need adjuvant chemotherapy (Dittner-Moormann et al., 2021). This is supported by a 2-year overall survival of 100% without adjuvant treatment (Aerts et al., 2013; Künkele et al., 2015). In addition, for patients with massive choroidal invasion alone, data from a multicentre trial in Latin America (Grupo de America Latina de Oncología Paediátrica [GALOP]) showed a probability of event-free survival of 100% without adjuvant treatment (GL Chantada et al., 2004; Guillermo Chantada et al., 2004; Pérez et al., 2018). In the present ESCP guidelines, massive choroidal invasion is considered an intermediate risk factor that may require adjuvant chemotherapy (debated among contributing centres).

1.5.2 Histopathologic processing and examination of enucleation specimen

Some guidelines were also proposed regarding the processing of the enucleated eye specimen with retinoblastoma, with the goal of optimizing the histopathologic analysis, enabling fresh tumour collection (for cellularity assessment, somatic genetic investigations, and biobanking) and homogenizing the categorization of pathological features (Mallipatna, 2017; Sastre et al., 2009). The enucleated eye is sent to the pathologist without fixative and should be processed by the pathologist as soon as possible after surgery (i.e. within 1 hour) to avoid denaturation of nucleic acids and proteins. Both the eye diameter and the optic nerve length should be measured, if possible before fixation. The surgical limit of the optic nerve should be submitted for microscopic evaluation. The eye should remain unopened until and during formalin fixation. The fresh tumour sample can be collected by means of aspiration using a large bore needle. We recommend introducing a 22-gauge needle through the sclera posteriorly to the lens under visual control, using a binocular microscope. When the needle is positioned in the tumour, tumour material is gently aspirated after connecting a syringe to the needle. In case of an insufficiently friable tumour, a few millilitres of culture medium can be injected first, which helps dilute the tumour material and facilitates aspiration. Once the material is collected, an aliquot can be analysed to evaluate tumour cellularity of the aspirate. After harvesting the fresh tumour sample, the eye is placed in a sufficient formalin volume to cover the globe and is fixed for at least 48 hours.

After fixation, the eye is entirely submitted for microscopic examination and the above cited risk factors should be mentioned in the final report. A different processing method, which consists of creating an opening in the sclera at the periphery of the area containing most of the tumour, is no longer recommended, due to the risk of tissue loss of this very friable tumour.

1.6 Genetics of retinoblastoma

Retinoblastoma results from biallelic inactivation of the *RB1* tumour suppressor gene in a retinal cell (Dyson, 2016). Retinoblastoma is non-heritable when inactivation of both alleles occurs in a retinal cell; it corresponds to about 55% of cases, and the median age at diagnosis is 2 years. A minority of non-heritable retinoblastoma cases are due to somatic MYCN-amplification, with lower age of onset (Rushlow et al., 2013). There is a hereditary predisposition to retinoblastoma when the patient carries a *RB1* pathogenic variant in an allele at the constitutional level; it corresponds to about 45% of cases, and the median age at diagnosis is 1 year. Patients with *RB1* constitutional (germline) pathogenic variants are also predisposed to other cancers including sarcoma and cutaneous melanoma. All non-heritable retinoblastomas are unilateral, whereas most heritable retinoblastoma are bilateral.

Diagnosis of retinoblastoma is established by current ophthalmologic and – when treatment involves enucleation - histologic criteria. All retinoblastoma patients should be offered genetic counselling and mutational analysis of the *RB1* gene to search for a genetic predisposition (Houdayer et al., 2004). When a *RB1* gene pathogenic variant has been determined, molecular testing can be extended to relatives, i.e. children, siblings, parents, and ancestors. This process rapidly and unambiguously defines the carrier status of each family member and guides ophthalmological follow-up of relatives at risk. Ophthalmological surveillance (including fundus examinations, performed under general anaesthesia for babies, except for new-borns in the first month of life examined without anaesthesia if no suspect lesion is seen) can be stopped in a relative when genetic testing concludes to the absence of the pathogenic variant identified in the family. *RB1* screening has been demonstrated to enhance the quality of clinical management of the patient and relatives (Richter et al., 2003).

The most informative genetic testing consists in tumour DNA analysis, as it enables detection of the two *RB1* pathogenic variants responsible for retinoblastoma development. Subsequent genetic testing in blood targeted on the two pathogenic variants can determine whether the patient carries one of these variants at the constitutional level or not, i.e. whether the patient is predisposed to retinoblastoma and other cancers or not. Tumour sample is available when the primary treatment is enucleation. In case of conservative treatment, only genetic testing in blood is usually performed. Blood only genetic testing is less informative as in case of negative result, the existence of an undetected pathogenic variant cannot be excluded; in this situation, ophthalmologic follow up is therefore recommended for all siblings. Indirect genetic studies allow to determine whether siblings share *RB1* alleles with the index case. In the absence of alteration of RB1, if one or both *RB1* alleles are shared, then followup must be prolonged.

The analysis of *RB1* gene on circulating tumour DNA on aqueous humour (Berry et al., 2017; Ghiam et al., 2019; Le Gall et al., 2021) or plasma has recently been demonstrated as a new approach to get access to tumour DNA in patients with conservative treatments (Jiménez et al., 2021; Kothari et al., 2020).

1.7 Rationale for adjuvant or neo-adjuvant systemic chemotherapy in unilateral retinoblastoma managed by enucleation

The present European Standard Clinical Practice guidelines do not intend to specify which unilateral retinoblastoma cases should be enucleated, but rather to provide recommendations on the handling of these cases by radiologists, pathologists and paediatric oncologists, in association with ophthalmologists.

1.7.1 Metastatic risk in retinoblastoma

The risk of metastatic retinoblastoma is lower in high-income countries than in middle- and low-income countries. Early detection, acceptance of primary enucleation, appropriate indications for conservative treatment (intravenous or intra-arterial chemotherapy) and protocols for neo-adjuvant or adjuvant chemotherapy based on available MRI and pathological assessments are the main factors for this reduction of metastatic rate in high-income countries.

The exact rate of metastasis is therefore difficult to determine, but ranges between 1% and 2.5% in high- and middle-income countries. Retinoblastoma may metastasize to the central nervous system (CNS), bone, bone marrow or lymph nodes and, rarely, to other sites such as the liver. CNS involvement occurs mainly by direct extension of the tumour via the optic nerve or the subarachnoidal space (leptomeningeal dissemination) but can also be parenchymal or paraspinal through hematogenous dissemination, and rarely as a direct CNS extension through a facial bone. In exceptional "trilateral retinoblastoma" cases, the tumour may also disseminate to the cerebrospinal fluid from a midline mass. The median time between primary enucleation with high pathologic risk factors and first evidence of metastases is 10 months (range, 2–24 months), among the small proportion of patients receiving adjuvant chemotherapy who develop metastases. In those untreated, this median delay is approximately 5 months (Munier et al., 2019).

Patients with clinical, radiological, or histological high-risk factors undergo systematically bone marrow and cerebrospinal fluid cytopathological analysis at detection of the high-risk features. During follow up, they may be repeated on a regular basis during and after (neo-) adjuvant chemotherapy, according to the centers and protocols. Malignant cells in bone marrow or cerebrospinal fluid need to be evaluated by immunohistochemistry or immunocytology, due to the high rate of false positives on cytology.

1.7.2 Rationale based on the existing literature

Some retinoblastoma patients will benefit from adjuvant therapy (chemotherapy, and in the most severe cases irradiation). These adjuvant treatments can reduce the overall risk of metastasis from 24% to 4% (Shields and Shields, 1999).

A few prospective studies listed below have addressed the need for adjuvant or neoadjuvant therapies in advanced unilateral retinoblastoma primarily managed by enucleation. Recent advances in local therapy have allowed to widen the indications of conservative management (Munier et al., 2019). Group D disease, previously considered to be at high risk of enucleation due to vitreous invasion, even localized, is no longer systematically an obstacle to conservative treatment of the globe, because of recent advances in intra-arterial and intravitreal chemotherapy (Munier et al., 2012). However, primary enucleation remains the standard therapy for advanced ocular disease with suspected risk of extraocular extension (Abramson et al., 2015; Ancona-Lezama et al., 2020), namely Group E and advanced Group D eyes. There is a total agreement on the need of postoperative histopathological assessment to determine risk factors for metastatic spread. Based on the presence of one or several factors the child will receive a risk-stratified adjuvant treatment after enucleation, to reduce the risk of metastasis. Retrospective data demonstrate that without adjuvant therapy ~20% of patients with histological intermediate- and high-risk factors developed metastatic disease (Honavar et al., 2002; Khelfaoui et al., 1996). After introduction of a risk-stratified adjuvant treatment, less than 6% of patients with these histological risk factors developed metastatic disease (Kaliki et al., 2011; Khelfaoui et al., 1996). Recent nonrandomized prospective trials using risk-stratified adjuvant chemotherapy demonstrate overall survival (OS) rates for children with advanced retinoblastoma as high as 100% for most risk groups (Aerts et al., 2013; Chévez-Barrios et al.,

2019). In 2009, the International Retinoblastoma Staging and Working Group established consensus guidelines for the pathological examination of the extension of retinoblastoma after enucleation (Sastre et al., 2009). The histopathological risk factors for metastatic spread include massive choroidal invasion, invasion of the anterior chamber, scleral invasion and optic nerve infiltration (retrolaminar or cut-end section involvement). Choroidal or scleral invasion favour hematogenous spread, whereas the optic nerve infiltration increases the risk of central nervous system (CNS) metastases. For a risk-stratified use of adjuvant treatment, histopathological risk factors are further subgrouped into low-risk, intermediate-risk and high-risk factors. Although the benefit of adjuvant chemotherapy is apparent, data supporting the prognostic impact of different intensities of chemotherapy in relation with individual histopathological risk factors are limited due to the limited number of patients and of events, restricting the feasibility of randomized clinical trials (GL Chantada et al., 2004; Chantada et al., 2007). Treatment for retinoblastoma in European referral centres is similar but not uniform, and a variety of different chemotherapy and radiotherapy regimens have been used for adjuvant treatment in the last decades, as summarized in a recent survey coordinated by the EuRbG and ERN PaedCan (Dittner-Moormann et al., 2021).

2. PATIENT GROUP

The present guidelines focus on advanced unilateral intraocular retinoblastoma (group E and advanced Groupe D, *International Classification of Retinoblastoma*), non-eligible for eye conservation, without evidence of extraocular extension on the clinical examination and MRI at diagnosis.

The non-conservative management of retinoblastoma involves onco-paediatric departments for the administration of systemic chemotherapy and the appropriate follow-up of treated children.

There are several circumstances in which systemic chemotherapy is required, with variable degree of consensus, to lower the risk of metastatic disease:

- Clinical risk factors at diagnosis before enucleation: buphthalmia and/or raised intraocular pressure, massive orbital inflammation (non-consensual)
- Imaging risk factors at diagnosis: trans-scleral extension, large optic nerve invasion superior to ~5 mm (non-consensual, also depends on the surgical management, and the histopathological evaluation, although it can be altered after neoadjuvant chemotherapy, frequently administered in these situations). In case of tumour invasion of the optic nerve section, adjuvant radiotherapy of the orbital cavity will be required after enucleation.
- Histopathological risk factors on the enucleated eye, classified as low-risk (not requiring adjuvant chemotherapy), intermediate-risk (requiring adjuvant chemotherapy alone) and high-risk factors, including tumour invasion of the optic nerve section (requiring both adjuvant chemotherapy and orbital radiotherapy).

2.1 Ophthalmological diagnostic criteria

Ophthalmological evaluation of any suspected retinoblastoma case must be performed by a specialized ophthalmologist in an ocular oncology department. As outlined below, diagnosis and therapeutic decisions rely on several details of the ophthalmological examination requiring a specific expertise in retinoblastoma.

2.1.1 Ophthalmological presentations of advanced retinoblastoma requiring enucleation

There is no international consensus over a threshold retinoblastoma stage above which primary enucleation is required. However, it is widely admitted that advanced Group D tumours (IRC classification) / advanced cT2b (TNMH classification) occupying two thirds or more of the vitreous cavity, or with massive vitreal and/or subretinal seeding, and advanced Group E tumours / advanced cT3a-e tumours usually require primary enucleation. The advent and improvements in selective ocular administration routes such as ophthalmic artery catheterization (Abramson et al., 2008; Yamane et al., 2004) or intravitreal injections (Munier et al., 2012) has recently allowed to widen indications of conservative management. Exceptionally, Group E /cT3b eyes with limited anterior segment invasion may be eligible to conservative management relying on intravitreal/intracameral chemotherapy injections (Cassoux et al., 2017a; Munier et al., 2017).

2.1.2 Ophthalmological criteria for (neo-)adjuvant chemotherapy

Upfront enucleation is recommended in unilateral retinoblastoma patients for advanced tumours with 2/3 or more of the ocular volume filled by the tumour or with massive vitreous and subretinal seeding. In such cases, significant buphthalmia (i.e., TNMH cT3c stage) should be ruled out before surgery as well as extra-ocular extension (i.e., TNMH cT4 stage), especially macroscopic retrolaminar optic nerve invasion.

Major buphthalmia may increase the risk of intraoperative rupture of the eyeball and therefore tumour dissemination in the orbit. Its diagnosis is mainly based on clinical ophthalmological examination but can also be evaluated on the MRI scan by comparison with the contralateral eye.

Yet, the indication of neoadjuvant chemotherapy is still debated and varies among centers in the following situations

- Buphthalmia (clinically detected as an enlargement of the globe and an increased corneal diameter) and/or raised intraocular pressure (above an empirical threshold of approximately 40 mmHg) with iris neovascularization (TNMH stage cT3c). In these situations, it is reasonable to propose neoadjuvant chemotherapy, most often administered intravenously. Neoadjuvant chemoreduction will result in a decrease in intraocular pressure and axial length of the globe, thus decreasing the risk of globe rupture during the enucleation procedure.
- Massive orbital inflammation (cT3e), without MRI evidence of extraocular disease, is also a criterion for neoadjuvant chemotherapy but remains debated.

The drawback of neoadjuvant chemotherapy is that it usually impedes the proper evaluation of histopathological risk factors on enucleated globe, that are no longer interpretable after chemoreduction. Therefore, after neoadjuvant chemotherapy and enucleation, adjuvant chemotherapy can be performed even if pathological risk factors are not observed (non-consensual) (Choucair et al., 2020).

2.2 Imaging diagnostic criteria for (neo-)adjuvant chemotherapy

Preoperative MRI must be performed before enucleation to assess potential optic nerve invasion or presence of trans-scleral tumour spread in very advanced cases. In patients with advanced disease and extra-scleral and/or marked macroscopic optic nerve involvement, intravenous chemotherapy prior to enucleation is recommended (Choucair et al., 2020).

2.2.1 Retrolaminar optic nerve invasion

Analysis of the optic nerve is important, as retrolaminar involvement is a risk factor for metastasis and positive optic nerve resection margins and meningeal sheath invasion are associated with poor prognosis.

Limited (microscopic) retrolaminar invasion of the optic nerve shows no abnormalities on the MRI scan or minimal enhancement of the distal part of the optic nerve on post-contrast T1-weighted sequences. More advanced (macroscopic) optic nerve invasion is associated with enlargement and variable enhancement of the optic nerve (Choucair et al., 2020). Subsequently, invasion of the meningeal sheaths of the optic nerve may further lead to leptomeningeal spread in the CNS.

The accuracy of MRI for detecting early retrolaminar invasion is not 100%. However, when performed with appropriate high-resolution sequences, its specificity is estimated up to 95% and its negative predictive value is high enough to exclude optic nerve invasion with a high degree of confidence (Brisse et al., 2015; De Jong et al., 2014).

In routine practice, an isolated distal enhancement of the optic nerve less than 3 mm on MRI corresponds to a pre- or intralaminar invasion or a very limited retrolaminar invasion. Enucleation with a disease-free cut section of the optic nerve is possible, provided that the ophthalmologist achieves a section of the optic nerve 10 mm posterior to the eyeball, as recommended.

The extent of invasion of the optic nerve (orbital, optic canal or prechiasmatic segment), the surgical cut-section level and the need for a combined anterior ophthalmologic and neuro-surgical approach should be determined on pre-treatment MR imaging.

2.2.2 Trans-scleral extension

Orbital fat invasion after transscleral extension is mainly observed in patients with advanced diagnosis. The normal low signal intensity of the sclera is interrupted, and the relatively low signal intensity of the tumour is clearly visible compared to the normal high signal intensity of the orbital fat.

If trans-scleral extension is confirmed histologically, adjuvant radiotherapy after enucleation is recommended by most, but not all of contributing centers, in addition to adjuvant chemotherapy. Noteworthy, the trans-scleral extension may not be observed histologically after systemic chemotherapy. In those cases, a multidisciplinary discussion must determine whether irradiation is decided based on MRI only.

2.3 Histopathological diagnostic criteria for adjuvant chemotherapy

2.3.1 Low-risk criteria (no adjuvant chemotherapy)

- No choroidal or optic nerve invasion
- Focal choroidal invasion
- Pre-laminar or intra-laminar optic nerve invasion
- Aqueous humor seeding

2.3.2 Intermediate-risk criteria (adjuvant chemotherapy: debated)

- Massive choroidal invasion
- Scleral invasion
- Post-laminar optic nerve invasion (not reaching the surgical section)
- Anterior chamber invasion (trabecular meshwork, Schlemm's canal, ciliary body)

Noteworthy, combination of post-laminar optic nerve invasion (not reaching the surgical section) and massive choroidal invasion, has been associated with higher rates of extraocular relapse, especially in tumours located in the peripapillary area (adjacent to the optic nerve head), suggesting that a combination of intermediate-risk factors may require higher-intensity chemotherapy (Chévez-Barrios et al., 2019).

Moreover, the benefit/risk balance of adjuvant chemotherapy in case of intermediate risk should be assessed with respect to the health system and socio-economic situation (low-, middle- or high-income countries) since adjuvant chemotherapy is not devoid of side effects, especially cytopenia, infections, etc.

2.3.3 High-risk criteria (adjuvant chemotherapy and radiotherapy)

- Post-laminar optic nerve invasion reaching the surgical section
- Post-laminar optic nerve invasion with invasion of optic nerve meningeal sheath
- Trans-scleral (extra-scleral) extension

3. TREATMENT DETAILS

3.1 Treatment

3.1.1 Enucleation

When indicated, enucleation is performed after approval by a multidisciplinary tumour board involving ideally ophthalmologists specialized in ocular tumours, paediatric oncologists, radiologists, pathologists, and clinical geneticists. Moreover, written and signed informed consent by both legal holders of the parental authority must be obtained.

Briefly, dilated fundus examination must be performed before enucleation in order to verify the ocular status, confirm the indication and laterality of the enucleation. The conjunctiva is detached from the limbus, all six oculomotor muscles are sectioned and maintained by absorbable sutures. Enucleation is performed, ideally using a special instrument equipped with a metal wire that will ensure proper haemostasis during ~5 minutes and optic nerve section as posterior as possible (approximately 8-10 mm posterior to the globe). A porous bioceramic or high-density polyethylene orbital implant coated by an absorbable mesh is inserted into the anophthalmic orbit, and oculomotor muscles are sutured onto the implant. Tenon capsule and conjunctiva are finally sutured, and a fornix conformer is inserted beneath the eyelids.

Exceptionally, in case of suspected retrolaminar optic nerve involvement on MRI longer than ~5 mm, enucleation is performed with neurosurgeons who will section the optic nerve at its emergence from the optic canal, or adjacent to the optic chiasma via an orbital or coronal access. In these cases, neoadjuvant chemotherapy is often administered.

3.1.2 Neo-adjuvant chemotherapy in case of high-risk ophthalmological or imaging features

Indications:

- Ophthalmological criteria: Buphthalmia, extremely elevated intraocular pressure, orbital inflammation (debated)
- Imaging criteria: trans-scleral extension, large postlaminar optic nerve invasion (superior to ~5 mm) on MRI at diagnosis.

3.1.3 Adjuvant chemotherapy in case of intermediate or high-risk histopathological features

Indications: Intermediate or high-risk histopathological criteria mentioned above

In case of high-risk criteria, adjuvant orbital radiotherapy will also be required, either by external-beam or by orbital brachytherapy (to reduce the exposure of facial periorbital structures and the risk of secondary malignancy, especially in patients with germline *RB1* alterations). The usual radiation dose for retinoblastoma is 45 Gy.

Recommended adjuvant treatment regimens, as reported in the based in the 2021 survey by the European Retinoblastoma Group (Dittner-Moormann et al., 2021) :

Histopathological risk level	Type of histopathological risk factor	Recommended adjuvant treatment
Low	Focal choroidal invasion	None
	Pre- or Intralaminar optic nerve infiltration	None
	Aqueous humour seeding	None
Intermediate	Massive choroidal invasion	3-6 × VEC or 2 × VCy
	Scleral invasion (without extraocular disease)	4-6 × VEC or 2 × EC + 2 × VCy
	Postlaminar optic nerve infiltration	6 × VEC or 2 × EC + 2 × VCy or 4 × VEC
Intermediate (debated)	Anterior segment infiltration (iris, trabecular meshwork, Schlemm's canal, or ciliary body - with variations in anatomical definitions)	2 × EC + 2 × VCy is an option
High	Trans-scleral extension (extraocular disease)	6 × VEC or 3 × EC + 3× VCy + high-dose chemotherapy (debated) Followed by orbital irradiation (45 Gy)
	Infiltration of resection margin of optic nerve	

EC= etoposide, carboplatin, VEC= vincristine, etoposide, carboplatin; VCy= vincristine, cyclophosphamide

3.2 Assessment schedule and modalities after enucleation

The suggested followup schedules indicated below are not homogenized to date across all European countries and centres.

1.1.1 Ophthalmological assessment schedule

- 1 month postoperatively (for ocular prosthesis prescription and control of orbital cavity healing)

- Follow-up for contralateral fundus examination under general anaesthesia:
    - every 4 weeks until 1 year of age
    - then every 6 weeks from 12 to 18 months of age
    - then every 12 weeks from 18 months of age

- Follow-up without general anaesthesia from ~4-5 year of age (when allowed by the child cooperation), every 6 months

1.1.2 Paediatric oncology assessment schedule

Enucleation without (neo-)adjuvant systemic chemotherapy:

- every year for 5 years
- then an additional visit 5-10 years later to give explanations to the then-teenager regarding the disease and its consequences.

Enucleation with (neo-)adjuvant systemic chemotherapy:

- every 3 months for 1 year
- then every year until 16 years old

Some centres recommend an "intensive" schedule, independently from the administration of chemotherapy:

- every 3 months until 4 years old
- then every 6 months until 8 years old
- Then every year until 16 years old

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5. APPENDIX 1 – Intraocular Classification of Retinoblastoma (ICRB) staging system

Group A	Retinoblastoma ≤ 3 mm (in basal dimension or thickness)
Group B	Retinoblastoma > 3 mm (in basal dimension or thickness) or • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Additional subretinal fluid (≤3 mm from margin)
Group C	Retinoblastoma with: • Subretinal seeds ≤ 3 mm from tumour • Vitreous seeds ≤ 3 mm from tumour • Both subretinal and vitreous seeds ≤ 3 mm from tumour
Group D	Retinoblastoma with: • Subretinal seeds > 3 mm from tumour • Vitreous seeds > 3 mm from tumour • Both subretinal and vitreous seeds > 3 mm from retinoblastoma
Group E	• Extensive retinoblastoma occupying >50% globe or retinoblastoma with • Neovascular glaucoma • Opaque media from haemorrhage in anterior chamber, vitreous or subretinal space • Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, or anterior chamber

Classification proposed by Shields et al (Shields et al., 2006) and derived from the International Intraocular Retinoblastoma Classification proposed by Murphree (Murphree, 2005)

6. APPENDIX 2 – International Retinoblastoma Staging System (IRSS)

Stage 0	Conservative treatment
Stage I	Eye enucleated, completely resected histologically
Stage II	Eye enucleated, microscopic residual tumor
Stage III: regional extension	A: overt orbital disease B: preauricular or cervical lymph node extension
Stage IV: metastatic disease	A: Hematogenous metastases 1. Single lesion 2. Multiple lesions B: CNS extension 1. Prechiasmatic lesion 2. CNS mass 3. Leptomeningeal disease

NB: In cases of bilateral disease, the staging depends on the eye with more advanced disease.
Abbreviation: CNS = central nervous system.
(Chantada et al., 2006)

7. APPENDIX 3 – TNMH staging of retinoblastoma

Clinical classification

Category	Subcategory	Description
cTX		**Unknown evidence of intraocular tumour**
cT0		**No evidence of intraocular tumour**
cT1		**Intra-retinal tumour(s) with subretinal fluid ≤ 5 mm from base of any tumour**
	cT1a	Tumours ≤ 3 mm and further than 1.5 mm from disc and fovea
	cT1b	Tumours > 3 mm or closer than 1.5 mm from disc or fovea
cT2		**Intraocular tumour(s) with retinal detachment, vitreous seeding, or subretinal seeding**
	cT2a	Subretinal fluid > 5 mm from the base of any tumour
	cT2b	Vitreous seeding and/or subretinal seeding
cT3		**Advanced intraocular tumour(s)**
	cT3a	Phthisis or pre-phthisis bulbi
	cT3b	Tumour invasion of choroid, pars plana, ciliary body, lens, zonules, iris, or anterior chamber
	cT3c	Raised intraocular pressure with neovascularization and/or buphthalmia
	cT3d	Hyphema and/or massive vitreous hemorrhage
	cT3e	Aseptic orbital cellulitis
cT4		**Extraocular tumour(s) involving orbit, including optic nerve**
	cT4a	Radiologic evidence of retrobulbar optic nerve involvement or thickening of optic nerve
	cT4b	Extraocular tumour clinically evident with proptosis and/or an orbital mass
cNX		Regional lymph nodes cannot be assessed
cN0		No regional lymph node involvement
cN1		Evidence of preauricular, submandibular, and cervical lymph node involvement
cM1		**Distant metastasis without microscopic confirmation**
	cM1a	Tumour(s) involving any distant site (e.g, bone marrow, liver) on clinical or radiologic tests
	cM1b	Tumour involving the CNS on radiologic imaging (not including trilateral retinoblastoma)
H		**Hereditary Trait**
	HX	Unknown or insufficient evidence of a constitutional RB1 gene mutation
	H0	Normal RB1 alleles in blood tested with demonstrated high-sensitivity assays
	H1	Bilateral retinoblastoma, retinoblastoma with an intracranial primitive neuroectodermal tumour (i.e., trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of a constitutional RB1 gene mutation

(Mallipatna, 2017)

Pathological definitions

Category	Subcategory	Description
pTX		**Unknown evidence of intraocular tumour**
pT0		**No evidence of intraocular tumour**
pT1		**Intraocular tumour(s) without any local invasion, or with focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve**
pT2		**Intraocular tumour(s) with local invasion**
	pT2a	Concomitant focal choroidal invasion and pre- or intralaminar involvement of the optic nerve head
	pT2b	Tumour invasion of stroma of iris and/or trabecular meshwork and/or Schlemm's canal
pT3		**Intraocular tumour(s) with significant local invasion**
	pT3a	Massive choroidal invasion (> 3 mm in largest diameter, or multiple foci of focal choroidal involvement totalling > 3 mm, or any full-thickness choroidal involvement)
	pT3b	Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve
	pT3c	Any partial-thickness involvement of the sclera within the inner two thirds
	pT3d	Full-thickness invasion into outer third of the sclera and/or invasion into or around emissary channels
pT4		**Extraocular tumour(s) involving orbit, including optic nerve**
	pT4a	Evidence of extraocular tumour: tumour at the transected end of the optic nerve, tumour in the meningeal spaces around the optic nerve, full thickness invasion of the sclera with invasion of the episclera, adjacent adipose tissue, extraocular muscle, bone, conjunctiva, or eyelids
pM1		**Distant metastasis with microscopic confirmation**
	pM1a	Pathological evidence of tumour at any distant site (e.g., bone marrow, liver, or other)
	pM1b	Pathological evidence of tumour in the cerebrospinal fluid or CNS parenchyma

(Mallipatna, 2017)