Egyptian National Guidelines for Retinoblastoma

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Abbreviations

BM (bone marrow)
CDDP (cisplatin)
CNS (central nervous system)
COG (Children's Oncology Group)
CPM (cyclophosphamide)
CSF (cerebrospinal fluid)
CT (computed tomography)
EBRT (external beam radiation therapy)
ETOP (etoposide)
EUA (examination under anaesthesia)
FAB (French American British)
HICs (high-income countries)
IHC (immunohistochemistry)
IIRC (International Intraocular Retinoblastoma Classification)
IRSS (International Retinoblastoma Staging System)
IT (intrathecal)
IV (intravenous)
LMICs (low- and middle-income countries)
LN (lymph node)
MRI (magnetic resonance imaging)
NCCN (National Comprehensive Cancer Network)
RB (retinoblastoma)
RT (radiation therapy)
SEER (Surveillance, Epidemiology and End Results)
VCR (vincristine)

Glossary:

Intraocular Retinoblastoma: localized to the eye. It may be confined to the retina or may extend to involve other structures such as the choroid, ciliary body, anterior chamber, and optic nerve head. Intraocular retinoblastoma, however, does not extend beyond the eye into the tissues around the eye or to other parts of the body. [1][2]

Extraocular Retinoblastoma: extends beyond the eye. It may be confined to the tissues around the eye (orbital retinoblastoma), it may have spread to the central nervous system, or it may have spread systemically to the bone marrow or lymph nodes (metastatic retinoblastoma). [3]

Enucleation: The surgical procedure that involves removal of the entire globe and its intraocular contents, with preservation of all other periorbital and orbital structures**.** [4]
Exenteration: surgical procedure involving removal of the entire globe and its surrounding structures including muscles, fat, nerves, and eyelids (extent determined by disease being treated). [4]

Local treatment: Treatment that is administered by the ophthalmologist directly to the tumor including: [5-12]

1) **Cryotherapy** through a cryoprobe that uses extreme cold to destroy tumor tissue on the peripheral retina.
2) **Laser therapy** traditional photocoagulation (argon laser), in which the laser was applied around the tumor to target the tumor vasculature.
3) **Brachytherapy (plaque radiation therapy)** which can provide an effective means for local control.
4) **Transthermal thermotherapy** which is application of infrared light directly to the tumor.
5) **Intravitreal chemotherapy** intravitreal injection of melphalan or topotecan to control vitreous seeds.
6) **Intra-arterial chemotherapy** Direct delivery of chemotherapy melphalan into the eye via cannulation of the ophthalmic artery.

The International Intraocular Retinoblastoma Classification Grouping System [13-15]

Group A

- Small intraretinal tumors away from the foveola and disc.
- All tumors are 3 mm or smaller in greatest dimension, confined to the retina **and** All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc.

Group B

- All other tumours confined to the retina not in Group A.
- Tumour-associated subretinal fluid less than 3 mm from the tumour with no subretinal seeding.
- Tumour located closer than 3 mm to the optic nerve or fovea.

Group C

- Discrete local disease with minimal subretinal or vitreous seeding.
- Subretinal fluid, present or past, without seeding involving up to one-fourth of the retina
- Local fine vitreous seeding may be present close to the discrete tumor.
- Local subretinal seeding less than 3 mm (2 DD) from the tumor

Group D

- Diffuse disease with significant vitreous or subretinal seeding.
- Tumour(s) may be massive or diffuse.
- Subretinal fluid present or past without seeding, involving up to total retinal detachment.
- Diffuse or massive vitreous disease may include **greasy** seeds or avascular tumour masses.
- Diffuse subretinal seeding may include subretinal plaques or tumour nodules.

Group E

- Presence of any one or more of the following poor prognosis features:
  1- Tumour touching the lens.
  2- Tumour anterior to anterior vitreous face involving ciliary body or anterior segment.
  3- Diffuse infiltrating retinoblastoma.
  4- Neovascular glaucoma.
  5- Opaque media from haemorrhage.
  6- Tumour necrosis with aseptic orbital cellulites.
  7- Phthisis bulbi.

Unilateral advanced intraocular group D disease: Large tumors filling the vitreous for which there is little or no likelihood of restoring vision, extension of tumor to the anterior chamber, or diffuse extensive intraocular distribution of RB seeds whether subretinal or in vitreous. [16][17]

Useful vision: The retention of functional visual acuity, sufficient for age-appropriate visual tasks. It varies with age, tumour location, and treatment goals. [18]

Executive Summary

This guidance provides a data-supported approach to the diagnosis, treatment and follow up of paediatric patients diagnosed with retinoblastoma.

Recommendations	Level Of recommendation
1-Work up for newly diagnosed retinoblastoma	
We recommend bilateral examination under anaesthesia and full ophthalmology assessment for all patients suspected to have retinoblastoma.	Strong Recommendation
We recommend MRI of brain and orbits with IV contrast prior to therapy in all patients.	Strong Recommendation
For all tumors stage II and above - according to IRSS- we recommend metastatic work up: Bilateral bone marrow biopsies, bone scan, CSF cytology and whole spine MRI	Strong recommendation
Pathology is not recommended for initial confirmation of diagnosis prior to therapy.	Strong Recommendation
We recommend family counseling for all children with RB.	Strong recommendation
2- Treatment of Unilateral Intraocular Retinoblastoma	
Surgery We recommend enucleation for: • IIRC Group E • Failed eye salvage with local treatment and systemic chemotherapy in groups C and D • Unilateral advanced intraocular group D disease with no hope of useful vision.	Strong Recommendation
Optic nerve resection margin is recommended to be at least 10 mm	Strong Recommendation
Histopathological assessment and staging of the enucleated eye is recommended for all patients.	Strong Recommendation
Treatment of Group A	
We recommend local treatment for all group A eyes.	Strong Recommendation
Treatment of Group B	
We recommend both local treatment and systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) for a total of 6 cycles with 21-28 days interval in between cycles.	Strong Recommendation
Treatment of Groups C and D	
We recommend both local treatment and systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) for a total of 6 cycles with 21-28 days interval in between cycles.	Strong Recommendation

We recommend routine EUA with every 1 cycle and if progressive disease we recommend enucleation and histopathology examination.	Strong Recommendation
If NO high risk features in pathology, we do not recommend further treatment after enucleation.	Strong Recommendation
If high risk features are present in pathology, we recommend giving total 6 cycles of systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) with 21-28 days interval in between cycles.	Strong Recommendation
We recommend starting systemic chemotherapy whithin 35 days of enucleation for high risk features.	Strong Recommendation
Treatment of Group E	
We recommend enucleation upfront for all group E eyes	Strong recommendation
If NO high risk features in pathology, we do not recommend further treatment after enucleation	Strong recommendation
If high risk features are present in pathology, we recommend giving total 6 cycles of systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) with 21-28 days interval in between cycles.	Strong Recommendation
We recommend starting systemic chemotherapy whithin 35 days of enucleation for high risk histology.	Strong Recommendation
3-Treatment of Bilateral Intraocular Retinoblastoma	
We recommend dictating treatment protocol by the most advanced eye.	Strong Recommendation
We recommend upfront enucleation of the most advanced eye followed by histopathology. If the better eye is group A, B or C, we recommend enucleation of group D eyes. If both eyes are group D we recommend chemoreduction and focal therapy for both eyes.	Strong Recommendation
We recommend chemoreduction for groups B, C and D eyes as well as local therapy similar to unilateral intraocular treatment protocols.	Strong Recommendation
4- Treatment of Extraocular Retinoblastoma	
We recommend systemic chemotherapy followed by radiation therapy for IRSS stages II-III orbital and regional lymph node involvement.	Strong Recommendation

For stage IV metastatic eyes, we recommend systemic chemotherapy, followed by high dose chemotherapy and stem cell rescue.	Strong Recommendation
Recommended systemic chemotherapy regimen includes 4 cycles of 4 drug regimen (VCR-CDDP-CPM-ETOP)	Strong Recommendation
5- Surveillance	
We recommend EUA every 3-4 weeks for patients receiving active anti-tumor treatment till the end of therapy.	Strong Recommendation
We recommend 1-2 months EUA starting at the end of therapy and continuing for 24 months thereafter for patients who present with unilateral disease and are younger than 2 years of age at presentation or bilateral disease of any age.	Strong Recommendation
We recommend life long follow up and counseling for bilateral RB patients and patients with positive family history of RB as well as sibling screening.	Strong Recommendation
For sibling screening we recommend EUA at intervals: • Every 2 weeks since birth till 8 weeks of age, • then monthly till 1 year of age, • then every 3 months till 3 years of age, • then every 6 months till 7 years of age	Strong recommendation
For unilateral retinoblastoma patients who are older than 2 years of age we recommend extending ophthalmology examination intervals post therapy, reaching 6 monthly by age of 5 and annually thereafter.	Strong recommendation
We recommend that RB survivors treated with chemotherapy or EBRT , follow up at oncology clinic every 3 months then for longer intervals as clinically warranted.	Strong Recommendation

Introduction

Retinoblastoma is the most common primary intraocular malignancy in children, accounting for approximately 2–4% of all pediatric cancers. It typically manifests at a median age of two years. Significant advances in multidisciplinary care combined with implementation of novel therapeutic modalities have improved survival rates in HICs, with survival exceeding 95%. However, these outcomes remain difficult to replicate in LMICs, where delayed diagnosis and limited access to specialized care, persist as major barriers to effective management and timely treatment. The principal therapeutic objective remains the preservation of life, followed by ocular salvage and visual function retention whenever feasible.[19][20]

Scope and purpose of the Guideline:

This guideline was developed aiming to enhance the quality of care for retinoblastoma patients by establishing a consistent standard of care nationwide. They focus on aiding in the early diagnosis, screening, proper referral, treatment in a multidisciplinary approach, and follow-up of retinoblastoma to achieve better clinical outcomes.

Target audience

Clinicians who are involved in the care and treatment of patients with retinoblastoma, including paediatric oncologists, ophthalmologists, radiologists, radiotherapy experts, pathologists, social workers, geneticists and palliative care specialists.

Methodology

 A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation.

 inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence).
- Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

 All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cut-off points or rank the guidelines (any guideline scoring above 50% on the rigour dimension was retained)

The COG and NCCN guidelines are the main sources used while formulating the national guidelines for retinoblastoma.

 Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent

recommendations. Detailed information on GRADE is available through the on the following sites:
. GRADE working group: http://www.gradeworkingroup.org
. GRADE online training modules: http://cebgrade.mcmaster.ca/
. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

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Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

These are made when there is greater uncertainty about the four factors above or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations.

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations

1-Work up for newly diagnosed retinoblastoma

We recommend bilateral examination under anaesthesia and full ophthalmology assessment for all patients suspected to have retinoblastoma.

Strong recommendation, high quality level of evidence (Systematic review and meta-analysis) [13][21-23]

We recommend MRI of brain and orbits with IV contrast prior to therapy in all patients

Strong recommendation, high quality level of evidence (Systematic review and meta-analysis) [13][21-23]

For all tumors stage II and above - according to IRSS- we recommend metastatic work up: Bilateral bone marrow biopsies, bone scan, CSF cytology and whole spine MRI

Strong recommendation, high quality level of evidence (Systematic review and meta-analysis, Multicenter Registry-Based Study) [24-26]

Pathology is not recommended for initial confirmation of diagnosis prior to therapy.

Strong recommendation, moderate quality level of evidence (Expert consensus review) [27]

We recommend family counseling for all children with RB.

Strong recommendation, moderate quality level of evidence (Expert consensus review)[28]

2- Treatment of Unilateral Intraocular Retinoblastoma

Surgery

We recommend enucleation for:

- IIRC Group E
- Failed eye salvage with local treatment and systemic chemotherapy in groups C and D
- Unilateral advanced intraocular group D disease with no hope of useful vision.

Strong recommendation, high quality level of evidence (Retrospective reviews, SIOP guideline recommendations)[29-31]

Optic nerve resection margin is recommended to be at least 10 mm

Strong recommendation, moderate quality level of evidence (Retrospective review of clinical trials)[32]

Histopathological assessment and staging of the enucleated eye is recommended for all patients

Strong recommendation, high quality level of evidence (Systematic review and meta-analysis)[1]

Treatment of Group A

We recommend local treatment for all group A eyes

Strong recommendation, high quality level of evidence (Systematic review and meta-analysis)[8][9]

Treatment of Group B

We recommend both local treatment and systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) for a total of 6 cycles with 21-28 days interval in between cycles.

Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

Treatment of Groups C and D

We recommend both local treatment and systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) for a total of 6 cycles with 21-28 days interval in between cycles.

Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

We recommend routine EUA with every 1 cycle and if progressive disease we recommend enucleation and histopathology examination.

Strong recommendation, high quality level of evidence (Retrospective reviews, SIOP guideline recommendations)[29-31]

If NO high risk features in pathology, we do not recommend further treatment after enucleation.
Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

If high risk features are present in pathology, we recommend giving total 6 cycles of systemic IV three drug chemotherapy (Vincristine-Carboplatin-Etoposide) with 21-28 days interval in between cycles.
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We recommend starting systemic chemotherapy whithin 35 days of enucleation for high risk features

Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

Treatment of Group E

We recommend upfront enucleation for all group E eyes

Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

If NO high risk features in pathology, we do not recommend further treatment after enucleation.
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Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

We recommend starting systemic chemotherapy whithin 35 days of enucleation for high risk features

Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials)[33][34]

3-Treatment of Bilateral Intraocular Retinoblastoma

We recommend dictating treatment protocol by the most advanced eye.
Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials, Systematic review)[34-36]

We recommend upfront enucleation of the most advanced eye followed by histopathology. If the better eye is group A, B or C, we recommend enucleation of group D eyes. If both eyes are group D we recommend chemoreduction and focal therapy for both eyes.
Strong recommendation, high quality level of evidence (Prospective clinical trial, systematic review of COG trials, Systematic review)[34-36]

We recommend chemoreduction for groups B, C and D eyes as well as local therapy similar to unilateral intraocular treatment protocols.

Strong recommendation, high quality level of evidence (Prospective clinical trial)[31]

4- Treatment of Extraocular Retinoblastoma

We recommend systemic chemotherapy followed by radiation therapy for stages II-III orbital and regional lymph node involvement.
Strong recommendation, moderate quality level of evidence (COG prospective clinical trial)[37]

For stage IV metastatic eyes, we recommend systemic chemotherapy, followed by high dose chemotherapy and stem cell rescue.
Strong recommendation, moderate quality level of evidence (COG prospective clinical trial)[37]

Recommended systemic chemotherapy regimen includes 4 cycles of 4 drug regimen (VCR-CDDP-CPM-ETOP) with 3 weeks between cycles.

Strong recommendation, moderate quality level of evidence (COG prospective clinical trial)[37]

5- Surveillance

We recommend EUA every 3-4 weeks for patients receiving active anti-tumor treatment till the end of therapy.
Strong recommendation, high quality level of evidence (systematic reviews, SEER based analysis)[38-40]

We recommend 1-2 months EUA starting at the end of therapy and continuing for 24 months thereafter for patients who present with unilateral disease and are younger than 2 years of age at presentation or bilateral disease of any age.

Strong recommendation, high quality level of evidence (systematic reviews, SEER based analysis)[38-40]

We recommend life long follow up and counseling for bilateral RB patients and patients with positive family history of RB as well as sibling screening
Strong recommendation, high quality level of evidence (systematic reviews, SEER based analysis)[38-40]

For sibling screening we recommend EUA at intervals:

- Every 2 weeks since birth till 8 weeks of age,
- then monthly till 1 year of age,
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Strong recommendation, high quality level of evidence (systematic reviews, SEER based analysis)[38-40]

For unilateral retinoblastoma patients who are older than 2 years of age we recommend extending ophthalmology examination intervals post therapy, reaching 6 monthly by age of 5 and annually thereafter.

Strong recommendation, high quality level of evidence (systematic reviews, SEER based analysis)[38-40]

We recommend that RB survivors treated with chemotherapy or EBRT , follow up at oncology clinic every 3 months then for longer intervals as clinically warranted.

Strong recommendation, high quality level of evidence (systematic reviews, SEER based analysis)[38-41]

Clinical indicators for monitoring:

- Time of initiation of chemotherapy
- Initial MRI brain and orbit
- Pathology of the enucleated eye
- EUA visits initially and between treatment
- Initial grouping of intraocular retinoblastoma

Update of this guideline

This guideline will be updated whenever there is new evidence.

Annexes

The international Retinoblastoma Staging System[1-3][13]

Stage 0:

- Eye has not been enucleated and no dissemination of disease.

Stage I:

- Eye enucleated, completely resected histologically.

Stage II:

- Eye enucleated, microscopic residual tumor.

Stage III:

- Regional extension
  III A: Overt orbital disease
  III B: Preauricular or cervical lymph node extension

Stage IV:

- Metastatic disease.
  IVa: Hematogenous metastasis (without CNS involvement)
  IVa1: Single lesion
  IVa2: Multiple lesions
  IVb: CNS extension (with or without any other site of regional or metastatic disease)
  IVb1: Prechiasmatic lesion

IVb2: CNS mass
IVb3: Leptomeningeal and CSF disease

High risk pathology features [1-3] [13]

- The main high-risk feature is extension of the tumour in the optic nerve to the margin of the surgical resection.
- Post laminar optic nerve invasion;
- Involvement of anterior segment;
- Massive invasion of choroid > 3mm;
- Invasion of sclera;
- Extra scleral tumour extension.
- Any degree of concomitant choroid and optic nerve involvement.

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