Philippine Retinoblastoma Clinical Practice Guidelines

Retinoblastoma Guideline Development Group

August 2024

Disclaimer

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Adherence to this guideline is encouraged but it should not restrict the clinicians in using their clinical judgment and considering the patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors, policymakers, hospital administrators, and employers can also utilize this CPG but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

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- Philippine Society of Ophthalmic Plastic & Reconstructive Surgery
- Philippine Society of Ocular Oncology
- Philippine College of Radiology
- Philippine Pediatric Society
- University of the Philippines - Philippine General Hospital
- Philippine Children's Medical Center
- East Avenue Medical Center
- Jose Reyes Memorial Medical Center
- St. Luke's Medical Center
- Cancer Warriors Foundation

List of Abbreviations

AAO	American Academy of Ophthalmology
AHOPCA	Associacion de Hemato-Oncologia Pediatrica de Centro America
ASCR	Autologous stem cell rescue
CNS	Central nervous system
COI	Conflict of interest
CP	Consensus Panel
CPG	Clinical Practice Guideline
CRS	Canadian Retinoblastoma Society
CSF	Cerebrospinal fluid
CT	Computed tomography
DOH	Department of Health
EBRT	External beam radiation therapy
EUA	Examination under anesthesia
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICRB	International Classification of Retinoblastoma
IIRC	International Intraocular Retinoblastoma Classification
IMRT	Intensity modulated radiotherapy
IRSS	International Retinoblastoma Staging System
LMIC	Low- and middle-income countries
MRI	Magnetic resonance imaging
PAO	Philippine Academy of Ophthalmology
PGH	Philippine General Hospital
PSPO	Philippine Society of Pediatric Oncology
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
Rb	Retinoblastoma
RCT	Randomized controlled trial
SC	Steering Committee
SIOP-PODC	International Society of Pediatric Oncology-Paediatric Oncology in Developing Countries
TWG	Technical Working Group
UBM	Ultrasound biomicroscopy

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Executive Summary

This CPG is a set of 10 key questions with 30 graded recommendations and three ungraded good practice statements on screening, diagnosis, referral and treatment of children with retinoblastoma. This guideline is intended to be used by clinicians in the primary healthcare setting and specialists in cancer centers. It may also serve as the basis for the DOH-approved standards of care and the development of the PhilHealth benefit package for retinoblastoma.

The guideline development process followed the framework developed by DOH, consisting of the following phases: Preparation, Evidence Generation, Appraisal and Implementation.[1] The summary of recommendations for the CPG is summarized in Table 1.

The recommendations in this CPG shall hold and will be updated after 3 years or when new evidence arises.

Table 1. Summary of recommendations for Retinoblastoma

Recommendations	Strength of recommendations	Certainty of Evidence
Question 1: Among children with a family history of Retinoblastoma, will serial dilated fundus examination be acceptable towards early detection when genetic testing is not available?		
Among children with a family history of Rb, we recommend serial dilated fundus examination.	Strong	Low
Question 2: Among children with suspicion of Retinoblastoma, what is the recommended work-up to accurately diagnose Retinoblastoma?		
Among children with suspicion of Rb, we recommend to clinically diagnose based on comprehensive history, physical examination, and indirect ophthalmoscopy done by a capable ophthalmologist.	Strong	Low
Among children with suspicion of Rb, we recommend multidisciplinary discussions, imaging using ultrasound, cranial and orbital MRI with contrast or cranial and orbital CT scan.	Strong	Low
Question 3: Among children diagnosed with Retinoblastoma, what is the recommended work-up to accurately stage retinoblastoma?		
Among children diagnosed with Rb, we recommend multidisciplinary team discussions and appropriate imaging done in experienced centers.	Strong	Low

Among children diagnosed with Rb, we recommend ocular B scan 2D ultrasound and MRI or high-quality CT scan with contrast of the head and orbit for initial staging purposes.	Strong	Low
Among children diagnosed with Rb, when MRI of the brain and orbit is available and accessible, we recommend its preference over CT scan of the brain and orbit with high quality contrast.	Strong	Low
Among children diagnosed with Rb showing signs of extraocular disease, we suggest performing lumbar puncture and/or bone marrow examination for screening of metastasis.	Weak	Very Low
Question 4: Among intraocular Retinoblastoma patients on active ocular salvage therapy, what is the optimal timing of examination under anesthesia (EUA) to evaluate treatment response and disease status?		
Among intraocular Rb patients on active ocular salvage therapy, we recommend EUA, evaluation of treatment response, and local consolidation therapy to be performed by an ophthalmologist on the scheduled day of chemotherapy delivery.	Strong	Very Low
Question 5: Among newly diagnosed children with intraocular Retinoblastoma, what are the indications for upfront enucleation and ocular salvage therapy?		
Upfront Enucleation		
Among newly diagnosed children with intraocular Rb, we recommend that upfront enucleation be performed for ICRB Group E.	Strong	Low
Among newly diagnosed children with intraocular Rb, we recommend that upfront enucleation be performed for ICRB Group D when the other eye is normal or Group A.	Strong	Low
Among newly diagnosed children with intraocular Rb with no access to globe sparing modality or are at risk of poor follow up, we recommend that primary enucleation be relatively indicated. Primary enucleation is an option especially but not limited to unilateral Rb cases.	Strong	Low
Ocular Salvage Therapy		
Among newly diagnosed children with intraocular Rb, we recommend ocular salvage therapy for ICRB Groups A, B, and C.	Strong	Low

Among newly diagnosed children with BILATERAL, intraocular Rb, we recommend ocular salvage therapy for ICRB Group D eyes when it is the better of two eyes.	Strong	Low
Among newly diagnosed children with intraocular Rb, we recommend against ocular salvage therapy when there is lack of access and availability to globe sparing modalities (chemotherapy and local therapy such as laser and cryotherapy) or risk of poor follow-up.	Strong	Low
Among Rb patients undergoing ocular salvage therapy with recalcitrant or residual vitreous or anterior chamber Rb seeds, we recommend intravitreal or intracameral chemotherapy delivery with intravenous or intra-arterial chemotherapy.	Strong	Low
Among Rb patients undergoing ocular salvage of one eye requiring chemoreduction, we recommend intravenous or intra-arterial chemotherapy delivery.	Strong	Low
Among Rb patients undergoing simultaneous ocular salvage of bilateral eye disease requiring chemoreduction, we recommend intravenous systemic chemotherapy delivery.	Strong	Low
Question 6: Among patients with intraocular retinoblastoma not responding to ocular salvage treatment of chemotherapy with local therapy, what are the indications of external beam radiation therapy and enucleation?		
Among patients with intraocular Rb not responding to or with failure of ocular salvage treatments, we recommend enucleation or salvage external beam radiation therapy.	Strong	Low
Among patients with intraocular Rb not responding to or with failure of ocular salvage treatments, we recommend preference for enucleation over salvage external beam radiation therapy for patients less than one year old due to the increased risk of radiation induced secondary malignancy.	Strong	Low
Among patients with intraocular Rb not responding to ocular salvage treatments, we recommend enucleation when at high risk for treatment abandonment.	Ungraded good practice statement	

Among patients with intraocular Rb not responding to ocular salvage treatment of chemotherapy with local therapy, trial of salvage EBRT is a reasonable option when it involves the last remaining eye.	Ungraded good practice statement	
Question 7: Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, what is the recommended chemotherapy regimen?		
Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, we recommend referral for pathologic review of every enucleated eye by an experienced pathologist or ophthalmic pathologist.	Ungraded good practice statement	
Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, we recommend that the Rb specialist and pediatric oncologist screen for extraocular disease or metastasis.	Strong	Low
Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, we recommend treatment with prophylactic chemotherapy.	Strong	Low
Among newly diagnosed IRSS stage 1 children with high-risk pathologic features in settings 1, 2 and 3, we recommend adjuvant chemotherapy with Carboplatin + Etoposide + Vincristine regimen.	Strong	Low
Among newly diagnosed IRSS stage 1 children with high-risk pathologic features in settings 1, 2 and 3 when there is Carboplatin shortage, we recommend giving Cyclophosphamide + Vincristine ± Doxorubicin.	Strong	Low
Question 8: Among newly diagnosed IRSS stage 2 children, what is the recommended chemotherapy regimen?		
Among newly diagnosed IRSS stage 2 children, we recommend adjuvant systemic chemotherapy utilizing Vincristine + Etoposide + Carboplatin either alone or alternating with Cyclophosphamide and an anthracycline AND radiation of the orbital and optic nerve up to chiasm.	Strong	Low

Question 9: Among newly diagnosed IRSS stage 3 (or orbital) retinoblastoma, what is the recommended treatment regimen?		
Among IRSS stage 3 children in settings 1 and 2, we recommend neoadjuvant systemic chemotherapy followed by enucleation, adjuvant systemic chemotherapy regimen utilizing Vincristine + Etoposide + Carboplatin either alone or alternating with Cyclophosphamide and an anthracycline and radiotherapy to orbits and optic nerve up to the chiasm.	Strong	Low
Among IRSS stage 3 children in setting 3, we recommend neoadjuvant systemic chemotherapy followed by enucleation, adjuvant systemic chemotherapy regimen utilizing Vincristine + Etoposide + Carboplatin either alone or alternating with Cyclophosphamide and an anthracycline OR Vincristine + Cisplatin + high-dose Cyclophosphamide and radiotherapy to orbits and optic nerve up to the chiasm.	Strong	Low
Among IRSS stage 3 children, we do not recommend primary exenteration of the orbit for Rb.	Strong	Low
Question 10: Among newly diagnosed IRSS stage 4 (or metastatic) retinoblastoma, what is the recommended treatment regimen?		
Among newly diagnosed IRSS stage 4 children, we recommend palliative care and/or low dose chemotherapy or oral metronomic chemotherapy.	Strong	Low
Among newly diagnosed IRSS stage 4 children with Rb metastasis in bone marrow, bone or other organs or tissue in setting 3, we recommend enucleation of the eye, radiation, chemotherapy and hematopoietic stem cell transplant if there is a chemotherapy response.	Strong	Moderate
Among newly diagnosed IRSS stage 4 children with Rb tumor involving the meninges of the brain and spinal cord in setting 3, we recommend palliative treatment.	Strong	Very Low

1. Introduction

Retinoblastoma is the most common primary intraocular malignancy in children, accounting for 3% to 5% of childhood malignancies. Most cases are diagnosed in children under five years old, with a median age diagnosis of two years. Retinoblastoma can be classified as familial or sporadic, bilateral or unilateral, and heritable or nonheritable. The hereditary form is associated with the loss of function of the RB1 gene due to an inherited or new germline mutation. All bilateral and familial forms are heritable. About two-thirds of all cases are unilateral, of which only 15% are heritable.[2]

The epidemiology of Retinoblastoma varies among countries in terms of incidence, stage at diagnosis, and survival. The incidence rate of Retinoblastoma in the United States and Europe is between two to five per million children aged 0-14 years, with survival rates of over 90% as cases are detected early.[2] Low to middle-income countries (LMIC) report higher incidence rates and challenges with delayed diagnosis and advanced stages, resulting in low survival.[3,4] The advanced stage at diagnosis is seen in up to 42.9% of patients from low-income countries, 19.7% from lower-middle-income countries, 5.4% from upper-middle-income countries, and 0.8% from high-income countries.[3] Three-year survival rates also differ among regions at 99.5% in high-income countries, 91.2% in upper-middle-income countries, 80.3% in lower-middle-income countries, and 57.3% in low-income countries.[3]

In the Philippines, the Rizal and Manila regional population-based cancer registries reported a high incidence rate of 6.9 per million children 0-14 years.[5] This information shows that an estimated 230 new cases are expected each year. However, a survey done from 2014-2016 of 16 centers nationwide reported only seeing a total of 83 new patients per annum, pointing to an issue of underdiagnosis.[6] Local data from the Philippine General Hospital (PGH) of 95 patients from 2014-2016 showed that 48% were Stage 3 and 4 diseases at diagnosis.[6] The 3-year overall survival rate was only 43%, and abandonment of treatment occurred at 11%.[6] Moreover, a 10-year multicenter retrospective study among retinoblastoma patients from eleven institutions in Luzon, Visayas, and Mindanao revealed that annually, a median of 58 ± 10 new cases were seen, with 71% having unilateral disease.[7] The median delay in consultation is nine months, the longest in patients with unilateral disease and those from the Visayas region. In addition, 47% of patients presented at diagnosis already had extraocular disease.[7]

The diagnosis and treatment of Retinoblastoma requires hospitals to have a multidisciplinary team, including a pediatric ophthalmologist, radiation oncologist, and pediatric oncologist, as well as specialized equipment.[8] At the health system level, a robust Retinoblastoma referral pathway is essential where complex cases are sent promptly to advanced centers with a well-equipped and experienced multidisciplinary care team. These pose a significant healthcare investment for a rare disease, especially in low- and middle-income countries. In the Philippines, surveys among eye and cancer centers on Retinoblastoma service delivery highlighted the problems of lack of treatment standards and access to multidisciplinary care.[6,9,10] Currently, there is no official assessment of the

capacity and resources of local Eye and Cancer Centers to provide comprehensive retinoblastoma care. The country also does not have a defined retinoblastoma referral pathway. However, the classification of Cancer and Eye Centers according to general oncologic and ophthalmic service capacity (basic comprehensive care, advanced comprehensive care, and national specialty centers) has started. The basis of this resource-stratified framework classification considered base facility (infrastructure), resource level (i.e., service capabilities), catchment population, diagnostic, medical and surgical services, fixed medical assets, surgical infrastructure and equipment, human resource assets, training, research, and other services.[11]

The National Integrated Cancer Control Act (NICCA) mandates the creation of Cancer Clinical Practice Guidelines (CPGs) for adult and pediatric populations. Well-implemented CPGs ensure appropriate, effective, and cost-efficient treatments are provided. Countries with national retinoblastoma CPGs, such as Canada and the United Kingdom, have streamlined patients' diagnosis, referral, and multidisciplinary treatment. Retinoblastoma survival rates in these countries are over 95%.[12] For low- and middle-income countries, the Pediatric Oncology in Developing Countries (PODC) committee of the International Society of Pediatric Oncology (SIOP) proposed retinoblastoma treatment guidelines contextualized according to the hospitals and the country's capacity to deliver care. Setting 1 applies to centers and countries with the fewest resources and minimal technology (e.g., low-dose chemotherapy, imaging, ophthalmologic and pathologic services). Setting 2 is for essential resources and Setting 3 is for centers and countries with modern resources and technologies.[13]

In their Administrative Order 2018-0019, the DOH provides the framework for quality CPG development.[1] Currently, only three pediatric cancers have local CPGs: Acute lymphoblastic leukemia, Burkitt's lymphoma, and Wilms tumor. Although a common retinoblastoma protocol, RB Metro Manila, has been used by PGH, East Avenue Medical Center, and Philippine Children's Medical Center since 2013, a national evidence-based CPG is needed to improve poor treatment outcomes.[14]

2. Objective, Scope, Target population and Target users

The Philippine Retinoblastoma Clinical Practice Guideline is composed of 10 key questions with 30 graded recommendations and three ungraded good practice statements that are directed towards the screening, diagnosis, referral and treatment of children with retinoblastoma to improve the overall clinical outcomes and survival of patients following a resource stratification. Through this guideline, the Rb GDG aims to provide locally applicable and standardized practice guidance for pediatric patients with Rb across healthcare setting.

This is intended to be used by clinicians in the primary healthcare setting and specialists in cancer centers. It may also serve as a basis for the DOH-approved standards of care and the development of the PhilHealth benefit package for retinoblastoma.

3. CPG Development Methodology

The guideline development process followed the framework developed by DOH, consisting of the following phases: Preparation, Evidence Generation, Appraisal, and Implementation. See Figures 1 and 2. It followed the ADAPTE process of CPG development.[15]

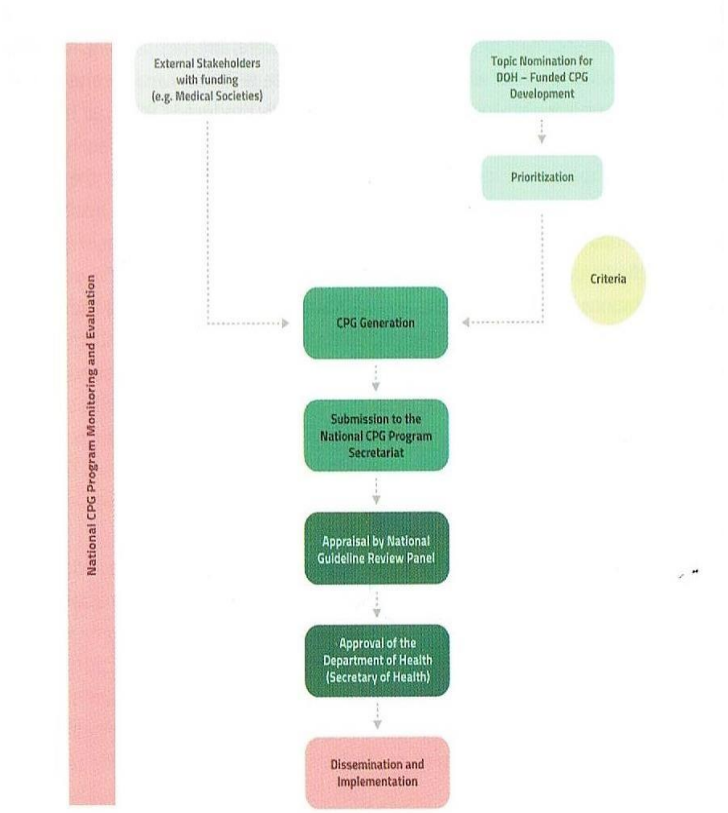

Figure 1. DOH Clinical Practice Guideline Development Process[1]

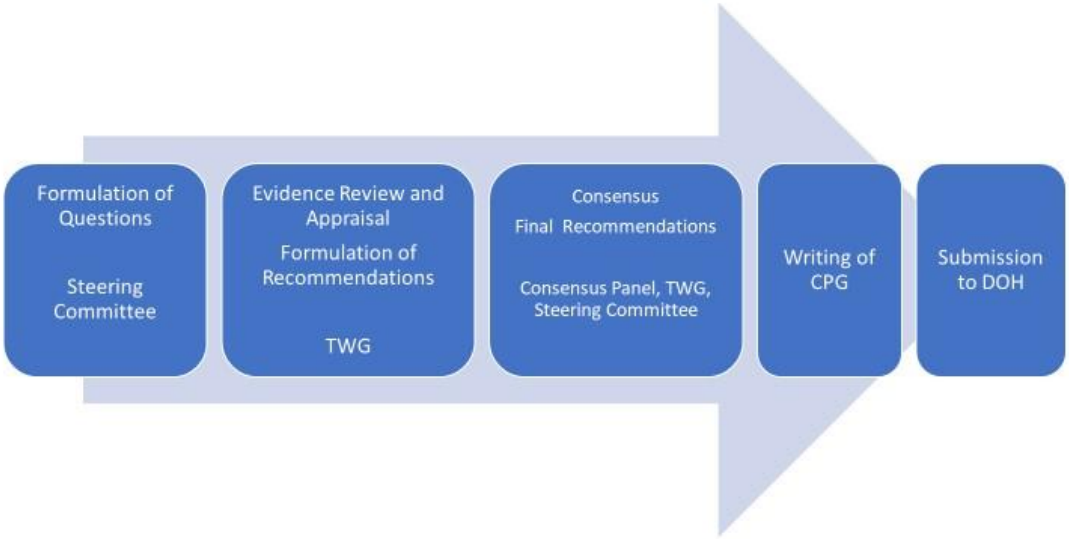

Figure 2. Flow of CPG Generation

A. Creation of Working Groups

The Steering Committee (SC) was composed of specialists, methodologist, non-medical doctor and policymaker: Ana Patricia Alcasabas, M.D. (Pediatric Oncologist), Gary John Mercado, M.D. (Ophthalmologist Ocular Oncologist), Nonette Cupino, M.D. (Radiation Oncologist), Clarito Cairo Jr. M.D. (Department of Health), Cherie Grace G. Quingking, M.D. (Methodologist) and Mr. Teddy S. Dizon (Layperson).

A Technical Working Group (TWG) was created to review and grade the evidence. The TWG was composed of clinical epidemiologists, evidence-based medicine practitioners, and biostatisticians.

A Consensus Panel (CP) was formed composed of content experts from the government and private sectors including primary care providers, pediatric clinicians, public health practitioners, program implementers, patient representatives, and representatives from different medical societies such as Pediatric Oncology, Ophthalmology, Radiation Oncology, Genetics, Pathology and Palliative Care.

All members of the steering committee, technical working group, and consensus panel accomplished a written conflict of interest (COI) declaration prior to their participation. COI declaration form was provided to document the disclosure of COIs. Also, an agreement to the publication of the CPG contributing to the formulation of recommendations is documented. The COIs were screened independently for recommendation of extent of participation or COI management. All disclosed COIs and corresponding action taken were reported and published in the annex of this document. Any serious COIs resulted in the member's exclusion from the project.

B. CPG Development

Identification of key clinical issues

The Steering Committee convened to identify key clinical issues. A total of 10 key questions needing recommendations were prioritized and formulated based on the issues identified. The questions were constructed using the PICO Framework (population, intervention/exposure, comparison, and outcomes).

PICO	Description
Population	Among pediatric age group at risk of, and newly diagnosed with Rb
Intervention	Screening, Diagnosis, Referral and Treatment
Comparator	Medical specialist and allied health professionals
Outcomes	Overall survival rate, disease-free survival, recurrence, and remission

Review and Grading of Evidence

Considering the time and resources to produce quality CPGs, it is recommended that existing guidelines be adapted to reduce duplication of effort and update existing guidelines in a shorter period of time. In this CPG development process, guideline adaptation by the ADAPTE method was considered to address specific health questions generated. Independent methodologists and reviewers determined if adaptation of any existing CPG was feasible and consequently created the evidence base and recommendation matrix.

The evidence reviewers utilized the ADAPTE method to review existing guidelines for inclusion in the evidence base and drafting of recommendation matrix. The ADAPTE collaboration has developed a systematic approach to aid in the adaptation of guidelines. The systematic approach aids in the use and modification of existing guidelines to customize an existing guideline to suit the local context while addressing relevant health questions. A systematic search of existing guidelines in multiple databases, including search for existing Retinoblastoma clinical practice guidelines as well as published and unpublished studies based on PICO, MeSH and free text through electronic databases including MEDLINE, Cochrane Library, and local databases. Latest versions of the guidelines were also searched to ensure currency of the recommendations. Assessment of the guidelines yielded from the systemic search were then given consideration for adaptation by assessment if it meets the qualities of a high-quality guideline using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument as well as if it can address the specific clinical questions. The AGREE II instrument provides a framework for assessing the quality of CPGs. The 23 items in the AGREE instrument assess the methods used for developing the guideline and quality of reporting. Assessment is focused on the rigor and overall score. The domains and criteria for the AGREE II tool are shown in Annex N. The guidelines were assessed for guideline quality, currency, content, consistency, and applicability. The characteristics and contents of the source guidelines are summarized in Annex C.

The ERE drafted the initial recommendation statements to include level of evidence based on the source guidelines and its references. All guidelines included utilized by recommended Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for evaluation of level of evidence. See Table 2.

Table 2. Quality of evidence using the GRADE Framework[16]

Quality of Evidence		Study Design	Lower if:	Higher if:
High	Further research is very unlikely to	Randomized controlled trials (RCTs)	Study quality: Poor quality of implementation	Stronger association: Large

	change confidence in the estimate of effect		of RCT Inconsistency of results Indirectness: Different population, intervention, outcomes Imprecise results: High probability of reporting bias	magnitude of effect, no plausible confounders Very large magnitude of effect, no major threats to validity Dose response gradient
Moderate	Further research is likely to have an impact on the confidence in the estimate of effect	Downgraded RCTs or upgraded observational studies		
Low	Further research is very likely to have an important impact on the confidence in the estimate of effect	Observational studies		
Very Low	Any estimate of effect is very uncertain	Case series or expert opinion		

The GRADE approach was also used to evaluate evidence on the diagnosis of retinoblastoma as shown in the tables below. See Tables 3 and 4.

Table 3. Factors that decrease the quality of evidence for studies of diagnostic accuracy and how they differ from evidence for other interventions[17]

Factors that determine the quality of evidence	Explanation of how the factor may differ from the quality of evidence for other interventions
Study design	<u>Different criteria for accuracy studies</u> Cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard (best possible alternative test strategy) are considered high quality and can move to moderate, low or very low depending on other factors.
Risk of bias (limitations in study design and execution)	<u>Different criteria for accuracy studies</u> ● Representativeness of the population that was intended to be sampled ● Independent comparison with the best alternative test strategy ● All enrolled patients should receive the new test and the best alternative test strategy

	● Diagnostic uncertainty should be given ● Is the reference standard likely to correctly classify the target condition?
Indirectness Patient population, diagnostic test, comparison test and indirect comparisons of tests	<u>Similar criteria</u> The quality of evidence can be lowered if there are significant differences between the populations studied and those for whom the recommendation is intended (in prior testing, the spectrum of disease or co-morbidity); if there are important differences in the tests studied and the diagnostic expertise of those applying them in the studies compared to the settings for which the recommendations are intended; or if the tests being compared are each compared to a reference (gold) standard in different studies and not directly compared in the same studies. <u>Similar criteria</u> Panels assessing diagnostic tests often face an absence of direct evidence about impact on patient-important outcomes. They must make deductions from diagnostic test studies about the balance between the presumed influences on patient-important outcomes of any differences in true and false positives and true and false negatives in relationship to test complications and costs. Therefore, accuracy studies typically provide low quality evidence for making recommendations due to indirectness of the outcomes, similar to surrogate outcomes for treatments.
Important Inconsistency in study results	<u>Similar criteria</u> For accuracy studies, unexplained inconsistency in sensitivity, specificity or likelihood ratios (rather than relative risks or mean differences) can lower the quality of evidence.
Imprecise evidence	<u>Similar criteria</u> For accuracy studies, wide confidence intervals for estimates of test accuracy, or true and false positive, and negative rates can lower the quality of evidence.

High probability of Publication bias	Similar criteria A high risk of publication bias (e.g., evidence only from small studies supporting a new test, or asymmetry in a funnel plot) can lower the quality of evidence.
Upgrading for dose effect, large effects residual plausible bias and confounding	Similar criteria For all these factors, methods have not been properly developed. However, determining a dose effect (e.g., increasing levels of anticoagulation measured by INR increase the likelihood for vitamin K deficiency or vitamin K antagonists). A very large likelihood of disease (not of patient-important outcomes) associated with test results may increase the quality evidence. However, there is some disagreement if and how dose effects play a role in assessing the quality of evidence in DTA studies.

Table 4. Quality Criteria of Diagnostic Accuracy Studies from QUADAS-2[18]

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 X 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without know-ledge of the results of the reference standard? If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?

Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?

Formulation of Recommendations

The summary of the findings and preliminary recommendations was created by the TWG and sent to the Steering Committee as well as the Consensus Panel for review. A face-to-face meeting was held with all the group members present to discuss the recommendations and issues or concerns arising. Panelists voted on the direction of recommendations (i.e., for or against) based on their evaluation of the potential positive and negative effects of an intervention or test on outcomes deemed "critical." A strong recommendation was made when the panel was confident that the benefits of the intervention or test outweighed any drawbacks, or vice versa. A weak recommendation was issued when the panel had uncertainties about the trade-offs, due to factors such as insufficient high-quality evidence, unclear estimates of benefit or harm, limited applicability to specific populations or settings, or when the expected benefits came with significant costs.

Factors influencing the strength of recommendations include the balance between benefits and harms, costs, feasibility and acceptability, values and preferences, baseline risks, and resource implications. See Table 5. The moderator facilitated the session using the nominal group technique for consensus building.

On applicability of the recommendations, the recommendation matrix developed was for finalization of the CP who were provided by the evidence reviewers with a guide on determining the strengths of recommendation. Recommendations may either be strong or weak. Strong recommendations refer to issues where the guideline development group may be confident that the benefits outweigh the risks or costs of an intervention, or vice versa, whereas weak recommendations are those where there is appreciable uncertainty on the calculus of benefits and risks. A summary of the implication of recommendation strength on each type of guideline user which is reproduced in full in Table 5.

Table 5. Implications of strength of recommendations to patients, clinicians and policy makers using the GRADE approach[16]

Strength of Recommendation		Implications of the recommendations		
		Patients	**Clinicians**	**Policy Makers**
Strong	The benefits outweigh the harm. There are no costs or access issues for the general population	Most people in the situation would want the recommended course of action and only very few would not; request for discussion if the intervention is not offered	Most patients should receive the recommended course of action. The recommendation can be used as a quality or performance indicator	The recommendation can be adopted as a policy in most situations
Weak	Best available evidence is very low to low quality The magnitude of benefits and risks is uncertain or closely balanced for the general population and applicable to a specific group, population or setting Benefits may not warrant the cost or resource requirements in all settings	Most people in the situation would want the recommended course of action, but many would not	Different choices are appropriate for different patients, and clinicians must help patients arrive at a management decision consistent with the patients' values and preferences	Policy making will require substantial debate and involvement of stakeholders

The recommendations presented were voted upon by the consensus panel and a minimum of 75% agreement was needed to reach consensus. A maximum of 3 rounds of voting was held until consensus was reached. Recommendations were stated as either strong or weak.

Due to resource and schedule difficulties encountered to convene the CP, the recommendations that did not reach 75% agreement after 3 rounds of voting, eDelphi technique was done. Two rounds of eDelphi was done to reach final consensus for the remaining recommendations.

The eDelphi using Google survey was facilitated by the research assistant. eDelphi gathered the voting of the CP was done as follows: A – accept completely, B – accept with some reservations, C – accept with major reservations, D – reject with some reservations, E – reject completely. After two rounds of eDelphi, all recommendation statements reached consensus of more than 75% voted A or B. Finally, the contextualization of recommendation statements is included based on the values, preferences and lived experiences shared by the CP.

Formulation of Good Practice Statement

The formulation of the good practice statements reflects the values, perspectives and preferences of both SC and CP. The ungraded good practice statements were carefully discussed and deemed to be necessary with high level of certainty that the overall benefits outweigh harms. The checklist for what makes a good practice statement is summarized in Table 6.[19,20]

Table 6. Checklist for Good Practice Statement[19]

A question applicable to any recommendation (but often violated in good practice statements): (i) Is the statement clear and actionable? Question particular to good practice statement: (ii) Is the message necessary regarding actual health care practice? (iii) After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences? (iv) Is collecting and summarizing the evidence a poor use of guideline panel's limited time and energy (opportunity cost is large)? (v) Is there a well-documented clear and explicit rationale connecting the indirect evidence? The answer to all questions (ii) to (v) should be yes to proceed with a good practice statement.

Review and Writing of the Final CPG Document

The final recommendations, and consensus issues, will be turned over to the scientific writer for the development of the final manuscript using the format from the 2002 Conference on Guideline Standardization (COGS).[21] In the next publications, there be three different versions will be prepared according to the target user: a detailed full text, a quick reference guide, and a layman's version for the public.

In the development this CPG, the funders, Philippine Academy of Ophthalmologists, Philippine Society of Pediatric Oncology, University of the Philippines – Philippine General Hospital Expanded Research Office and St. Jude Children's Research Hospital have neither imposed nor exerted influenced on the generating PICO questions, evidence gathering and synthesis, development and finalization of recommendations, and finalization of this CPG document.

Self-evaluation of the Final CPG Document

Three non-medical individuals, 1 male and 2 females, independently evaluated the CPG document using the AGREE II Reporting Tool.

External Review of CPG Document

The guideline developer solicited feedback from policymakers, general practitioners and specialists from August 8 to 22, 2024 using AGREE II Reporting Tool. The feedback was deliberated by the SC and incorporated in the finalization of this document. The external evaluation covered six domains: (1) scope and purpose, (2) stakeholder involvement, (3) rigor of development, (4) clarity of presentation, (5) applicability, and (6) editorial independence. Additionally, the overall guideline assessment was included as part of the evaluation conducted by all six CPG external evaluators (see Appendix O).

Submission to the DOH for Appraisal

The final draft will be subjected to the approval of the National Guideline Review Panel of the Department of Health.

The approved CPG the steps for information dissemination, impact assessment, and updating of recommendations will be done. The need to update the CPG will be determined annually by the members of the Steering Committee based on review of current literature. If an update is necessary, the CPG Task Force will be reconvened.

4. Recommendation and Evidence Summaries

4.1 Among children with a family history of Retinoblastoma, will serial dilated fundus examination be acceptable towards early detection when genetic testing is not available?

Recommendation
Among children with a family history of Rb, we recommend serial dilated fundus examination. ***(Strong recommendation, low certainty of evidence)***

Consensus Issues

Ideally, all retinoblastoma patients should undergo genetic testing for genomic RB1 mutation. Those positive for a mutation have familial retinoblastoma and their relatives (children) are at risk for getting the disease. Likewise, these children may also develop a second retinoblastoma in the other eye.

Currently, genetic testing for RB1 mutation is not available in the Philippines and the resources required to send the specimen overseas are an out-of-pocket expense.

In Settings 1 and 2, clinical screening for the early detection of retinoblastoma should be prioritized for at-risk children, particularly in lower-middle-income countries like the Philippines, where genetic testing may not be readily available. According to the World Bank, lower-middle-income countries are defined as those with a gross national income (GNI) per capita between $1,146 and $4,515. Clinical screening is especially recommended for two groups of children: (1) those with a family history of retinoblastoma, and (2) those who have recently been diagnosed and treated for the condition.

Review Methods

Without publication date filter, a systematic search was done from September 2022 to June 2023, using international (i.e., Medline, Central, and Google Scholar) and local databases (i.e., HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms ((“at risk children” OR “with family history”) AND “Retinoblastoma” AND “screening”). No additional filter was applied for comprehensive search.

No relevant randomized controlled trials were found during the search. Two clinical practice guidelines were included after appraisal using AGREE II Tool for ADAPTE.

Evidence Summary and Source of Guideline Recommendations

Children "at risk" was defined as a person with family history of retinoblastoma in a parent, sibling, or first- or second-degree relative.[22] Ideally, it is recommended that risk stratification with genetic counseling and testing serve as the basis for screening and present a risk-stratified schedule for ophthalmic screening examinations for countries with available resources. Systematic screening of children at elevated risk because of family history of retinoblastoma has two purposes: (1) to provide a method for detecting disease at the earliest possible stage and (2) to focus care on the children at highest risk, while decreasing unnecessary evaluations for children at low or no risk above that of the general population.[22] Table 7 summarizes the screening recommendations for pediatric patients at risk for developing retinoblastoma.

Table 7. Screening Recommendations Among at Risk Pediatric Patients

Summary of Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
All children at elevated risk for retinoblastoma above the population risk require serial dilated fundus examination by an ophthalmologist with experience in retinoblastoma. Depending on the clinical setting and resources, this may be an ocular oncologist, pediatric ophthalmologist, retina specialist, or comprehensive ophthalmologist.	ADAPTE	Low	AAO (2017)[23]
We recommend screening for at-risk children from birth up to the age of 7 years. After age 7 years, no further screening of asymptomatic children is recommended.	ADAPTE	Low	AAO (2017)[23]
We recommend that all infants and children, in whom someone has observed a white pupil (either in person or in a photograph), have a full dilated-eye examination including red reflex test within 72 hours by an ophthalmologist or medical practitioner who is fully aware of the importance of leukocoria as a sign of Rb.	ADAPTE	Consensus statement	AAO (2017)[23]
Examinations under anesthesia are strongly considered for any child who is unable to participate in an office examination sufficiently to allow thorough examination of the retina based on the decisions on the basis of	ADAPTE	Low	AAO (2017)[23]

available resources and expert clinician preference.			
We recommend that following completion of treatment, EUAs for children at risk of developing new Rb tumors continue as often as every 3 weeks, or at longer intervals as tumor activity decreases, until risk of new tumors and recurrences are low, and the child is able to cooperate in clinic (at about 3 years of age).	ADAPTE	Moderate	CRS (2009)[8]

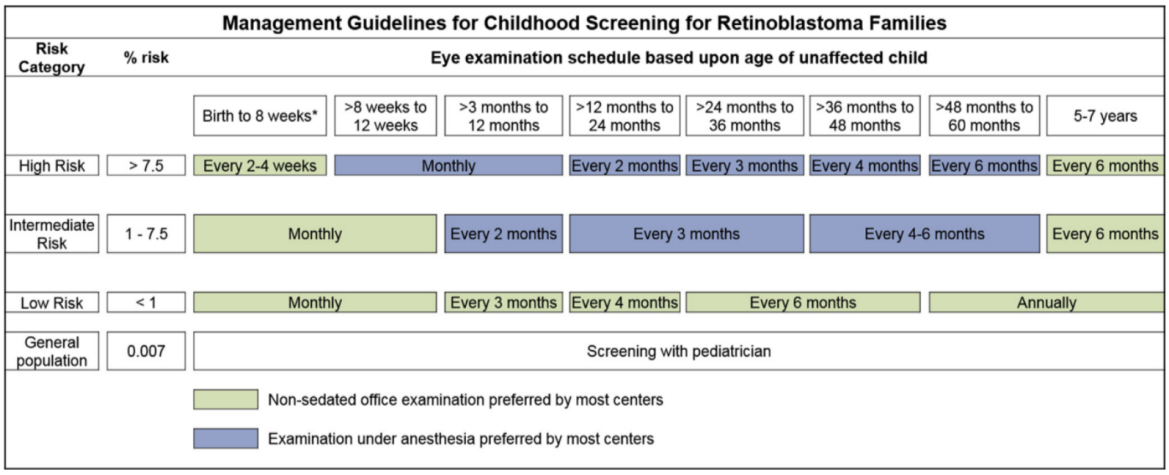

Figure 3. Management guidelines for childhood screening for Rb families[23]

The presented schedules are general guidelines and reflect a schedule for examination in which no lesions of concern are noted (see Figure 3). It may be appropriate to examine some children more frequently. Decision regarding examination methods, examination under anesthesia (EUA) versus non-sedated examination in the clinic are complex and best decided by the clinician in discussion with the patient's family. The preference of most clinical centers involved in the creation of this consensus statement is reflected but individual centers may make policy decisions based on available resources and expert clinician preference. Examination under anesthesia is strongly recommended for any child who is unable to participate in a clinic examination sufficiently to allow thorough examination of the retina. Clinical centers may prefer EUA for high- and intermediate-risk children (calculated risk >1% from birth to 8 weeks of age).

4.2 Among children with suspicion of Retinoblastoma, what is the recommended work-up to accurately diagnose Retinoblastoma?

Recommendations

1. **Among children with suspicion of Rb, we recommend to clinically diagnose based on comprehensive history, physical examination, and indirect ophthalmoscopy done by a capable ophthalmologist. *(Strong recommendation, low certainty of evidence)***
2. **Among children with suspicion of Rb, we recommend multidisciplinary discussions and imaging using B scan ocular ultrasound, cranial and orbital MRI with contrast or cranial and orbital CT scan. *(Strong recommendation, low certainty of evidence)***

Consensus Issues

The diagnosis of Retinoblastoma is mainly clinical through a detailed history and comprehensive ophthalmic examination.

Accuracy, availability, accessibility, cost-effectiveness, and safety were implied when selecting additional diagnostic tests for pediatric patients suspected with Retinoblastoma. The tests may include B scan ocular ultrasound, contrast enhanced MRI or CT scan, and its use will depend on the suspected degree of the disease and the test's availability. After the ophthalmologist has examined and made an initial assessment, a clear rationale as to why these diagnostic tests need to be used should be established.

The current reference guidelines reiterated that, if the facility does not have minimum equipment, and cannot diagnose and treat, the attending medical doctor must refer the patient to capable centers.

Review Methods

Without publication date filter, a systematic search was done from September 2022 to June 2023, using international (i.e., Medline, Central, and Google Scholar) and local databases (i.e., HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms "Retinoblastoma" AND "diagnostics". No additional filter was applied for comprehensive search.

No relevant randomized controlled trials were found during the search. One clinical practice guideline and one study were included after appraisal using AGREE II Tool for ADAPTE.

Evidence Summary and Source of Guideline Recommendations

Early detection and immediate referral of children with retinoblastoma (Rb) increases the possibility of saving lives and eyes and preserving useful vision. Diagnosis of retinoblastoma is mainly clinical and focused on the findings of a dilated fundus examination utilizing indirect ophthalmoscopy. Diagnosis of retinoblastoma includes clinical evaluation, physical examination and diagnostics which are useful for staging of retinoblastoma (see Table 8). B scan ultrasound, contrast enhanced cranio-orbital MRI or CT scan are other ancillary diagnostic tests used for confirmation and staging of retinoblastoma. These are discussed further in Clinical Question 3.

Table 8. Clinical evaluation and physical examination

Clinical Evaluation	Remarks
Visual Acuity	Age-appropriate visual acuity measurement should be recorded on initial ophthalmic evaluation.
External Eye Examination	Attention must focus on the presence of ophthalmological signs such as: leukocoria, strabismus, buphthalmos, proptosis, conjunctival hyperemia, chemosis, iris heterochromia, rubeosis iridis, and increased intraocular pressure.
Dilated Fundus Examination	Detailed and extensive evaluation of the fundus should describe the appearance, size and location of the suspected lesions and associated vitreoretinal signs such as retinal detachment and vitreous seeds. Retinal evaluation should extend up to the ora serrata.
Physical Examination	Evaluation for enlarged ipsilateral preauricular and cervical lymph nodes must be performed. Also evaluate for signs of metastatic disease such as bone pain and neurological deficits.

Table 9 discusses the recommendations from other groups for the clinical evaluation of at-risk pediatric patients.

Table 9. Q4.2 Recommendations from Other Groups

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
We recommend that all infants and children in whom someone has observed a white pupil (either in person or in a photograph) have a full dilated eye examination including red reflex test within 72 hours by an ophthalmologist or medical practitioner	ADAPTE	Consensus statement	CRS (2009)[8]

who is fully aware of the importance of leukocoria as a sign of Rb.			
We recommend that any child with strabismus or suspected strabismus be seen by the child's pediatrician or family doctor.	ADAPTE	Consensus statement	CRS (2009)[8]
We recommend that the red reflex test be applied to any child with strabismus or suspected strabismus.	ADAPTE	Consensus statement	CRS (2009)[8]
We recommend urgent referral (within 72 hours) to an ophthalmologist of any child with strabismus or suspected strabismus and an abnormal red reflex.	ADAPTE	Consensus statement	CRS (2009)[8]
We recommend that appointments with ophthalmology or tertiary Rb centers should be given within 72 hours for the above signs of abnormality, which constitutes an emergency.	ADAPTE	Consensus statement	CRS (2009)[8]
All patients should undergo a complete ophthalmological examination under anesthesia, including tonometry and slit-lamp examination, by an experienced ophthalmologist using indirect ophthalmoscopy.	ADAPTE	-	SIOP-PODC (2013)[13]
In programs where conservative therapy is undertaken with chemoreduction and localized therapy, a digital camera for documenting the fundoscopic findings may be helpful.	ADAPTE	-	SIOP-PODC (2013)[13]

4.3 Among children diagnosed with Retinoblastoma, what is the recommended work-up to accurately stage Retinoblastoma?

Recommendations

1. **Among children diagnosed with Rb, we recommend multidisciplinary team discussions and appropriate imaging done in experienced centers. *(Strong recommendation, low certainty of evidence)***
2. **Among children diagnosed with Rb, we recommend B scan ocular ultrasound and MRI or high-quality CT scan with contrast of the head and orbit for initial staging purposes. *(Strong recommendation, low certainty of evidence)***
3. **Among children diagnosed with Rb, when MRI of the brain and orbit is available and accessible, we recommend its preference over CT scan of the brain and orbit with high quality contrast. *(Strong recommendation, low certainty of evidence)***
4. **Among children diagnosed with Rb showing signs of extraocular disease, we suggest performing lumbar puncture and/or bone marrow examination for screening of metastasis. *(Weak recommendation, very low certainty of evidence)***

Consensus Issues

Accuracy, availability, accessibility, cost-effectiveness, and safety were implied when selecting diagnostic tests for staging retinoblastoma patients in either Setting 1 or 2.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (i.e., Medline, Central, and Google Scholar) and local databases (i.e., HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms “Retinoblastoma” AND “staging”. No additional filter was applied for comprehensive search.

No relevant randomized controlled trials were found during the search. Three clinical practice guidelines were included after appraisal using AGREE II Tool for ADAPTE.

Evidence Summary and Source of Guideline Recommendations

Pediatric patients diagnosed with Retinoblastoma were staged using the available classification systems, American Joint Committee on Cancer Clinical Staging System (AJCC), International Classification for Intraocular Retinoblastoma (ICRB), and

International Retinoblastoma Staging System (IRSS). A disease-staging system for children with retinoblastoma is essential for the initial evaluation of the extent of extraretinal dissemination and prediction of survival.

Classification and staging of disease severity require examination under anesthesia (EUA), imaging studies, and pathology review. The intraocular staging for retinoblastoma, the International Intraocular Retinoblastoma Classification (IIRC), is based on the extent and size of tumor involvement in the eye under EUA.

B scan ocular ultrasound is able to reveal the pathognomonic signs for diagnosis and determine the intraocular extent of retinoblastoma. It has limited accuracy in determining extraocular extension. Both plain and contrast enhanced MRI and CT scan of the orbit and brain demonstrate extent of spread of cancer within the eye, out of eye or into optic nerves, and any tumor in the suprasellar or pineal area (trilateral retinoblastoma). While CT is easy and quick in most centers and shows the pathognomonic calcification of Rb, it does incur radiation exposure that may increase the risk of second primary malignant tumors in individuals with germline RB1 mutation.[8]

MRI is preferable for these cases, since it entails no radiation exposure. MRI is also more sensitive in delineating suspicious involvement of the optic nerves, and meningeal disease of the brain and spinal cord.[8] These are summarized in Table 10.

Table 10. Summary of Considerations for Imaging[24,25]

Imaging	Considerations
Ultrasound (B-Scan)	B scan ocular ultrasound is an inexpensive modality available in most eye treatment facilities. The procedure requires no sedation. It can detect the presence of intralesional calcification which is highly suggestive of retinoblastoma. These areas of calcification will manifest highly reflective echoes with acoustic shadowing. The intraocular extent of disease can be assessed with this modality, specifically the tumor location and size as well as associated features like retinal detachment and vitreous seeding. B scan ultrasound can measure globe enlargement (buphthalmos) and with limited accuracy detect areas of possible extrascleral extension. For retinoblastoma, high frequency B-scan ultrasonography (20–50MHz), also known as ultrasound biomicroscopy (UBM), has been shown to be essential for determining the proximity of the tumor to the anterior portion of eye.[26]
MRI brain + orbit with contrast enhancement	Similar to ultrasound, MRI can delineate intraocular tumors, measure its size and detect for intralesional calcification. Calcifications will manifest as signal voids. Associated retinal detachments are likewise detected and the quality of the vitreous and subretinal fluid is assessed. MRI more accurately

	shows extraocular extension of the tumor as evidenced by the presence of extrascleral nodules, gross orbital tumor and widening of the optic nerve. Cranial MRI will detect for intracranial retinoblastoma extension and for pinealoblastoma or trilateral disease. MRI does not use ionizing radiation and therefore does not contribute to the risk of developing secondary malignant neoplasms. The test is motion sensitive hence sedation is necessary for most children. MRI is expensive and made even more because of the need for sedation.
CT brain + orbit with contrast enhancement	CT scan can delineate intraocular tumors, measure its size and more definitely detect for intralesional calcification. Associated retinal detachments are likewise detected. CT scan may show extraocular extension of the tumor as evidenced by the presence of extrascleral nodules, gross orbital tumor and widening of the optic nerve but with less definition as compared to MRI. Similarly Cranial CT will detect for intracranial retinoblastoma extension and for pinealoblastoma or trilateral disease but with less details. CT scan utilizes ionizing radiation and may contribute to increasing the risk of developing secondary malignant neoplasms especially with repeated testing and in infants under 1 year of age. CT imaging is generally avoided in retinoblastoma, especially in patients with a germline RB1 mutation. This modality is quicker and less expensive than MRI, usually requires no sedation and is generally more available even in low resource areas.

Lumbar puncture and/or bone marrow examination should be considered when patients have either clinical, imaging or pathologic features of extraocular disease. On physical examination, these children may present with proptosis and ocular motility limitations. Evaluation of the CSF or bone marrow can distinguish between IRSS stage II or III (extra-ocular or orbital disease) and stage IV (metastatic dissemination). The centrifuged CSF, bone marrow aspirate and bone marrow biopsy should be reviewed by a pathologist.

When the staging workup is completed, treatment planning depends on the clinical scenario (unilateral vs. bilateral disease) and on the stage (intraocular, extraocular or metastatic) of disease. The risks and benefits of the proposed treatment plan are weighed, and the final decisions are made in a multidisciplinary team discussion that include the parents. The priority is to save the child's life, second to save the eye(s), and finally, to optimize visual function for patients with either unilateral or bilateral Rb.

As for diagnostic accuracies of the three diagnostic modalities, two meta-analyses by de Graaf et. al. (2014) and Cho et. al. (2021) included studies that analyzed the accuracy of MRI versus histopathologic evaluation of enucleated eyes. Accuracy results are shown in Table 11. The use of ultrasound (B-scan) is also comparable with the use of MRI in the diagnosis of retinoblastoma with an accuracy of 94.9%. However,

a B-scan ultrasound cannot determine tumor extension into the orbit, lymph nodes, optic nerves and brain.

Table 11. Diagnostic Accuracy of Imaging Modalities for Retinoblastoma

Study/Year/ Country	Population	Intervention	Comparison	Results
Kim, et al (2019)[27] India	97 eyes of 97 patients who underwent primary enucleation for unilateral retinoblastoma	Preoperative imaging (CT scan or MRI), with modality dependent on age	Histopathology : evidence of prelaminar, laminar, or retrolaminar optic nerve tumor involvement.	**CT Scan**: Specificity – 20% Sensitivity – 88.89% PPV- 50% NPV- 66.67% **MRI** Specificity – 40% Sensitivity – 93.55% PPV- 66.67% NPV- 82.86%
Brisse et al (2007)[28] France	A total of 150 patients enucleated for retinoblastoma	CT scan or MRI	Histopathology optic nerve invasion	**CT Scan**: Specificity – 100% Sensitivity – 0% PPV- not assessed NPV- 94% **MRI** Specificity – 95% Sensitivity – 60% PPV- 60% NPV- 95%
Murad et al (2021)[29] Pakistan	220 patients. Children (6 months — 5 years of age) presenting with any of the features such as leukocoria	Ultrasound (B-Scan)	MRI	Specificity – 98.8% Sensitivity – 94.2% PPV- 99.1% NPV- 92.2% Accuracy - 94.9%

	(white pupil), strabismus (squint), red eye and poor vision were included			

Table 12 summarizes the recommendations from other groups for the diagnostic testing and imaging that should be done for patients suspected of retinoblastoma.

Table 12. Q4.3 Recommendations from Other Groups

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
We recommend the following diagnostics for staging: B scan Ultrasound, magnetic resonance imaging (MRI) orbit with cranial CT scan for screening. For patients with extra-ocular disease or optic nerve involvement, bone marrow aspirate or biopsy and lumbar tap for cerebrospinal fluid cytology should be done for staging.	ADAPTE	Consensus statement	Ancona-Lazema et.al (2020)[30]
At least a head and orbital contrast-enhanced computed tomography (CT) scan should be done, but magnetic resonance imaging (MRI) is preferable, if available, because MRI provides a more accurate imaging of the optic nerve extension.	ADAPTE	Consensus statement	SIOP-PODC (2013)[13]
A lumbar puncture with examination of the CSF and an extensive bone marrow evaluation, preferably including at least two sites, of both the aspirate for cytology and biopsies, should be done in all patients with stage 2 or more progressed disease.	ADAPTE	Consensus statement	SIOP-PODC (2013)[13]

4.4 Among intraocular Retinoblastoma patients on active ocular salvage therapy, what is the optimal timing of examination under anesthesia (EUA) to evaluate treatment response and disease status?

Recommendation

Among intraocular Rb patients on active ocular salvage therapy, we recommend EUA, evaluation of treatment response, and local consolidation therapy to be performed by an ophthalmologist on the scheduled day of chemotherapy delivery. *(Strong recommendation, very low certainty of evidence)*

Consensus Issues

No noted consensus issues.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (Medline, Central, and Google Scholar) and local databases, (i.e., HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms “Retinoblastoma” AND “examination under anesthesia” OR “EUA”. No additional filter was applied for comprehensive search.

No relevant randomized controlled trials were found during the search. One clinical practice guideline was included after appraisal using AGREE II Tool for ADAPTE.

Evidence Summary and Source of Guideline Recommendations

There were no systematic reviews, meta-analyses, or randomized controlled trials that directly examined diagnostic effectiveness regarding optimal timing of examinations under anesthesia (EUA) to evaluate immediate treatment response and disease status. The certainty of evidence is very low due to very serious issues of imprecision, risk of bias, and indirectness, as the best available evidence does not directly answer the question.

Current practice involves conducting patient follow-ups by an ophthalmologist, which is consistent with other studies following the Associacion de Hemato-Oncologia Pediatrica de Centro America (AHOPCA) Retinoblastoma Protocol, and Canadian Retinoblastoma Society (2009). The outline of the follow up procedures can be seen in Figure 4.

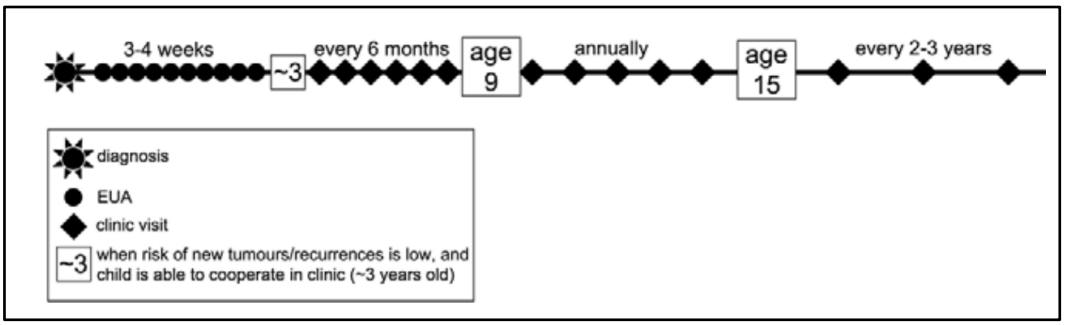

Figure 4. Schedule of EUA and clinic visits for children with Retinoblastoma[8]

Immediately upon diagnosis, the child undergoes EUA immediately and every 3 to 4 weeks thereafter, depending on the extent of tumor activity and the ocular salvage therapy plan. Chemo-assisted therapies like chemothermotherapy and chemocryotherapy involves the tandem treatment of systemic or intra-arterial chemotherapy with local therapies of laser and cryotherapy. Thermotherapy has synergistic effect with carboplatin-based chemotherapy. The current Vincristine + Eptoposide + Carboplatin (VEC) regimen is given in a 21–28-day cycle and should be done in conjunction with local laser and cryotherapy. The VEC regimen for ocular salvage with local therapy is performed for a minimum of 6 cycles but extendable depending on tumor response and systemic chemotherapy limitations. Continued pure local therapies can be continued for persistent active tumors.

When Rb tumors remain inactive after treatment for a significant period of time, and the risk is low for new tumors and/or recurrences, the active follow-up for surveillance of new tumors can transition to the clinic, as long as the child can cooperate (at approximately 3 years of age), with examination every 6 months. After age 9, long-term follow-up begins, with annual clinic visits. After age 15, clinic visits may occur every 2–3 years, for the lifetime of the patient.

The Canadian Retinoblastoma Society recommends active follow up until age 9 years, or 5 years after the last active treatment is performed and Long-term follow-up for Rb covers the period of follow- up after 9 years of age or beyond 5 years after the last active treatment.[8] This was based on three observation studies. The certainty of evidence is very low due to very serious issues on imprecision, risk of bias, and indirectness, as the best available evidence does not directly answer the question. The three other recommendations cited by Canadian Retinoblastoma Society were based on expert opinion and consensus.[8]

An additional consideration is offering a timely molecular diagnosis of RB1 mutations. The intervention enables earlier detection and treatment for patients at risk with retinoblastoma; empowers families to make informed family-planning decisions; and costs less than conventional surveillance. One genetic study shows that the costs from

repeated clinical examinations of children in these families substantially exceeds the cost of molecular testing, which can be carried over in succeeding generations.[31]

Table 13 highlights the recommendations from other groups regarding the timing of EUA for patients suspected to have retinoblastoma.

Table 13. Q4.4 Recommendations from Other Groups

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
We recommend the examination of an enucleated socket for infection, fit of prosthesis and implant exposure or extrusion at every EUA and clinic visit	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that following completion of treatment, EUAs for children at risk of developing new Rb tumors continue as often as every 3 weeks, or at longer intervals as tumor activity decreases, until risk of new tumors and recurrences are low, and the child is able to cooperate in clinic (at about 3 years of age). The frequency of examinations will be highest when the child has a proven RB1 germline mutation.	ADAPTE	Very Low	CRS (2009)[8]
We recommend that following the end of EUAs, clinic visits for retinal exams should continue every 6 months to age 9, annually to age 15, and every 2–3 years there- after for life.	ADAPTE	Consensus statement	CRS (2009)[8]
We recommend that children without the RB1 mutation confirmed through a molecular blood test do not require EUA or intense surveillance.	ADAPTE	Consensus statement	CRS (2009)[8]

4.5 Among newly diagnosed children with intraocular Retinoblastoma, what are the indications for upfront enucleation and ocular salvage therapy?

Recommendations

Upfront Enucleation

1. **Among newly diagnosed children with intraocular Rb, we recommend that upfront enucleation be performed for IIRC Group E. *(Strong recommendation, low certainty of evidence)***
2. **Among newly diagnosed children with intraocular Rb, we recommend that upfront enucleation be performed for IIRC Group D when the other eye is normal or Group A. *(Strong recommendation, low certainty of evidence)***
3. **Among newly diagnosed children with intraocular Rb with no access to globe sparing modality or are at risk of poor follow up, we recommend that primary enucleation can be relatively indicated. Primary enucleation is an option especially but not limited to unilateral Rb cases. *(Strong recommendation, low certainty of evidence)***

Ocular Salvage Therapy

4. **Among newly diagnosed children with intraocular Rb, we recommend ocular salvage therapy for ICRB Groups A, B, and C. *(Strong recommendation, low certainty of evidence)***
5. **Among newly diagnosed children with intraocular Rb, we recommend ocular salvage therapy for ICRB Group D eyes when it is the better of two eyes. *(Strong recommendation, low certainty of evidence)***
6. **Among newly diagnosed children with intraocular Rb, we recommend against ocular salvage therapy when there is lack of access and availability to globe sparing modalities (chemotherapy and local therapy) or risk of poor follow-up. *(Strong recommendation, low certainty of evidence)***
7. **Among Rb patients undergoing ocular salvage therapy with recalcitrant or residual vitreous or anterior chamber Rb seeds, we recommend intravitreal or intracameral chemotherapy delivery with intravenous or intra-arterial chemotherapy. *(Strong recommendation, low certainty of evidence)***

8. **Among Rb patients undergoing ocular salvage of one eye disease requiring chemoreduction, we recommend intravenous or intra-arterial chemotherapy delivery.** ***(Strong recommendation, low certainty of evidence)***

9. **Among Rb patients undergoing simultaneous ocular salvage of bilateral eye disease requiring chemoreduction, we recommend intravenous systemic chemotherapy delivery.** ***(Strong recommendation, low certainty of evidence)***

Consensus Issues

Indications of upfront enucleation (eye surgery) or ocular salvage (attempt to save the eye) vary. Once these indications are present, that is when you are obliged to do the appropriate surgery. Ocular salvage refers to all possible ocular salvage procedures.

Enucleation would cure a high proportion of children with retinoblastoma. It is therefore important that ocular salvage treatments are not offered to patients with intraocular disease in a setting without facilities or experience in such procedures. Conservative therapy is usually not a priority in Setting 1, where most children die of extraocular retinoblastoma. When there is lack of access to globe sparing modalities, resource limitations or risk of poor follow-up, the guideline recommends primary enucleation as the relatively indicated treatment.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (i.e., Medline, Central, and Google Scholar) and local databases (i.e., HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms “Retinoblastoma” AND “enucleation” AND “ocular salvage”. No additional filter was applied for comprehensive search.

No relevant randomized controlled trials were found during the search. Two clinical practice guidelines were included after appraisal using AGREE II Tool for ADAPTE.

Evidence Summary and Source of Guideline Recommendations

Enucleation removes the affected eye and a portion of the optic nerve and can be either a primary or secondary treatment for retinoblastoma.[32] Primary enucleation is used to treat unilateral intraocular retinoblastoma whereas secondary enucleation is indicated when conservative treatment has failed or in the presence of phthisical (e.g., wasting, shrinking, nonfunctioning) eyes after high-dose chemotherapy.[33,34] It is important for clinicians to be aware of the indications and the implications of enucleation both from a psychosocial perspective and with respect to the impact of

monocular vision after unilateral enucleation. However, it is equally important to consider the negative impact of globe salvage on a child's development. Patients undergoing enucleation have 1/3 fewer examinations under anesthesia (EUAs) compared to those managed conservatively and this is particularly relevant given the potential toxicity of anesthesia to the developing brain.[35,36]

In developed countries, less than 1% of children present with buphthalmosi and fewer than 20% present with significant risk factors upon pathology examination.[37,38] In more than 95% of cases, enucleation results in complete tumor removal with less than 5% having microscopically residual disease after enucleation. Hence, upfront enucleation is the treatment of choice for children with intraocular unilateral retinoblastoma.[13] Even in developing countries, enucleation is considered as an excellent way to cure the disease when Rb is confined within the eye.[36,39-40]

The Canadian Retinoblastoma Society recommends unilateral enucleation to be the safest treatment in unifocal Rb with IIRC Group D and E eyes.[8] Upfront removal of both eyes (bilateral primary enucleation) may be recommended to avoid the risk of systemic metastasis if both eyes present with Group E disease with an extremely poor visual potential Furthermore, the guideline states that it may also not be in the best interest of the child to be exposed to chemotherapy or radiation-related morbidities with little possibility of a good outcome. A delay in enucleation may put the child at risk for extra- ocular Rb and life-threatening metastatic disease.[41,42]

The Canadian Retinoblastoma Society also considered performing enucleation for the following conditions: (1) recurrent tumors when all other treatment modalities have failed, (2) for complications such as total retinal detachment, complete media (vitreous) opacity and total hyphema (blood filling the eye) that prevent evaluation and treatment of potentially progressive tumor.[8]

In countries with setting 1, many patients present with enlarged eyeballs or buphthalmia.[43,44] Severely buphthalmic eyes may be difficult to enucleate upfront. This scenario is especially important to avoid in settings with no radiotherapy since this will be needed to prevent tumor recurrence in the seeded areas. The SIOP-PODC recommends pre-enucleation chemotherapy to reduce tumor volume in severely buphthalmic eyes, thereby reducing the risk of eye rupture and tumor residue at the optic nerve margin.[45,46] There is an increased risk of accidental rupture of the globe, leading to seeding of tumor cells around the surgical site which would necessitate intensive chemotherapy and orbital radiotherapy.

Table 14 discusses recommendations on the timing of enucleation from other groups.

Table 14. Q4.5 Recommendations from Other Groups

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
Upfront enucleation is recommended when specific indications are present: ● Buphthalmos (previous neoadjuvant chemotherapy) ● Anterior chamber involvement (at diagnosis) ● Invasion of the iris and / or ciliary body ● Neovascular glaucoma ● Iris neovascularization ● Massive tumor involving 50% or> of the vitreous. ● Necrotic tumor with orbital inflammation	ADAPTE	Consensus Statement	Peru (2020)[47]
We recommend that enucleation be performed for IIRC Groups D and E eyes when the other eye is normal or Group A.	ADAPTE	Consensus statement	CRS (2009)[8]
We recommend that upfront enucleation without neoadjuvant chemotherapy be performed for any IIRC Group E eyes, which impose risk for difficult-to-treat systemic metastases.	ADAPTE	Low level of evidence	CRS (2009)[8]
We recommend enucleation for recurrent tumors when all other treatment modalities (including EBRT) have failed, to prevent tumor spread outside the eye or when complications prevent evaluation and treatment of progressive disease.	ADAPTE	Consensus statement	CRS (2009)[8]
We recommend that primary enucleation be relatively indicated when there is lack of access or availability to globe sparing modality or risk of poor follow up in areas with limited resources. Primary enucleation is an option especially but not limited to unilateral Rb cases.	ADAPTE	Good Practice Statement	CRS (2009)[8]

4.6 Among patients with intraocular retinoblastoma not responding to ocular salvage treatment of chemotherapy with local therapy, what are the indications of external beam radiation therapy and enucleation?

Recommendations

1. **Among patients with intraocular Rb not responding to ocular salvage treatments, we recommend enucleation or salvage external beam radiation therapy when chemotherapy and focal therapy has failed to control the tumors. *(Strong recommendation, low certainty of evidence)***
2. **Among patients with intraocular Rb not responding to ocular salvage treatments, we recommend preference for enucleation over salvage external beam radiation therapy for patients less than one year old with failed globe sparing treatment due to the risk of secondary malignancy. *(Strong recommendation, low certainty of evidence)***
3. **Among patients with intraocular Rb not responding to ocular salvage treatments, we recommend enucleation when at high risk for treatment abandonment. *(Ungraded good practice statement)***
4. **Among patients with intraocular Rb not responding to ocular salvage treatment of chemotherapy with local therapy, trial of salvage EBRT is a reasonable option when it involves the last remaining eye. *(Ungraded good practice statement)***

Consensus Issues

No noted consensus issues.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (i.e., Medline, Central, and Google Scholar) and local databases (i.e., HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms “Retinoblastoma” AND “External Beam Radiation Therapy” OR “EBRT” AND “Enucleation” AND “Ocular salvage” AND “Treatment Response”. No additional filter was applied for comprehensive search.

No relevant randomized controlled trials were found during the search. One clinical practice guideline was included after appraisal using AGREE II Tool for ADAPTE.

Evidence Summary and Source of Guideline Recommendations

For many years external beam radiotherapy (EBRT) was the treatment of choice for Rb. In bilateral disease, the more advanced eye was usually enucleated, and the better eye was conserved with EBRT. Worldwide, radiotherapy is now rarely given as primary treatment for Rb as excellent results are achievable with chemotherapy/focal combination therapy.[36,48]

Patients with Rb previously treated with EBRT have an increased risk (up to 50%) of to developing secondary non-Rb malignancies.[35,48-51] Greater knowledge of these side effects such as facial deformities, cataracts, and dry eyes as well as the attendant risk of subsequent tumor development such as sarcoma, after EBRT, encouraged the switch to primary systemic chemotherapy plus focal therapy for the past decades.[35,52] These risks are especially high for those treated with EBRT prior to 1 year of age, but secondary non-Rb malignancies may occur after radiation given at any age.[37]

National Retinoblastoma Strategy Canadian Guidelines for Care recommends EBRT when chemotherapy/focal therapy has failed to control the tumors, and it remains a very useful treatment for Rb.[8] Furthermore, it recommends that orbital EBRT may supplement chemotherapy for orbital tumor recurrence or residual following enucleation. Brachytherapy is an excellent treatment for small, isolated tumors situated well away from the optic nerve or macula, and/or when tumor recurs focally following chemotherapy or EBRT.

To reduce risk of inducing secondary non-Rb malignancies or cosmetic deformities, stereotactic or intensity modulated radiotherapy (IMRT) radiation techniques can result in delivery of a lower radiation dose to normal tissues surrounding the target area.[53-55]

Enucleation of the remaining eye may still be required to save the child's life despite the use of radiotherapy after failed chemotherapy and focal therapy.

In developing countries, EBRT offers the benefit of less intensive follow-up and are likely to be cured with one 6-week course of radiotherapy, whereas children treated with chemo reduction, and local therapy usually need a more intensive, longer follow-up to consolidate tumor response and treat later relapses.[13] Therefore, the availability of a high- quality EBRT facility is a priority in this scenario, especially in setting 2. For settings that continue to use EBRT, surgery for removal of radiation-induced cataracts that occur in almost all patients within a few years of irradiation should be available.

Table 15 summarizes the recommendations for the use of external beam radiation therapy based on other groups.

Table 15. Q4.6 Recommendations from Other Groups

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
External beam radiation therapy (EBRT) remains a very useful treatment for retinoblastoma as salvage therapy when chemotherapy/focal therapy has failed to control the tumors.	ADAPTE	Low level of evidence	CRS (2009)[8]
Due to the risk of secondary malignancy, we recommend against salvage EBRT for patients less than one year old with failed globe sparing treatment.	ADAPTE	Very low level of evidence	CRS (2009)[8]
Salvage EBRT in bilateral retinoblastoma should be considered in eyes with visual potential, when focal consolidation treatment is likely to damage vision, or when tumors are too large or numerous for further focal treatment.	ADAPTE	Good Practice Statement	Chan, et al (2009)[56]

Management of Retinoblastoma

Consensus Issues

The availability of services in developing countries guides the choice of treatment, so it is essential to identify the local facilities in which to either establish a new retinoblastoma program or optimize an existing one. Settings were categorized based on resource availability as Setting 1, 2 and 3. (See **Appendix F.**)

The applicability of the recommended setting-based treatment recommendations for the management of retinoblastoma is important as our situation in the Philippines has all three.

Review Methods

Without publication date filter, a systematic search was done from September 2022 to June 2023, using international (Medline, Central, and Google Scholar) and local database, HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms were "Retinoblastoma" AND "Treatment".

No relevant randomized controlled trials were found during the search. One clinical practice guideline was included after appraisal using AGREE II Tool for ADAPTE.

Summary of Evidence

General Recommendation from National Retinoblastoma Strategy Canadian Guidelines for Care has general recommendations for treatment for retinoblastoma regardless of stage.[8] These are summarized in Table 16.

Table 16. General Recommendations for the Treatment of Retinoblastoma

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
We recommend that children with Rb be cared for by a multidisciplinary team that provides coordinated and collaborative care in and shared between specialized centers, where expertise, up-to-date protocols, and modern equipment are available for the optimal management of Rb [*Consensus*].	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that tertiary Rb centers work together to assure optimal care for each child. This might include	ADAPTE	Consensus Statement	CRS (2009)[8]

referral of children from one center to another for consultation or to access specific technical or human resources.			
We recommend that enrolment in a formal clinical trial remain the gold standard for improving treatment and care of children with cancer, including Rb.	ADAPTE	Consensus Statement	CRS (2009)[8]

Consensus based recommendations were highlighted for in referring patients for appropriate care as highlighted by Canadian Retinoblastoma Society, which are summarized in Table 17 below.

Table 17. General Recommendations for Referring Patients with Suspected Rb

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
We recommend that any child with signs consistent with Rb be referred to an ophthalmologist or optometrist to receive a full retinal examination with dilated pupil and have a detailed history taken to confirm or rule out a diagnosis of Rb.	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that secondary and tertiary centers accept direct referrals with suspicion of Rb from primary healthcare providers, such as optometrists and family practitioners [Consensus].	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that primary healthcare providers immediately refer all Rb cases to a secondary or tertiary Rb center.	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that all children referred with any possibility of Rb be seen within 72 hours, or as soon as possible, at the secondary or tertiary Rb center for thorough ocular and systemic examination to confirm or rule out a diagnosis of Rb. (If a secondary or tertiary Rb center is not easily accessible, the patient should be	ADAPTE	Consensus Statement	CRS (2009)[8]

referred immediately to a pediatric ophthalmologist, retinal specialist or local ophthalmologist or, if they cannot be reached, to an emergency department.			
We recommend that difficult unilateral cases (e.g., very young child; potential to save the eye; unilateral multifocal and (or) germline RB1 mutation), or risk for extraocular disease and bilateral cases be referred from a secondary center to a tertiary center.	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that enrolment in a formal clinical trial remain the gold standard for improving treatment and care of children with cancer, including Rb.	ADAPTE	Consensus Statement	CRS (2009)[8]
We recommend that any child with high-risk pathological features be referred to a tertiary center.	ADAPTE	Consensus Statement	CRS (2009)[8]

4.7 Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, what is the recommended chemotherapy regimen?

Recommendations

1. **Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, we recommend referral for pathologic review of every enucleated eye by an experienced pathologist or ophthalmic pathologist. *(Ungraded good practice statement)***
2. **Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, we recommend that the Rb specialist and pediatric oncologist screen for extraocular disease or metastasis. *(Strong recommendation, low certainty of evidence)***
3. **Among newly diagnosed IRSS stage 1 children with high-risk pathologic features, we recommend treatment with prophylactic chemotherapy. *(Strong recommendation, low certainty of evidence)***
4. **Among newly diagnosed IRSS stage 1 children with high-risk pathologic features in settings 1, 2 and 3, we recommend adjuvant chemotherapy with Carboplatin + Etoposide + Vincristine regimen. *(Strong recommendation, low certainty of evidence)***
5. **Among newly diagnosed IRSS stage 1 children with high-risk pathologic features in settings 1, 2 and 3 when there is Carboplatin shortage, we recommend giving Cyclophosphamide + Vincristine ± Doxorubicin. *(Strong recommendation, low certainty of evidence)***

Consensus Issues

No specific consensus issues noted.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (Medline, Central, and Google Scholar) and local database, HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms “Retinoblastoma” AND “Treatment”.

No relevant randomized controlled trials were found during the search. One clinical practice guideline was included after appraisal using AGREE II Tool for ADAPTE.

Background

The International Retinoblastoma Staging System (IRSS), a classification system for extraocular disease, describes Stage I as patients who had eye enucleation, with tumor completely resected histologically.[57] Although enucleation has a cure rate of more than 90%, histopathologic investigation is essential to identify patients at high risk for recurrence.[56] The high-risk histopathologic features (HRFs) are as follows: post laminar optic nerve invasion, massive posterior uveal invasion (≥ 3mm), concomitant focal choroid (<3mm) and optic nerve involvement (laminar and prelaminar), anterior chamber seeding, ciliary body infiltration, and iris infiltration.[58] A systematic assessment of the HRFs was developed by the College of American Pathologists in order to facilitate synoptic reporting of pathologic findings.[59]

A retrospective study in 2002 by Honavar et. al proved the effectiveness of receiving adjuvant chemotherapy to prevent metastasis post enucleation in patients with HRFs.[60] Their protocol reviewed 80 retinoblastoma patients with HRFs post enucleation, and they reported a statistically significant difference (P=0.02) in the incidence of metastasis between patients given adjuvant chemotherapy at 4% (2/46) while 24% for those who had not (8/24). Two chemotherapy regimens were used in the study: vincristine, doxorubicin, and cyclophosphamide in 21 patients, and vincristine, etoposide, and carboplatin in 25 patients. Although there were two regimens used, the benefits of one over the other cannot be compared due to the limited number of metastases recorded.

Moreover, a retrospective case series done in 2011 by Kaliki et. al demonstrated the effectiveness of the vincristine, etoposide, and carboplatin regimen in reducing occurrence of metastasis.[61] Their study was done in 51 post enucleation patients with HRFs Adjuvant chemotherapy with vincristine, etoposide, and carboplatin resulted in zero metastasis during a mean follow up of 66 months.

A more recent 5-year prospective study done in 2019 by Chévez-Barrios et. al reviewed the histopathology of 321 IRSS Stage I patients from USA and India.[56] Adjuvant chemotherapy with vincristine, etoposide, and carboplatin was given to those presenting with HRFs, while those who did not present with HRFs were subsequently observed. They reported discordance between the original versus the central histopathologic review, hence emphasizing the importance of an experienced pathologist post-enucleation. Results showed a 96% 2-year event-free survival to IRSS stage 1 patients who had HRFs and adjuvant chemotherapy while 99% 2-year event-free survival to those who did not have HRFs and were observed.

On the other hand, a study involving retinoblastoma IRSS Stage I patients in low- and middle-income countries (LMICs) was done by Luna-Fineman et. al in 2019.[62] Delayed enucleation and neoadjuvant chemotherapy were given to 59 out of 161 patients with buphthalmos and those perceived to be at risk for enucleation refusal and/or

abandonment. These two parameters are common in LMICs due to delay in diagnosis, debilitating surgery, low education and socioeconomic status, and distance from treatment facility. Two to three cycles of neoadjuvant chemotherapy with vincristine, etoposide, and carboplatin were initially given. Enucleation proceeded thereafter, then six cycles of chemotherapy was completed regardless of presence of HRFs. The remaining 102 patients underwent upfront enucleation and histopathologic review for HRFs. Results showed that the five-year abandonment-sensitive event free survival rate was 68% for patients who had delayed enucleation while 89% for those who underwent upfront enucleation. Although data showed a lower survival rate for the delayed enucleation group, the authors reported it to still be an effective strategy in LMICs since mortality due to the disease is definite if patients completely refuse or abandon treatment.

Evidence Summary and Source of Guideline Recommendations

Adjuvant prophylactic chemotherapy was recommended by the two source guidelines from Canadian Retinoblastoma Society[8] and SIOP-PODC Graduated-Intensity Retinoblastoma Guidelines[13].

The source guideline for recommendation was SIOP-PODC guideline.[13] The guideline recommends that carboplatin-based regimens should be the first choice, including cyclophosphamide, vincristine, and doxorubicin with the possible addition of doxorubicin may be an alternative if carboplatin-based regiments not available. The recommendation was based on a Phase II trial of 20 patients with 85%; there were nine complete responses and eight partial responses. Hematologic toxicity was the only observed toxicity with the latter regimen.

The recommendations from other groups on the chemotherapy regimen for IRSS Stage 1 patients with high-risk features is shown in Table 18.

Table 18. Q4.7 Recommendations from Other Groups

Guideline Recommendations	Method	Certainty of Evidence	Guideline Code
When high-risk features are observed, including invasion of optic nerve, sclera, choroid, or anterior segment, we recommend treatment with prophylactic chemotherapy, preferably with enrolment in a clinical study.	ADAPTE	Low level of evidence	CRS (2009)[8]

4.8 Among newly diagnosed IRSS stage 2 children, what is the recommended chemotherapy regimen?

Recommendation

Among newly diagnosed IRSS stage 2 children, we recommend adjuvant systemic chemotherapy utilizing Vincristine + Etoposide + Carboplatin either alone or alternating with Cyclophosphamide and an anthracycline followed with orbital and optic nerve radiotherapy up to chiasm. *(Strong recommendation, low certainty of evidence)*

Consensus Issues

No specific consensus issues noted.

The external reviewer shared a commentary that in some cases, radiation therapy volumes may be confined to the optic canal with an appropriate margin. This approach allows for less toxicity and sparing of the pituitary gland.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (Medline, Central, and Google Scholar) and local database, HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms “Retinoblastoma” AND “Treatment”.

No relevant randomized controlled trials were found during the search. One clinical practice guideline was included after appraisal using AGREE II Tool for ADAPTE.

Background

IRSS Stage 2 is defined as eye enucleation with microscopic residual tumor either scleral or at cut-end of optic nerve or rupture of eye during surgery.[55] IRSS Stage 2 and 3 are managed similarly with external-beam radiotherapy, and chemotherapy. The chemotherapy regimens used by different groups composed of vincristine, etoposide, platinum agents (carboplatin, cisplatin), cyclophosphamide and anthracyclines (idarubicin, doxorubicin).[63]

A study by Chantada et. al reported on the treatment results of patients with tumor invasion on the cut end of the optic nerve.[64] A retrospective study was done where three different chemotherapy protocols were utilized on 26 IRSS Stage 2 and 3 patients who also underwent enucleation and radiation therapy. Protocol 1 employed a standard dose of intravenous chemotherapy with cyclophosphamide, vincristine, and doxorubicin, followed by intrathecal therapy. On the other hand, protocols 2 and 3 both

received a higher dose of intravenous chemotherapy with carboplatin, and etoposide alternating with cyclophosphamide, idarubicin, and vincristine without intrathecal therapy. Protocol 3 utilized a 10% lower dose of carboplatin versus protocol 2. Results showed an overall 5-year event-free survival rate of 70%. In addition, there was no significant difference in outcomes between protocols.

A case series using another chemotherapy regimen was done by Honavar et. al in India in 2017.[63] Twenty IRSS Stage 2 patients were given 3-6 cycles of high dose vincristine, etoposide, and carboplatin, followed by enucleation or exenteration, orbital radiotherapy, then completed a total of 12 cycles of chemotherapy. After treatment, 90% of patients did not have local recurrence or systemic metastasis at a mean of 36 months follow-up. In addition, patients had an acceptable cosmetic outcome.

A more recent prospective trial by Dunkel et. al in 2022 done in USA, Argentina, Egypt, and Brazil evaluated an intensive multimodal therapy for extraocular retinoblastoma.[65] IRSS Stage 2 retinoblastoma patients were given four cycles of induction chemotherapy with vincristine, cisplatin, cyclophosphamide, and etoposide. Radiation therapy followed thereafter wherein the clinical target volume for stage 2 disease included the orbit. Results showed that 1-year event free survival rate and overall survival rate was 88.1%, while 3-year event free survival rate and overall survival rate was 88.1%. These data thus reflect the effectiveness of the multimodal therapy for stage 2 patients.

Evidence Summary and Source of Guideline Recommendations

The source guideline for recommendation was SIOP-PODC guideline.[13] Recommendations were based on three observational studies with one study from Central American Association of Pediatric Hematology Oncology (AHOPCA) proposed a protocol-directed therapy aimed to standardize the approach and to improve outcomes of patients with retinoblastoma with adjuvant chemotherapy consisted of vincristine, etoposide, and carboplatin.[62] (See Table 19.)

Table 19. SIOP-PODC Chemoreduction specifically in specialty centers for RB[13]

Setting	Treatment	Chemotherapy Regimen	Level of Evidence
Setting 1: Level 2 or 3 hospitals with Ophthalmology Unit	Not recommended, refer to higher level center.	-	Very low
Setting 2: Eye Specialty Center with Basic and Basic Comprehensive Services	Only for selected cases of groups A–C eyes, where chemoreduction and local therapy can be safely provided	Regimen 1 Vincristine + Etoposide + Carboplatin	Very low

Setting 2: Eye Specialty Center with Basic and Basic Comprehensive Services	Only for selected cases of group A–C eyes where chemoreduction and local therapy	Regimen 1 Vincristine + Etoposide + Carboplatin	Low
Setting 3: National Eye Specialty Center or Level 3 with Eye specialty and Cancer Specialty Treatment services	Intra-arterial chemotherapy can be provided	-	Low

4.9 Among newly diagnosed IRSS stage 3 (or orbital) retinoblastoma, what is the recommended treatment regimen?

Recommendations

1. **Among IRSS stage 3 children in settings 1 and 2, we recommend neoadjuvant systemic chemotherapy followed by enucleation, adjuvant systemic chemotherapy regimen utilizing Vincristine + Etoposide + Carboplatin either alone or alternating with Cyclophosphamide and an anthracycline and followed by radiotherapy to orbits and optic nerve up to the chiasm. *(Strong recommendation, low certainty of evidence)***
2. **Among IRSS stage 3 children in setting 3, we recommend neoadjuvant systemic chemotherapy followed by enucleation, adjuvant systemic chemotherapy regimen utilizing Vincristine + Etoposide + Carboplatin either alone or alternating with Cyclophosphamide and an anthracycline OR Vincristine + Cisplatin + high-dose Cyclophosphamide and followed by radiotherapy to orbits and optic nerve up to the chiasm. *(Strong recommendation, low certainty of evidence)***
3. **Among IRSS stage 3 children, we do not recommend exenteration of the orbit for Rb. *(Strong recommendation, low certainty of evidence)***

Consensus Issues

No specific consensus issues noted.

The external reviewer shared a commentary that in some cases, radiation therapy volumes may be confined to the optic canal with an appropriate margin. This approach allows for less toxicity and sparing of the pituitary gland. And include regional lymph nodes in the clinical target volume, if indicated.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (Medline, Central, and Google Scholar) and local database, HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms were “Retinoblastoma” AND “Treatment”.

No relevant randomized controlled trials were found during the search. One clinical practice guideline was included after appraisal using AGREE II Tool for ADAPTE.

Background

IRSS Stage 3 is described as regional extension of tumor either as an overt orbital disease or with extension to the preauricular or cervical lymph node.[57] IRSS Stage 2 and 3 are managed similarly with external-beam radiotherapy, and chemotherapy. The chemotherapy regimens used by different groups composed of vincristine, etoposide, platinum agents (carboplatin, cisplatin), cyclophosphamide and anthracyclines (idarubicin, doxorubicin).

The preference to enucleation vs exenteration was studied by Radhakrishnan in India.[66] A prospective study was done to determine the outcomes of 28 IRSS Stage 3 patients given 3 cycles of neoadjuvant chemotherapy with vincristine, carboplatin, and etoposide. This was proceeded by enucleation or exenteration, external-beam radiation therapy, and then 9 cycles of adjuvant chemotherapy with vincristine, and carboplatin. Results revealed overall survival was 40.4% and event free survival was at 33.33% at 26 months. Authors reported that all patients who received neoadjuvant chemotherapy were enucleated successfully thereby avoiding the need for exenteration.

There were several studies who reviewed the effectivity of various chemotherapy regimens for IRSS Stage 3 patients. A prospective study done by Chawla et. al in 2016 compared two chemotherapy regimens for 54 IRSS Stage 3 patients and determined their outcomes.[67] Neoadjuvant chemotherapy, enucleation, orbital external-beam radiotherapy, and followed by adjuvant chemotherapy was done for all patients. Vincristine, etoposide, and carboplatin were given to Group A patients while carboplatin and etoposide alternating with cyclophosphamide, idarubicin, and vincristine was given to Group B patients. Results showed that 1-year survival probability was 81% for group A while 79% for group B. However, the 4-year survival probability was 63% for group A while 25% for group B. These data revealed that the combination of vincristine, etoposide, and carboplatin was a more effective therapy for IRSS Stage 3 patients.

A recent prospective trial by Dunkel et. al done in 2022 in USA, Argentina, Egypt, and Brazil evaluated an intensive multimodal therapy for extraocular retinoblastoma.[65] IRSS Stage 3 retinoblastoma patients were given four cycles of induction chemotherapy with vincristine, cisplatin, cyclophosphamide, and etoposide. Radiation therapy followed thereafter. The clinical target volume for stage 3 disease included the orbit, if stage 2 features were present, residual tumor, and regional lymph nodes after induction therapy. Results showed that 1-year event free survival rate and overall survival rate was 88.1%, while 3-year event free survival rate and overall survival rate

was 88.1%. These data thus reflect the effectiveness of the multimodal therapy for stage 3 patients.

Evidence Summary and Source of Guideline Recommendations

The source guideline recommendation was the SIOP-PODC guideline.[13] Recommendations were based on one review and two observational studies. Preferred management is multimodal with a combination of initial high-dose chemotherapy, surgery, external beam radiotherapy and prolonged chemotherapy for 12 cycles.[68] According to Ali et al, observational studies have shown that systemic chemotherapy alone is unlikely to eradicate residual orbital disease, orbital exenteration alone is unlikely to achieve surgical clearance.[68] External beam radiotherapy is unlikely to prevent systemic metastasis and there is histopathologic evidence of viable tumor cells present even in phthisical eyes following neoadjuvant chemotherapy. The latter two observational studies recommend the regimens to use.

4.10 Among newly diagnosed IRSS stage 4 (or metastatic) retinoblastoma, what is the recommended treatment regimen?

Recommendations

1. **Among newly diagnosed IRSS stage 4 children, we recommend palliative care and/or low dose chemotherapy or oral metronomic chemotherapy. *(Strong recommendation, low certainty of evidence)***

2. **Among newly diagnosed IRSS stage 4 children with Rb metastasis in bone marrow, bone or other organs or tissue in setting 3, we recommend enucleation of the eye, chemotherapy, local control radiation and hematopoietic stem cell transplant if there is a chemotherapy response. *(Strong recommendation, moderate certainty of evidence)***

3. **Among newly diagnosed IRSS stage 4 children with Rb tumor involving the meninges of the brain and spinal cord in setting 3, we recommend palliative treatment. *(Strong recommendation, very low certainty of evidence)***

Consensus Issues

No specific consensus issues noted.

Review Methods

A systematic search was done from September 2022 to June 2023, using international (Medline, Central, and Google Scholar) and local database, HERDIN). Unpublished studies were requested through the Steering Committee. Keywords used were a combination of MeSH and free text search with the terms were “Retinoblastoma” AND “Treatment”.

No relevant randomized controlled trials were found during the search. Two clinical practice guidelines were included after appraisal using AGREE II Tool for ADAPTE.

Background

IRSS Stage 4 is defined as metastatic disease via hematogenous spread (Stage 4a) or with central nervous system (CNS) extension with or without other sites of metastatic disease (Stage 4b).[57]

The latest management guideline for IRSS Stage 4 as presented by the Indian Council of Medical Research last 2023 stated that stage 4a patients with metastasis to bone

and bone marrow may be treated with curative intent.[69] Use of autologous bone marrow transplant may be done depending on response to neoadjuvant chemotherapy, enucleation, and radiotherapy to the orbit. On the other hand, stage 4b patients with central nervous system involvement may be treated with palliative intent which involves palliative chemotherapy, intrathecal chemotherapy, palliative radiotherapy, and best supportive care.

Similarly, the Canadian Retinoblastoma Society recommended enucleation, adjunctive chemotherapy, and hematopoietic stem cell transplant if with response to chemotherapy to patients with metastasis to the bone marrow, bone, or other organs or tissues.[8] Meanwhile, for tumor spread to the meninges of the brain and spinal cord, palliative treatment is considered. Treatment with enucleation, adjunctive chemotherapy, hematopoietic stem cell transplant if with response to chemotherapy, and periodic intrathecal chemotherapy is given If with spread to the CSF.

The clinical practice guidelines from Peru also recommended palliative chemotherapy to patients with metastasis to the CNS.[47] Meanwhile, if metastasis does not involve the CNS, neoadjuvant chemotherapy utilizing the PEVC or GALOP regimen prior to enucleation is recommended. The PEVC regimen includes vincristine, cisplatin, cyclophosphamide, and etoposide for a duration of 21 days. The GALOP regimen employs 4 cycles of idarubicin, vincristine, and cyclophosphamide alternating with 4 cycles of etoposide, and carboplatin for a total duration of 21 days. After enucleation, adjuvant chemotherapy, and external beam radiation therapy is given.

With regards to intrathecal chemotherapy, one case report by Rodriguez et. al detailed a trial done on a 4-year-old Stage 4b patient in Argentina where a high-dose intra-arterial chemotherapy targeting the ophthalmic artery and chiasm plus intrathecal chemotherapy was done.[70] Three cycles of carboplatin, melphalan, and intrathecal topotecan were employed and noted partial resolution of the orbital tumor mass and the chiasmatic lesion. In addition, there was complete resolution of tumor in the CSF. Enucleation followed and histopathology results noted complete tumor necrosis. Although the patient reported was eventually lost to follow-up post-surgery, the results of this study may be an area for further research especially on stage 4b patients.

Looking at palliative chemotherapy, a recent Children's Oncology Trial (2022) done in USA, Argentina, Egypt, and Brazil evaluated an intensive multimodal therapy for extraocular retinoblastoma.[65] IRSS Stage 4a or 4b patients were given four cycles of chemotherapy and those with more than or equal to a partial response were given one cycle of high-dose carboplatin, thiotepa, and etoposide with autologous hematopoietic stem-cell support. Radiotherapy then follows if residual tumor is present post chemotherapy. Based on the study, 1-year event free survival was at 82.6% for stage 4a, and 28.3% for stage 4b, while 3-year event free survival was at 76.7% for Stage 4a, and 14.2% for 4b. The authors noted that the regimen used was resource intensive and may not be available in most low-income countries.

Metronomic chemotherapy (MC) is defined as frequent and regular intake of chemotherapeutic drugs to maintain a low and active concentration at a prolonged duration without causing unnecessary toxicity.[71] A randomized controlled trial was done by Pramanik et. al in India wherein the effect of metronomic therapy versus placebo on progression-free survival (PFS) in 108 pediatric patients with primary extracranial, nonhematopoietic solid malignant tumor that progressed after 2 regimens of chemotherapy was assessed.[72] The diagnosis of the patients was as follows: bone sarcoma, neuroblastoma, rhabdomyosarcoma, esthesioneuroblastoma, non-rhabdomyosarcoma soft-tissue sarcoma, retinoblastoma, and others. The treatment arm was given a regimen including celecoxib and thalidomide alternating with etoposide and cyclophosphamide. Results showed that 100% (52/52) of the patients had disease progression in the placebo group, while 96.4% (53/56) in the MC group. In addition, the median PFS was 46 days in the placebo group while 49 days in the MC group. The overall survival was 85 days for both the placebo group and the MC group. These results indicate that MC did not improve the patients' 6-month PFS. However, the authors noted that in a post hoc subgroup analysis, there was statistically significant increase in PFS among patients who received more than 3 cycles of chemotherapy and those who did not have a bone tumor.

Evidence Summary and Source of Guideline Recommendations

Recommendations were based on two source guidelines, the SIOP-PODC, which highlights settings-based approach for the treatment of metastatic Rb.[13] The recommendations were based on one observational study with a very small sample size of 11 wherein treatment of High-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR) was provided as intervention. This was provided at a median of 5.7 months from the diagnosis of metastasis resulting in seven children having disease-free survival (median follow-up 39 months).

The CRS has the same recommendations with SIOP-PODC but are focused on what type of extraorbital or systemic metastatic involvement with adjuvant and neoadjuvant chemotherapy, followed by local control and consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue.[8] Based on one observational study, extraocular Rb treatment protocols generally include orbital radiation for orbital recurrence post-enucleation, systemic chemotherapy, stem cell/bone marrow transplant, and intrathecal chemotherapy for CNS disease with meningeal spread. Recommendations are mostly consensus based on the CRS guidelines for treatment for metastatic Rb.[8]

5. Research Implications/Gaps

In general, there is a scarcity of published guidelines and clinical trials due to the low incidence of retinoblastoma. This is particularly true for diagnostic accuracy studies involving CT scan. There is also a need to standardize the definition of high-risk pathologic features; different studies used various criteria. The small sample size of retinoblastoma patients precludes the conduct of clinical trials to determine the efficacy of different chemotherapy regimens. Finally, Annexes F to M are in this guideline to help the users of the guidelines adhere to the Rb's comprehensive standards of care.

6. Dissemination and Implementation

The Retinoblastoma GDG will consider various channels to effectively disseminate the manuscript. The CPG will undergo screening by the DOH Disease Prevention and Control Bureau for recognition and implementation as a National Practice Guideline by the DOH and the Philippine Health Insurance Corporation (PHIC). To target healthcare professionals, The Philippine Academy of Ophthalmology and the Philippine Society of Pediatric Oncology will disseminate the CPG, the clinical pathways and algorithms through lectures for different stakeholders in national and regional meetings. Special emphasis will be placed on the management algorithms for both unilateral (Appendix H) and bilateral disease (Appendix I), based on the recommended staging systems outlined in Appendix J, to guide clinicians in developing patient treatment plans. Additionally, Appendix K will include recommended practices for pathology reports to standardize the documentation of pathological findings, while Appendix L will feature a checklist for MRI radiology reports used in staging patients. These societies will also create spearhead the creation of a national Retinoblastoma tumor board open for all hospitals where specialists can provide expert guidance on the management of patients using the CPG algorithm and recommendations. Copies of this CPG will be distributed to other specialty societies involved in Retinoblastoma care such as the Philippine College of Radiology, Philippine Radiation Oncology Society, Philippine Society of Pathologist and the Philippine Pediatric Society.

The evidence summaries and the full CPG manuscript will be posted online in the Compendium of DOH-Approved Clinical Practice Guidelines website (https://doh.gov.ph/dpcb/doh-approved-cpg/) and on professional society websites. To target hospitals and the local government, the GDG will create a steering committee in collaboration with the Omnibus Health Guidance Team and the Sub technical Working group for childhood cancer. For hospitals, sample interventions include a list of necessary medical equipment and manpower for optimal treatment of

retinoblastoma and a defined referral network for complicated cases. For the local government, it would be a coordinated referral pathway for early detection.

The GDG aims to improve the effectiveness of its clinical practice guidelines by creating an implementation checklist and defining key monitoring indicators for all strong recommendations. These indicators will be established after consultations with the GDG and DOH. The Philippine Academy of Ophthalmology and the Philippine Society of Pediatric Oncology will implement annual feedback mechanisms through online surveys, email, or feedback forms to gather comments, suggestions, and experiences on the CPG. This feedback will provide valuable insights for continuous improvement and ensure alignment with clinical practice needs. The societies will also benchmark clinical patient outcomes against national and international standards to drive continuous improvement.

7. Applicability Issues

All recommendations are based on the best available evidence and current resources. The CPG focused on the availability, accessibility, and cost of diagnostic tests and pharmacological treatments in low- and middle-income settings, specifically the Philippines. Panel members, mostly practicing physicians, ensured the recommendations' applicability to both private and public healthcare facilities, including urban and rural areas. While most diagnostic tests are available in urban settings, pathology and ophthalmology expertise for histopathologic staging and treating retinoblastoma may be limited in some areas. As a result, the consensus panel provided recommendations for both basic and advanced retinoblastoma centers. A review of the available PhilHealth case rates for retinoblastoma diagnosis and treatment was conducted and included in the appendix.

Facilitators and barriers to the implementation of the Retinoblastoma CPG were identified from the discussions of the multidisciplinary and multistakeholder steering and consensus panels. Facilitators mentioned included public funding support for medications and services, accessible expert consultations for second opinions on diagnosis and management, and advocacy activities on early detection. The barriers included limited PhilHealth case rate coverage for procedures, significant out-of-pocket costs for treatment and surveillance, the lack of retinoblastoma ophthalmology and pathology experts nationwide, and the unavailability of medicines and equipment, such as lasers. This information provided context for the formulation of recommendation statements for the local setting.

This CPG does not necessarily supersede the consumers’ (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

8. Updating of the Guidelines

The Retinoblastoma Clinical Practice Guidelines (CPG) will undergo updates every three years, starting in 2026 or when new or major evidence from large-scale local and international studies emerge on priority topics, or when there are changes in available resources (medicine, technologies) or national policies.

The Department of Health (DOH) will periodically review the relevance and applicability of the guidelines and make updates as needed. The update process will follow the procedures outlined in the DOH Manual on Practice Guideline Development, and the GRADE approach will be used.

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10. Appendices

Appendix A. Members of the Guideline Development Group

Steering Committee

Ana Patricia Alcasabas, M.D.
Gary John Mercado, M.D.
Nonette Cupino, M.D.
Clarito U. Cairo Jr. M.D.

Technical Working Group

Cherie Grace G. Quingking, MD
Mr. Teddy S. Dizon
Ms. Jennel Mae T. Pimentel
Ms. Gaby B. Gascon
Ms. Roselle Guisihan

Consensus Panel

Dan Nicer, MD
Beatriz Gepte, MD
Maria Luz Del Rosario, MD
Alex Sua, MD
Thonnie Rose O. See, MD
Leandro Gatchalian, MD
Jochrys Estanislao, MD
Florentina U. Ty, MD
Krystle Anne Blasco, MD
Dennis Doromal, MD
Andrei P. Martin, MD
Pamela Astudillo, MD
Sandee Worak-Tan, MD
Ms. Carmen Auste
Carlos Naval, MD

Editorial Team
Leslie Anne M. del Barrio, MD
Isabella O. Santos, MD

Appendix B. Summary of COI Declarations

The COI declaration and management of Guideline Development Group (GDG) members were independently assessed and documented. Throughout the course of CPG development, strict adherence to COI management recommendations were observed by the members.

Name	Affiliation	Declared COI	COI Management
Ana Patricia Alcasabas, M.D.	Philippine Society of Pediatric Oncology	No COI	Must declare COI
Gary John Mercado, M.D.	Philippine Academy of Ophthalmology	No COI	Must declare COI
Nonette Cupino, M.D.	Philippine Radiation Oncology Society	No COI	Must declare COI
Clarito U. Cairo Jr. M.D.	Department of Health	Non-financial COI	Must declare COI and limited in providing government perspectives
Dan Nicer, MD	Philippine College of Radiology	Non-financial COI	Must declare COI and may voted
Beatriz Gepte, MD	Philippine Children's Medical Center	Non-financial COI	Must declare COI and may voted
Maria Luz Del Rosario, MD	St. Luke's Medical Center	Non-financial COI	Must declare COI and may voted
Alex Sua, MD	Philippine Ophthalmic Pathology Society	Non-financial COI	Must declare COI and may voted

Thonnie Rose O. See, MD	Philippine Ophthalmic Pathology Society	Non-financial COI	Must declare COI and may voted
Leandro Gatchalian, MD	Vitreo Retina Society of the Philippines	Non-financial COI	Must declare COI and may voted
Jochrys Estanislao, MD	Jose Reyes Memorial Medical Center	Non-financial COI	Must declare COI and may voted
Florentina U. Ty, MD	Philippine Pediatric Society	Non-financial COI	Must declare COI and may voted
Krystle Anne Blasco, MD	Philippine College of Radiology	Non-financial COI	Must declare COI and may voted
Dennis Doromal, MD	Philippine Radiation Oncology Society	Non-financial COI	Must declare COI and may voted
Andrei P. Martin, MD	St. Luke's Medical Center	Non-financial COI	Must declare COI and may voted
Pamela Astudillo, MD	Philippine General Hospital	Non-financial COI	Must declare COI and may voted
Sandee Worak-Tan, MD	Philippine Society of Ophthalmic Plastic & Reconstructive Surgery	Financial COI	Must declare COI and cannot vote in certain questions
Ms. Carmen Auste	Cancer Warriors Foundation	Non-financial COI	Must declare COI and may voted
Carlos Naval, MD	Philippine Academy of Ophthalmology	Non-financial COI	Must declare COI and may voted

Appendix C. AGREE II Score of Source Guidelines

Source Guidelines	Scope and Purpose	Stakeholders	Rigor	Clarity	Applicability	Independence	Overall Score
RB-LA (2019)	69.4	30.6	30.2	91.7	0	25.0	50.0
RB-SIOP-PODC (2013)	94.4	91.7	88.5	97.2	95.8	100.0	83.3
RB-India (2010)	77.8	77.8	46.9	80.6	43.8	37.5	50.0
RB-AAO (2017)	91.7	38.9	22.9	61.1	0	75.0	50.0
RB-Canada (2009)	97.2	100.0	97.9	100.0	95.8	100.0	83.3
RB-Peru (n.d.)	94.4	80.6	61.5	91.7	81.3	41.7	66.7
RB-RECIST (2021)	77.8	72.2	18.8	69.4	4.2	100.0	50.0
RB-ABS (2014)	86.1	63.9	35.4	77.8	4.2	41.7	50.0
RB-Graaf (2012)	86.1	50.0	21.9	75.0	4.2	41.7	50.0
RB-AAFP (2006)	75.0	61.1	17.7	100.0	4.2	66.7	50.0
RB-Kenya (2019)	88.9	72.2	25.0	100.0	18.8	33.3	50.0
RB-EMQN (2002)	75.0	55.6	21.9	86.1	12.5	4.2	33.3
RB-PPS (2004)	75.0	66.7	47.9	100.0	14.6	41.7	50.0

Appendix D. Summary of the PICO of Source Guidelines

SCOPE	RB-SIOP-PODC (2013)	RB-Canada (2009)	RB-India (2010)	RB-LA (2019)	RB-AAO (2017)	RB-Peru (n.d.)	RB-RECIST (2021)	RB-ABS (2014)	RB-Graaf (2012)	RB-AAFP (2006)	RB-Kenya (2019)	RB-EMQN (2002)	RB-PPS (2004)
Population	Patients with unilateral and bilateral retinoblastoma	Patients with retinoblastoma	Patients with retinoblastoma	Patients with recurrent retinoblastoma	Children at risk for retinoblastoma	Patients 0-10 years old with retinoblastoma	Patients with retinoblastoma	Patients with uveal melanoma and retinoblastoma	Patients with retinoblastoma	Patients with retinoblastoma	Patients with retinoblastoma	Patients with retinoblastoma	Patients with retinoblastoma
Intervention	Staging, Treatment	Screening, Diagnosis, Treatment, Follow-Up	Initial examination, Workup, Treatment, Histopathology, Imaging	Classification, Treatment	Screening	Diagnosis, Treatment	Response criteria	Treatment (brachytherapy)	Imaging	Screening, Diagnosis, Treatment	Screening, Diagnosis, Treatment, Follow up, Histopathology	Molecular Analysis	Screening
Professionals	Physicians	Healthcare professionals	Opthalmologists, pediatricians, ocular oncologists, pediatric oncologists, and general physicians	Clinicians	Clinicians, healthcare professionals, opthalmologists	Healthcare professionals	Clinicians	Clinical practitioners	Physicians	Healthcare professionals	Healthcare workers	QA professionals	Clinical practitioners
Outcome	diagnostic accuracy, cure rate, overall survival	overall survival			Sensitivity	Overall survival, quality of life	progression-free survival	overall survival	diagnostic accuracy	5-year survival, ocular survival, overall survival	overall survival		accuracy, reliability
Healthcare setting	LMICs		district hospital, private clinics, hospitals		Primary level of care	primary, secondary, tertiary levels of care		secondary and tertiary levels of care		primary, secondary, tertiary levels of care	primary, secondary, tertiary levels of care	secondary and tertiary levels of care	Primary level of care

Appendix E. Summary of CPG Questions and Source Guidelines

Qs	RB-SIOP-PODC (2013)	RB-Canada (2009)	RB-India (2010)	RB-LA (2019)	RB-AAO (2017)	RB-Peru (n.d.)	RB-RECIST (2021)	RB-ABS (2014)	RB-Graaf (2012)	RB-AAFP (2006)	RB-Kenya (2019)	RB-EMQN (2002)	RB-PPS (2004)
Q1	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No
Q2	No	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	No
Q3	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	No
Q4	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No
Q5	Yes	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	No
Q6	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	Yes	No	No
Q7	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	No
Q8	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	No
Q9	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	No
Q10	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	No

Appendix F. Retinoblastoma Treatment Settings

The Pediatric Oncology in Developing Countries (PODC) Committee of the International Society of Pediatric Oncology (SIOP) has developed a classification system to categorize retinoblastoma (Rb) service delivery capacity into three distinct levels. This system is based on the availability and quality of resources across several key areas: imaging, oncology treatment, ophthalmologic care, pathology assessment, and genetic testing.

Resource availability	Setting 1 (Basic)	Setting 2 (Intermediate)	Setting 3 (Advanced)
Imaging	Not available or CT only	CT and occasionally MRI	MRI
Oncology treatment	Low-dose chemotherapy, Cobalt RT	Moderate-dose chemotherapy; Cobalt RT; Linear accelerator RT	Moderate- and high-dose chemotherapy; 3D RT; autologous hematopoietic stem cell rescue linear accelerator (optional)
Ophthalmologic treatment	Minimal	Cryotherapy, laser therapy, EBRT	Cryotherapy; laser-TTT; EBRT (3D, IMRT); digital camera for fundoscopy; Intra-arterial chemotherapy; plaque ablation (optional)
Pathology assessment	Minimal, low-specialty, diagnosis confirmation	Low specialty, limited risk assessment	High-quality specialty, accurate risk assessment
Genetic testing	Not available	Not available	Limited availability, usually low resolution
Criteria for reclassification of setting	Ophthalmologist with training in conservative therapy Availability of laser therapy, cryotherapy, and RT Safe pediatric anesthesiology <5% mortality rate related to toxicity of chemotherapy Pathology assessment capable of accurate disease staging	Increased availability of localized therapies (laser-TTT, cryotherapy, and plaque ablation) <5% mortality related to toxicity of intensive chemotherapy regimen Second-line therapies for intraocular and extraocular relapse Highly specialized pathologic assessment capable of accurately stratifying patients to treatment	

References:

Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, Israels T, Leal-Leal C, Bakhshi S, Qaddoumi I, Abramson DH, Doz F; SIOP-PODC Graduated-Intensity Retinoblastoma Guidelines Writing Committee. SIOP-PODC recommendations for graduated-intensity treatment of retinoblastoma in developing countries. Pediatr Blood Cancer. 2013 May;60(5):719-27. doi: 10.1002/pbc.24468. Epub 2013 Jan 17. PMID: 23335388.

Worak-Tan SJ, Sampang MT, Rondaris MV. Capacity to Treat Retinoblastoma in the Philippines. Philipp J Ophthalmol [Internet]. 2023 Jul [cited 2023 Jun 13];48:57-66. Available from: https://paojournal.com/wp-content/uploads/2023/11/004-ORIGINAL-RESEARCH_PJO-JUL-DEC2023-WORAK_V6.pdf

Another treatment stratification was proposed by the Canadian Retinoblastoma Society in 2009, where the human and physical resources are summarized to optimize Rb care.

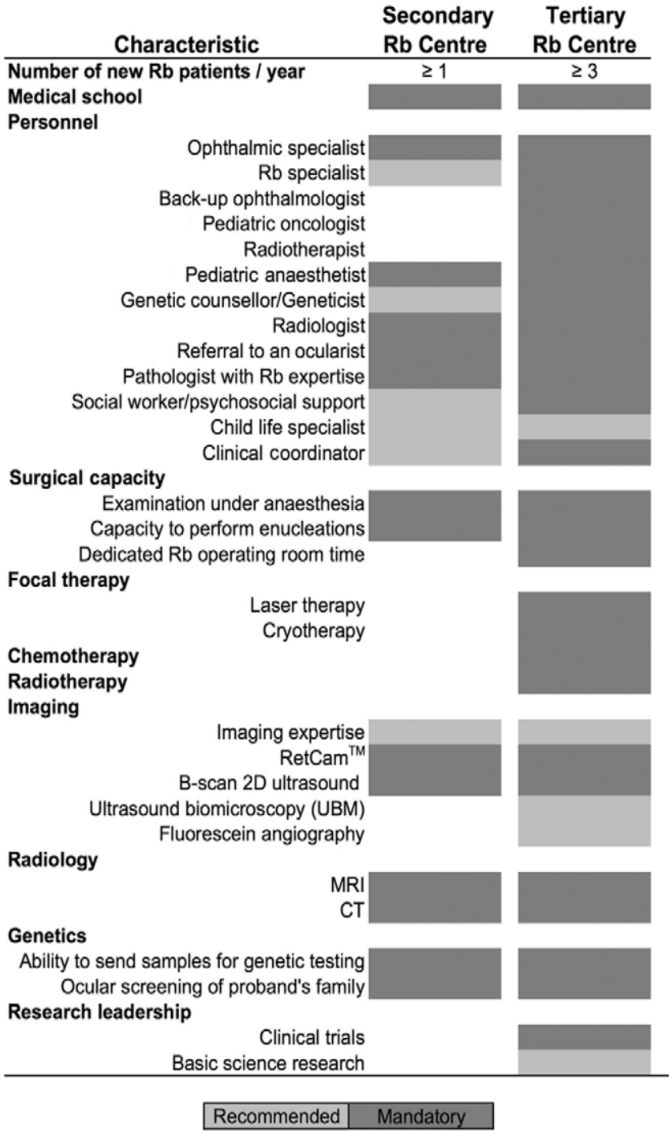


Figure 5. Optimal staffing and resources for secondary and tertiary Rb centers

Reference:

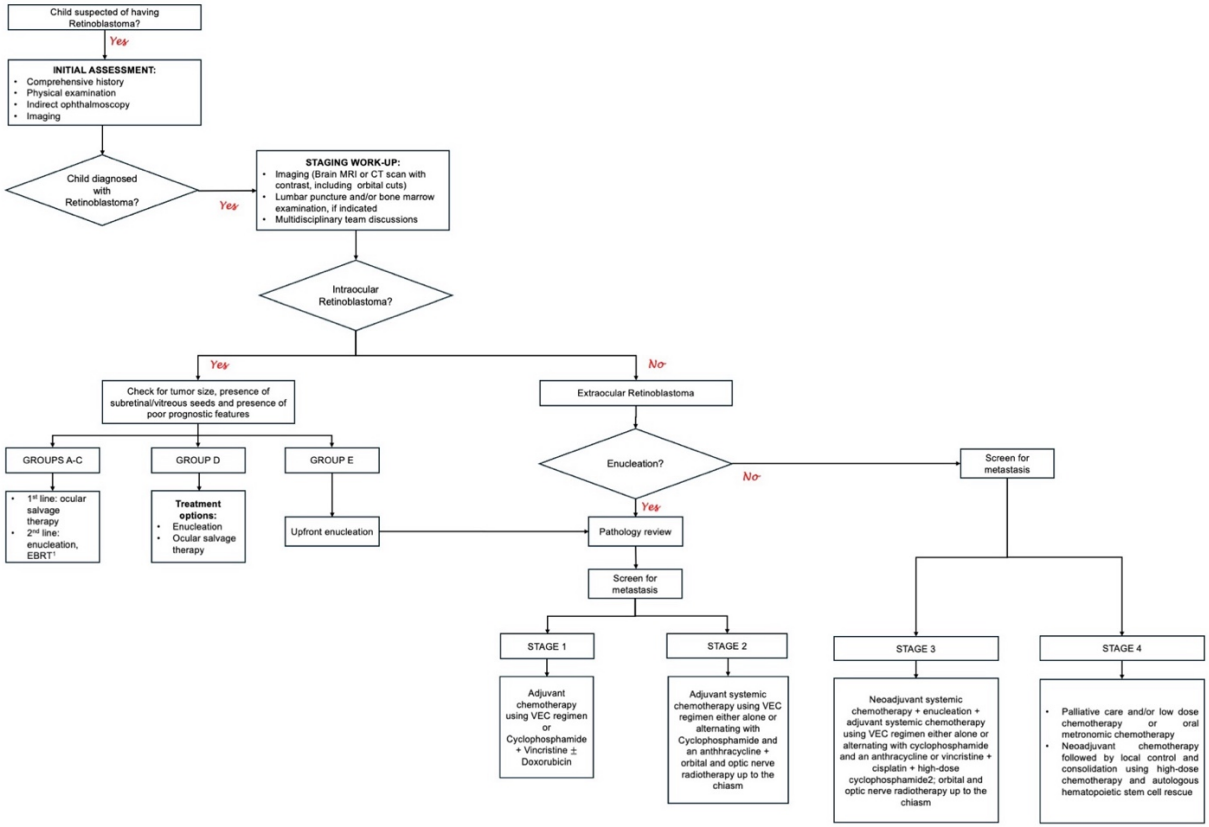
Canadian Retinoblastoma Society. National Retinoblastoma Strategy Canadian Guidelines for Care: Stratégie thérapeutique du rétinoblastome guide clinique canadien. Can J Ophthalmol. 2009;44 Suppl 2:S1-88. doi: 10.3129/i09-194. PMID: 20237571.

Appendix G. Philippine Eye Center Requirements

In January 2021, the Department of Health issued Department Order No. 2021-0001, which outlines the macroplan for specialty centers in the country, including those for eye care. A specialty center is a hospital unit or department that provides specialized care and procedures requiring specific training and equipment. The order includes a resource stratification framework to assess the service capabilities of each facility. Below shows the capabilities of specialty and intermediate centers including retinoblastoma care.

Criteria	**Specialty**			**Intermediate**
Level of Care	National Specialty Center	Advanced Comprehensive Eye center (ACC)	Basic Comprehensive Eye Center (BCC)	Ophthalmology Unit for L2 Hospital
Licensing Standard	(Designated)	L2 plus teaching and training Facility	L2 plus teaching and training Facility	L1 plus departmentalized with intensive care
General Description of Service Capability	Capable of managing **ALL Ophthalmic cases** with both General & Subspecialty Ophthalmology Clinics Treats complex cases with specialized instruments and have facilities for special investigation	Same as BCC **PLUS** services for Orbit, Oculoplastics **Ophthalmic Oncology (Retinoblastoma)** Ocular Pathology	Provides comprehensive range of services to at least included Glaucoma, Retina, Cataract, External Disease, and pediatric Ophthalmology	Is linked to a comprehensive eye center Provide care that can diagnose and medically manage cataract, glaucoma, retina, external eye and trauma

Appendix H. Unilateral Retinoblastoma Management Algorithm



Abbreviations: EBRT, external beam radiation therapy; IRSS, International Retinoblastoma Staging System; VEC, vincristine + etoposide + carboplatin

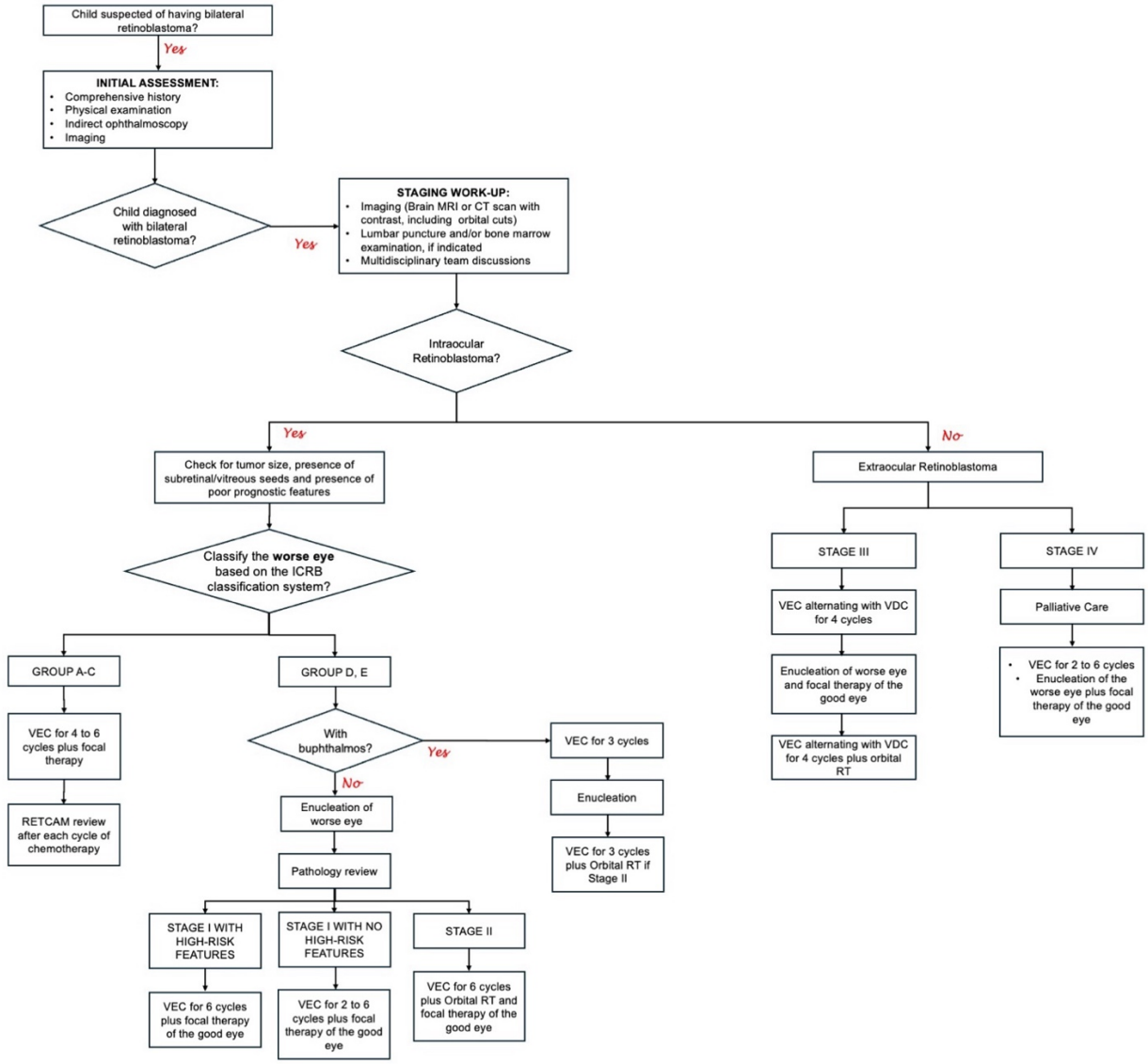
[1] EBRT is not recommended for patients less than 1 y/o due to the risk of secondary malignancy

[2] regimen that can be used in setting

* A separate clinical pathway will be developed.

Reference: Berry JL. Retinoblastoma: Treatment and outcome. In: Passe EA, Pappo AS, Armbsy C, editors. UptoDate. Waltham, MA: UptoDate; 2024.

Appendix I. Bilateral Retinoblastoma Management Algorithm



Source: Retinoblastoma Metro Manila [unpublished]

Appendix J. Retinoblastoma Staging Systems

The Reese–Ellsworth (RE) classification system for RB was developed in the 1960s to predict the probability of maintaining sight and control of local disease with EBRT but was not designed to predict the likelihood of metastases or patient survival. In 2005, the International Classification of Retinoblastoma (ICRB) emerged and has been shown to assist in predicting those who are likely to be cured by chemo-reduction and focal therapy. Both the RE and ICRB are for the intraocular staging of Rb. Another classification system, the International Retinoblastoma Staging System (IRSS), was proposed in 2006 which aimed to incorporate the entire spectrum of the disease (Chantada et. al, 2006). Patients were classified according to disease extent, and presence of extra-ocular extension. The AJCC/UICC10 staging system (TNM) emerged as a universal staging system for all cancers and included both intraocular and extraocular RB. The most recent revision of the AJCC/UICC staging is the eighth edition, effective for cancers diagnosed on or after January 1, 2010. This revision came after the international classification and can be used to describe the extent of RB in detail, particularly for those cases where the disease has spread outside of the eye.

Reese–Ellsworth (RE) Classification System

Group 1	very favorable for saving [or preserving] the eye ● 1A: one tumor, smaller than 4-disc diameters (DD), at or behind the equator ● 1B: multiple tumors smaller than 4 DD, all at or behind the equator
Group 2	favorable for saving [or preserving] the eye ● 2A: one tumor, 4 to 10 DD, at or behind the equator ● 2B: multiple tumors, with at least one 4 to 10 DD, and all at or behind the equator
Group 3	doubtful for saving [or preserving] the eye ● 3A: any tumor in front of the equator ● 3B: one tumor, larger than 10 DD, behind the equator
Group 4	unfavorable for saving [or preserving] the eye ● 4A: multiple tumors, some larger than 10 DD ● 4B: any tumor extending toward the front of the eye to the ora serrata (front edge of the retina)
Group 5	very unfavorable for saving [or preserving] the eye ● 5A: tumors involving more than half of the retina ● 5B: vitreous seeding (spread of tumors into the jelly-like material that fills the eye)

International Classification Systems for Intraocular Rb (ICRB)

Group A	Small Intra-retinal tumors away from foveola and disc 1. All tumors are 3mm in greatest dimensions, confined to the retina AND 2. All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc
Group B	All remaining discrete tumors confined in the retina 1. All other tumors confined to the retina not in Group A 2. Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding
Group C	Discrete Local disease with minimal subretinal or vitreous seeding 1. Tumor(s) are discrete 2. Subretinal fluid, present or past, without seeding involving up to ¼ retina 3. Local fine vitreous seeding may be present close to discrete tumor 4. Local subretinal seeding less than 3 mm (2 DD) from the tumor
Group D	Diffuse disease with significant subretinal or vitreous seeding 1. Tumor(s) may be massive or diffuse 2. Subretinal fluid present or past without seeding involving up to total retinal detachment 3. Diffuse or massive vitreous seeding may include “greasy seeds” or avascular tumor masses 4. Diffuse subretinal seeding may include subretinal plaques or tumor nodules
Group E	Presence of any one or more of these poor prognostic features 1. Tumor touching the lens 2. Tumor anterior to anterior vitreous face involving ciliary body or anterior segment 3. Diffuse infiltrating retinoblastoma 4. Neovascular retinoblastoma 5. Opaque media from hemorrhage 6. Tumor necrosis with aseptic orbital cellulites 7. Phthisis bulbi

International Rb Staging System (IRSS)

Stage 0	Patients treated conservatively
Stage I	Eye enucleated, completely resected histologically
Stage II	Eye enucleated, microscopic residual tumor (cut end of optic nerve is positive for tumor)
Stage III	Regional extension a. Overt orbital disease b. Pre-auricular or cervical lymph node extension
Stage IV	Metastatic disease a. Hematogenous metastasis (without CNS involvement) 1. Single lesion 2. Multiple lesions b. CNS extension (with or without any other site of regional or metastatic disease) 1. Pre-chiasmatic lesion 2. CNS mass 3. Leptomeningeal and CSF disease

AJCC (2017) Staging Systems

pT1		Intraocular tumor(s) without any local invasion, or with focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve head
pT2		Intraocular tumor(s) with local invasion
	pT2a	Concomitant focal choroidal invasion and pre-or intralaminar involvement of the optic nerve head
	pT2b	Tumor invasion of stroma of iris
pT3		Intraocular tumor(s) with significant local invasion
	pT3a	Massive choroidal invasion (>3mm in largest diameter, or multiple foci of focal choroidal involvement totaling >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 the outer third of the sclera and/or invasion into or around emissary channels
cT4		Extraocular tumor(s) involving orbit, including optic nerve
	cT4a	Evidence of extraocular tumor: tumor at the transected end of the optic nerve, tumor 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.

Appendix K. Retinoblastoma Pathology Reporting

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Note:

External reviewer shared that the determination of tumor site in the specimen at the pathology laboratory using transillumination may have some practicality concerns.

Reporting Template

Protocol Posting Date: June 2021

Select a single response unless otherwise indicated.

CASE SUMMARY: (RETINOBLASTOMA)

Standard(s): AJCC-UICC 8

___ Retinoblastoma

CLINICAL

+Treatment History

___ No known preoperative therapy

___ Preoperative therapy given (specify, if known): _____

___ Not specified

SPECIMEN

Procedure (select all that apply)

___ Enucleation

___ Partial exenteration

___ Complete exenteration

___ Other (specify): _____

___ Not specified

Total Length of Optic Nerve

Measurement should include optic nerve attached to globe and any additionally submitted optic nerve segments

Specify in Millimeters (mm)

___ Exact measurement: _____ mm

___ At least: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined (explain): _____

Tumor Sampling for Molecular Studies

___ Yes

___ No

___ Not known

Specimen Laterality

___ Right

___ Left

___ Not specified

TUMOR

Tumor Site (macroscopic examination / transillumination) (select all that apply)

___ Superotemporal quadrant of globe

___ Superonasal quadrant of globe

___ Inferotemporal quadrant of globe

___ Inferonasal quadrant of globe

___ Superior quadrant of globe

___ Inferior quadrant of globe

___ Nasal quadrant of globe

___ Temporal quadrant of globe

___ Anterior chamber

___ Other (specify): _____

___ Cannot be determined: _____

Tumor Site after Sectioning (select all that apply)

___ Superonasal

___ Inferonasal

___ Superotemporal

___ Inferotemporal

___ Superior quadrant of globe

___ Inferior quadrant of globe

___ Nasal quadrant of globe

___ Temporal quadrant of globe

___ Anterior chamber

___ Other (specify): _____

___ Cannot be determined: _____

Tumor Size after Sectioning

___ Cannot be determined: _____

___ Size can be determined

Greatest Basal Diameter of Tumor

Specify in Millimeters (mm)

___ Exact measurement: _____ mm

___ At least: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined: _____

+Basal Diameter at Cut Edge of Tumor

Specify in Millimeters (mm)

___ Exact measurement: _____ mm

___ At least: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined: _____

Greatest Thickness of Tumor

Specify in Millimeters (mm)

___ Exact measurement: _____ mm

___ At least: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined: _____

+Thickness at Cut Edge of Tumor

Specify in Millimeters (mm)

___ Exact measurement: _____ mm

___ At least: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined: _____

+Percentage of Vitreous Cavity Occupied by Tumor

___ Specify percentage: _____ %

___ Other (specify): _____

___ Cannot be determined: _____

+Distance from Anterior Edge of Tumor to Limbus at Cut Edge

Specify in Millimeters (mm)

___ Exact distance: _____ mm

___ Greater than: _____ mm

___ At least: _____ mm

___ Less than: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined: _____

+Distance from Posterior Margin of Tumor Base to Edge of Optic Disc

Specify in Millimeters (mm)

___ Exact distance: _____ mm

___ Greater than: _____ mm

___ At least: _____ mm

___ Less than: _____ mm

___ Less than 1 mm

___ Other (specify): _____

___ Cannot be determined: _____

Tumor Growth Pattern

___ Endophytic

___ Exophytic

___ Combined endophytic / exophytic

___ Diffuse

___ Anterior diffuse

___ Other (specify): _____

___ Cannot be determined: _____

Histologic Grade

___ G1 (tumor with areas of retinocytoma [fleurettes or neuronal differentiation accounting for more than half of tumor])

___ G2 (tumor with many rosettes [Flexner–Wintersteiner or Homer Wright rosettes accounting for more than half of tumor])

___ G3 (tumor with occasional rosettes [Flexner–Wintersteiner or Homer Wright rosettes accounting for less than half of tumor])

___ G4 (tumor with poorly differentiated cells without rosettes and/or with extensive areas [more than half of tumor] of anaplasia)

___ GX (grade cannot be assessed)

+Histologic Grade Comment: _____

+Anaplasia Grade

Grade based on the highest level of anaplasia in the tumor, with at least 30% of the tumor being able to be graded.

___ Mild

___ Moderate

___ Severe

___ Cannot be determined: _____

+Histopathologic Features Suggesting MYCN Amplification

Unilateral retinoblastoma with more rounded, undifferentiated cells, with prominent nucleoli, and absence of nuclear molding, differentiated rosettes, and extensive calcification. The histology of MYCN retinoblastoma is more similar to neuroblastoma than it is to RB1−/− retinoblastoma.

___ Not identified

___ Present

Other Ocular Structures Involved by Tumor (select all that apply)

___ Cornea

___ Anterior chamber

___ Iris

___ Angle

___ Lens

___ Ciliary body

___ Vitreous

___ Retina

___ Sub-retinal space

___ Sub-retinal pigment epithelial space

___ Optic nerve head

___ Choroid, minimal (solid tumor nest less than 3 mm in maximum diameter [width or thickness])

___ Choroid, massive (solid tumor nest 3 mm or more in maximum diameter [width or thickness])

___ Sclera (direct invasion into inner half)

___ Sclera (direct invasion into outer half without episcleral invasion)

___ Sclera (direct invasion into outer half with episcleral invasion)

___ Sclera (within intrascleral emissarial canals)

___ Vortex vein

___ Orbit

___ Other (specify): _____

___ Cannot be determined: _____

Extent of Optic Nerve Invasion

___ None identified

___ Anterior to lamina cribrosa

___ Within lamina cribrosa

___ Posterior to lamina cribrosa but not to end of nerve

___ To cut end of optic nerve

___ Other (specify): _____

___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS

Margin Status (select all that apply)

___ All margins negative for tumor

___ Tumor present at surgical margin of optic nerve

___ Extrascleral extension present (for enucleation specimens)

___ Other (specify): _____

___ Cannot be determined: _____

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status

___ Not applicable (no regional lymph nodes submitted or found)

___ Regional lymph nodes present

___ All regional lymph nodes negative for tumor

___ Tumor present in regional lymph node(s)

Number of Lymph Nodes with Tumor

___ Exact number (specify): _____

___ At least (specify): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

Number of Lymph Nodes Examined

___ Exact number (specify): _____

___ At least (specify): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)

___ Not applicable

___ Bone marrow: _____

___ Liver: _____

___ Cerebrospinal fluid: _____

___ CNS parenchyma: _____

___ Other (specify): _____

___ Cannot be determined: _____

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th Edition)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

TNM Descriptors (select all that apply)

___ Not applicable

___ m (multiple primary tumors)

___ r (recurrent)

___ y (post-treatment)

pT Category

___ pT not assigned (cannot be determined based on available pathological information)

___ pT0: No evidence of intraocular tumor

 # CAP Author's Note: Tumors with focal choroidal invasion ONLY (not meeting criteria for pT3a) without concomitant optic nerve invasion and tumors with pre-or intralaminar involvement of the optic nerve head ONLY without concomitant choroidal invasion are included in pT1 category.

___ pT1: Intraocular tumor(s) without any local invasion, focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve head#

pT2: Intraocular tumor(s) with local invasion

___ pT2a: Concomitant focal choroidal invasion and pre- or intralaminar involvement of the optic nerve head

___ pT2b: Tumor invasion of stroma of iris and / or trabecular meshwork and / or Schlemm's canal

___ pT2 (subcategory cannot be determined)

pT3: Intraocular tumor(s) with significant local invasion

___ pT3a: Massive choroidal invasion (greater than 3 mm in largest diameter, or multiple foci of focal choroidal involvement totaling greater than 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 the outer third of the sclera and / or invasion into or around emissary channels

___ pT3 (subcategory cannot be determined)

___ pT4: Evidence of extraocular tumor: tumor at the transected end of the optic nerve, tumor 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

pN Category

___ pN not assigned (no nodes submitted or found)

___ pN not assigned (cannot be determined based on available pathological information)

___ pN0: No regional lymph node involvement

___ pN1: Regional lymph node involvement

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)

pM1: Distant metastasis with histopathologic confirmation

___ pM1a: Histopathologic confirmation of tumor at any distant site (e.g., bone marrow, liver, or other)

___ pM1b: Histopathologic confirmation of tumor in the cerebrospinal fluid or CNS parenchyma

___ pM1 (subcategory cannot be determined)

Heritable Trait (H) Status

___ 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, any retinoblastoma with an intracranial primitive neuroectodermal tumor (ie, trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of a constitutional RB1 gene mutation

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)

___ None identified

___ Calcifications

___ Mitotic rate (specify number of mitoses per mm2): _____ mitoses per mm2

___ Apoptosis

___ Necrosis

___ Basophilic deposits

___ Inflammatory cells

___ Hemorrhage (specify site): _____

___ Retinal detachment

___ Neovascularization (specify site): _____

___ Treatment effect (specify): _____

___ Other (specify): _____

COMMENTS

Comment(s): _____

References:

1. Gallie BL, Ellsworth RM, Abramson DH, Phillips RA. Retinoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? Br J Cancer. 1982 Apr;45(4):513-21. doi: 10.1038/bjc.1982.87. PMID: 7073943; PMCID: PMC2010981.
2. Dimaras H, Khetan V, Halliday W, Orlic M, Prigoda NL, Piovesan B, Marrano P, Corson TW, Eagle RC Jr, Squire JA, Gallie BL. Loss of RB1 induces non-proliferative retinoma: increasing genomic instability correlates with progression to retinoblastoma. Hum Mol Genet. 2008 May 15;17(10):1363-72. doi: 10.1093/hmg/ddn024. Epub 2008 Jan 22. PMID: 18211953.
3. Eagle RC Jr, Chévez-Barrios P, Li B, Al Hussaini M, Wilson M. Tumours of the neurosensory retina. In: Grossniklaus HE, Eberhart CG, Kivelä TT, eds. WHO Classification of Tumours of the Eye, 4th edition. Lyon: International Agency for Research on Cancer; 2018;111-117.
4. Tumors of the Eye and Ocular Adnexa [Internet]. [place unknown]: American Registry of PathologyArlington, Virginia; 2021. Tumors of the Neurosensory Retina and Retinal Pigment Epithelium; [cited 2024 Aug 13]; p. 191-232. Available from: https://doi.org/10.55418/9781933477923-ch09
5. Eagle RC Jr. High-risk features and tumor differentiation in retinoblastoma: a retrospective histopathologic study. Arch Pathol Lab Med. 2009 Aug;133(8):1203-9. doi: 10.5858/133.8.1203. PMID: 19653710.
6. Mendoza PR, Specht CS, Hubbard GB, Wells JR, Lynn MJ, Zhang Q, Kong J, Grossniklaus HE. Histopathologic grading of anaplasia in retinoblastoma. Am J Ophthalmol. 2015 Apr;159(4):764-76. doi: 10.1016/j.ajo.2014.12.014. Epub 2014 Dec 19. PMID: 25528954; PMCID: PMC4361305.
7. Rushlow DE, Mol BM, Kennett JY, Yee S, Pajovic S, Thériault BL, Prigoda-Lee NL, Spencer C, Dimaras H, Corson TW, Pang R, Massey C, Godbout R, Jiang Z, Zacksenhaus E, Paton K, Moll AC, Houdayer C, Raizis A, Halliday W, Lam WL, Boutros PC, Lohmann D, Dorsman JC, Gallie BL. Characterisation of retinoblastomas without RB1 mutations: genomic, gene expression, and clinical studies. Lancet Oncol. 2013 Apr;14(4):327-34. doi: 10.1016/S1470-2045(13)70045-7. Epub 2013 Mar 13. PMID: 23498719.

Appendix L. Retinoblastoma MRI Protocol Checklist

Retinoblastoma Checklist for MRI radiology reports
Parameters:
Tumor Characteristics SI relative to vitreous body; moderately high on T1-W and low on T2-W Laterality
Growth Pattern Tumor size and location; in contact with optic nerve Buphthalmia
Tumor extension Optic nerve and meningeal sheath invasion Ocular wall invasion (choroid and sclera) Extraocular extension
Anterior eye segment Anterior chamber depth Enhancement Tumor invasion, ciliary body
Brain Trilateral retinoblastoma; pineal gland and supra- or parasellar region Leptomeningeal metastases Malformations

SI - Signal Intensity

Reference:

de Graaf P, Göricke S, Rodjan F, Galluzzi P, Maeder P, Castelijns JA, Brisse HJ; European Retinoblastoma Imaging Collaboration (ERIC). Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. Pediatr Radiol. 2012 Jan;42(1):2-14. doi: 10.1007/s00247-011-2201-5. Epub 2011 Aug 18. PMID: 21850471; PMCID: PMC3256324.

Appendix M. Retinoblastoma PhilHealth Benefit Package

Below case rates is an unpublished project of PSPO. The project team followed the methodological approach of case rates adjustment based on PhilHealth Circulars No. 2024-0001and 2024-0012. Noting that the annual limit for PhilHealth benefits usage is 45 days per year.

Types	ICD-10 code	Peso Benefit Package		Claims/ Usage
		HCI	MD	
DIAGNOSIS				
Malignant neoplasm of retina	ICD10:C69.2	15,379	6,591	Every 90 days
STAGING				
Examination under Anesthesia	None	None	None	None
Imaging (CT scan or MRI)	None	None	None	None
Lumbar tap	RVS:62270	5,200	2,184	Every 90 days
Bone marrow biopsy	RVS:38220	9,230	4,914	Every 90 days
TREATMENT				
Surgery				
Enucleation of eye; without implant	RVS: 65101	7,020	8,736	Every 90 days
Enucleation of eye; with implant, muscles attached	RVS: 65105	7,020	8,736	Every 90 day
Enucleation of eye; with implant, muscles not attached	RVS: 65103	7,020	8,736	Every 90 day
Destruction of localized lesion of retina; photocoagulation	RVS:67210	7,020	8,736	Every 90 day
Implantation of Intravitreal Drugs	RVS:67027	22,490	18,564	Every 90 days
Placement of central venous catheter; percutaneous or cutdown	RVS: 36488	7,150	5,460	Every 90 day
Chemotherapy	RVS:96408	7,270	2,184	Everyday
Radiation Treatment (RT)				
Therapeutic radiology treatment planning	RVS: 77261	12,480	10,920	Every 90 days
Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy	RVS: 77421	13,500	16,800	Every 90 days
Linear Accelerator RT	RVS: 77401	2,860	1,040	Everyday
Cobalt RT	RVS: 77401	1,560	1,040	Everyday
Intensity Modulated RT (IMRT)	RVS: 77418	5,200	2,184	Everyday

Reference: Online Services | PhilHealth [Internet]; [cited 2024 Aug 5]. Available from: https://www.philhealth.gov.ph/services/.

Appendix N. AGREE II Reporting Checklist

This is independently rated by three non-medical reviewers. This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☒ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	1, 7
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	1-5, 9
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	1-5, 9
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and*	☒ Name of participant ☒ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA)	67-69

individuals involved in formulating the final recommendations.	☒ A description of the member's role in the guideline development group	
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☒ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	9-17
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	1, 7
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	8-18
8. EVIDENCE SELECTION CRITERIA	☒ Target population (patient, public, etc.) characteristics	8-18

Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.	☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☒ Language (if relevant) ☒ Context (if relevant)	
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	8-18
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	8-18
11. CONSIDERATION OF BENEFITS AND HARMS	☒ Supporting data and report of benefits	8-18

Report the health benefits, side effects, and risks that were considered when formulating the recommendations.	☒ Supporting data and report of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	8-18
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☒ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	8-18
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated	57

	☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	8-18, 19-54
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	8-18, 19-54
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	1-5
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of	73-94

	guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☒ How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals o Solutions linked to barrier analysis (see Item 18) o Tools to capitalize on guideline facilitators (see Item 18) o Outcome of pilot test and lessons learned	73-94
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course)	73-94

	☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☒ Advice on the frequency and interval of measurement ☒ Operational definitions of how the criteria should be measured	56
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	lii, 18
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	68-69

Appendix O. External Evaluation

This was independently reviewed by six independent external reviewers prior. Reviewers reviewed this document from August 8 to 22, 2024. They did not receive any monetary or non-monetary compensation for this review. This external review was done prior to submission to DOH National Practice Guideline Program Secretariat's appraisal.

CPG External Evaluators

External Evaluator	Sex	Affiliation	Specialization
Dr. Rolando Enrique Domingo	M	World Health Organization	Policy Maker
Dr. Laura Melissa Stephanie San	F	Dr. Jose Fabella Memorial Hospital	Pediatric Oncology
Dr. Maria Wilma Turalde-Mapili	F	UP – Philippine General Hospital	Pediatrics
Dr. Jose M. Carnate, Jr.	M	UP – College of Medicine	Pathology
Dr. Andrea Kristina Monzon-Pajarillo	F	Ilocos Training and Regional Medical Center	Pediatric Ophthalmology and Strabismus
Dr. Aveline Marie Du Ylanan	F	St. Luke's Medical Center	Radiation Oncology

CPG External Evaluation Summary

EXTERNAL EVALUATION	Evaluator's Rating						Results	Remarks
	1	2	3	4	5	6		
DOMAIN 1. SCOPE AND PURPOSE	5.7	5.7	7.0	7.0	7.0	7.0	93.65	Passed
DOMAIN 2. STAKEHOLDER INVOLVEMENT	5.7	6.7	6.0	6.3	7.0	6.0	89.68	Passed
DOMAIN 3. RIGOR OF DEVELOPMENT	6.5	5.4	7.0	6.8	7.0	6.6	93.45	Passed
DOMAIN 4. CLARITY OF PRESENTATION	6.3	5.7	6.3	7.0	7.0	7.0	93.65	Passed
DOMAIN 5. APPLICABILITY	5.3	6.5	6.0	7.0	6.8	5.5	88.10	Passed
DOMAIN 6. EDITORIAL INDEPENDENCE	6.5	7.0	7.0	6.5	7.0	6.0	95.24	Passed
OVERALL GUIDELINE ASSESSMENT	6.0	6.0	7.0	7.0	7.0	6.0	92.86	Passed

CPG External Evaluation Details

EXTERNAL EVALUATION	Evaluator's Rating					
	1	**2**	**3**	**4**	**5**	**6**
DOMAIN 1. SCOPE AND PURPOSE	**5.7**	**5.7**	**7.0**	**7.0**	**7.0**	**7.0**
The overall objective(s) of the guideline is (are) specifically described.	6.0	6.0	7.0	7.0	7.0	7.0
The health question(s) covered by the guideline is (are) specifically described.	6.0	6.0	7.0	7.0	7.0	7.0
The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	5.0	5.0	7.0	7.0	7.0	7.0
DOMAIN 2. STAKEHOLDER INVOLVEMENT	**5.7**	**6.7**	**6.0**	**6.3**	**7.0**	**6.0**
The guideline development group includes individuals from all relevant professional groups.	6.0	6.0	5.0	7.0	7.0	4.0
The views and preferences of the target population (patients, public, etc.) have been sought.	6.0	7.0	6.0	5.0	7.0	7.0
The target users of the guideline are clearly defined.	5.0	7.0	7.0	7.0	7.0	7.0
DOMAIN 3. RIGOR OF DEVELOPMENT	**6.5**	**5.4**	**7.0**	**6.8**	**7.0**	**6.6**
Systematic methods were used to search for evidence.	7.0	5.0	7.0	7.0	7.0	7.0
The criteria for selecting the evidence are clearly described.	6.0	5.0	7.0	7.0	7.0	7.0
The strengths and limitations of the body of evidence are clearly described	6.0	5.0	7.0	6.0	7.0	7.0
The methods for formulating the recommendations are clearly described.	6.0	6.0	7.0	7.0	7.0	7.0
The health benefits, side effects, and risks have been considered in formulating the recommendations.	7.0	5.0	7.0	7.0	7.0	7.0
There is an explicit link between the recommendations and the supporting evidence.	6.0	6.0	7.0	6.0	7.0	6.0
The guideline has been externally reviewed by experts prior to its publication.	7.0	5.0	7.0	7.0	7.0	7.0
A procedure for updating the guideline is provided.	7.0	6.0	7.0	7.0	7.0	5.0

DOMAIN 4. CLARITY OF PRESENTATION	**6.3**	**5.7**	**6.3**	**7.0**	**7.0**	**7.0**
The recommendations are specific and unambiguous.	6.0	6.0	6.0	7.0	7.0	7.0
The different options for management of the condition or health issue are clearly presented.	7.0	5.0	7.0	7.0	7.0	7.0
Key recommendations are easily identifiable.	6.0	6.0	6.0	7.0	7.0	7.0
DOMAIN 5. APPLICABILITY	**5.3**	**6.5**	**6.0**	**7.0**	**6.8**	**5.5**
The guideline describes facilitators and barriers to its application.	5.0	7.0	6.0	7.0	7.0	7.0
The guideline provides advice and/or tools on how the recommendations can be put into practice.	5.0	7.0	6.0	7.0	7.0	7.0
The potential resource implications of applying the recommendations have been considered.	6.0	7.0	7.0	7.0	7.0	4.0
The guideline presents monitoring and/or auditing criteria.	5.0	5.0	5.0	7.0	6.0	4.0
DOMAIN 6. EDITORIAL INDEPENDENCE	**6.5**	**7.0**	**7.0**	**6.5**	**7.0**	**6.0**
The views of the funding body have not influenced the content of the guideline.	7.0	7.0	7.0	7.0	7.0	6.0
Competing interests of guideline development group members have been recorded and addressed.	6.0	7.0	7.0	6.0	7.0	6.0
OVERALL GUIDELINE ASSESSMENT	**6.0**	**6.0**	**7.0**	**7.0**	**7.0**	**6.0**
Rate the overall quality of this guideline.	6.0	6.0	7.0	7.0	7.0	6.0
I would recommend this guideline for use.	**Yes**	**Yes**	**Yes with mod.**	**Yes**	**Yes**	**Yes with mod.**