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Advances in imaging to optimize the diagnosis and characterization of retinoblastoma: A systematic review

Avances en imagenología para optimizar el diagnóstico y la caracterización del retinoblastoma: una revisión sistemática

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ABSTRACT

Introduction: Retinoblastoma is the most common intraocular malignant tumor in childhood and may spread to the optic nerve. Early diagnosis and timely treatment are crucial to prevent enucleation and visual sequelae. The aim of this study was to analyze and evaluate the scientific evidence on both new and conventional imaging techniques used to assess tumor extent. **Materials and Methods:** A systematic review of studies published between 2020 and 2025 in English and Spanish on imaging techniques for the diagnosis of retinoblastoma was conducted. The search was performed in PubMed, ScienceDirect, Scielo, and Google Scholar. Observational studies, clinical studies, and systematic reviews were included, while genetic or molecular research without clinical diagnostic application, studies in adults, animals, or *in vitro* models, as well as articles focused solely on treatment or prognosis, were excluded. **Results:** Seventeen studies were included. Magnetic resonance imaging, particularly high-resolution MRI, demonstrated the highest sensitivity and specificity for detecting postlaminar optic nerve invasion and other high-risk features. Ultrasound and computed tomography were useful for identifying masses and calcifications but had a lower capacity to assess optic nerve invasion and extraocular extension. Advanced retinal imaging techniques and microvascular flow imaging provided improved accuracy for characterization and follow-up, although the available evidence remains limited. **Conclusions:** High-resolution magnetic resonance imaging is established as the key technique for evaluating retinoblastoma, while emerging modalities are complementary and promising; however, their clinical utility requires confirmation through prospective studies with stronger scientific evidence.

Keywords: Retinoblastoma, diagnostic imaging, magnetic resonance imaging, computed tomography, ultrasonography, child.

RESUMEN

Introducción: El retinoblastoma es el tumor maligno intraocular más frecuente en la infancia y puede diseminarse al nervio óptico. El diagnóstico y tratamiento oportuno son cruciales para evitar enucleación y secuelas visuales. El objetivo del estudio fue evaluar la evidencia científica sobre las técnicas imagenológicas nuevas y convencionales, que son utilizadas para evaluar la extensión del tumor. **Materiales y métodos:** Se realizó una revisión sistemática de estudios publicados entre 2020-2025 en inglés y español sobre técnicas imagenológicas para el diagnóstico del retinoblastoma. La búsqueda se realizó en PubMed, ScienceDirect, SciElo y Google Scholar. Se incluyeron estudios observacionales, clínicos y revisiones sistemáticas, y se excluyeron investigaciones genéticas o moleculares sin aplicación diagnóstica clínica, estudios en adultos, animales o modelos *in vitro*, así como artículos centrados únicamente en tratamiento o pronóstico. **Resultados:**

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Se incluyeron 17 estudios. La resonancia magnética, especialmente la de alta resolución, mostró la mejor sensibilidad y especificidad para detectar invasión poslaminar del nervio óptico y otros factores de alto riesgo. La ecografía y la tomografía computarizada fueron útiles para identificar masas y calcificaciones, pero presentaron menor capacidad para evaluar invasión del nervio óptico.

Palabras clave: retinoblastoma, diagnóstico por imagen, resonancia magnética, tomografía computarizada, ultrasonografía, niño.

1. Introduction

Retinoblastoma (Rb) is the most common primary intraocular malignancy in childhood. Its incidence is approximately 1 case per 17,000 live births, with an estimated 8,000 new cases diagnosed worldwide each year [1]. Middle-income countries account for approximately 69% of cases; low-income countries, 20%; and high-income countries, 11% [2]. In Ecuador, there are no comprehensive epidemiological data for this type of cancer; however, according to the World Health Organization (WHO), approximately 1,000 children and adolescents are diagnosed with cancer annually. In 2023, 88 cases of retinoblastoma were treated at the Francisco Icaza Bustamante Hospital [3].

Currently, the only known cause is mutations in the retinoblastoma gene (RB1), located on chromosome 13q14.2 [4]. Autosomal dominant inheritance is observed in 30-40% of cases, while the sporadic non-hereditary form accounts for the remaining 60-70% [1].

Approximately 70-75% of retinoblastoma cases are unilateral and sporadic, typically presenting between the second and third years of life; the remaining 25% are bilateral and hereditary, usually manifesting within the first year [2].

Clinical manifestations of retinoblastoma include leukocoria—characterized by a white pupillary reflex in the affected eye, often noticeable in flash photography—which is the most common presentation (60-80%) [5]. Other clinical features include strabismus, ocular redness, or scleral vascular congestion. Less frequent symptoms include visual impairment, hyphema, proptosis, and photophobia [4]. Once the tumor develops, it may invade adjacent structures such as the optic nerve, uveal tract, sclera, and conjunctiva [6]. Metastatic disease occurs in approximately 10-15% of patients and may spread through the subarachnoid space to the brain and spinal cord [4,7].

The diagnosis and characterization of retinoblastoma rely primarily on a combination of clinical presentation and imaging studies, including indirect ophthalmoscopy, ocular ultrasonography (B-scan), and magnetic resonance imaging (MRI). Computed tomography (CT) and biopsies are generally avoided due to the increased risk of metastasis or secondary malignancies [8]. MRI provides valuable guidance for assessing the likelihood of complete tumor resection and estimating disease extent [9]. Emerging imaging techniques include optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA), among others [10]. Table 1 summarizes the main imaging modalities, their clinical utility, and limitations, and provides a framework for this review [11,12].

This systematic review compares conventional imaging techniques with emerging modalities in terms of diagnostic accuracy, aiming to analyze the available scientific evidence on new strategies applied to the diagnosis of retinoblastoma. By synthesizing findings from recent studies, this review seeks to identify the most effective methods for tumor evaluation and characterization at both national and international levels. Evidence from Latin America remains limited, and in countries such as Ecuador, studies are scarce or nonexistent. Hence, this review includes global literature published in English and Spanish over the past five years (2020-2025). Ultimately, this work aims to strengthen evidence-based diagnosis of retinoblastoma and contribute to improved tumor characterization through advanced imaging techniques.

Table 1. Main imaging techniques used for the diagnosis of retinoblastoma

Technique	Diagnostic utility	Limitations
Ocular Ultrasonography	Detection of intraocular mass, calcifications, and involvement of the interior segment, iris, ciliary body, and anterior chamber angle.	Operator-dependent; limited sensitivity in detecting small tumors or extraocular invasion.
Fluorescein Angiography	Evaluation of iris neovascularization, dilation of retinal vessels, intrinsic tumor vasculature, venous leakage, and microvascular abnormalities.	Requires intravenous contrast; risk of allergic reactions.
CT	Detection of intraocular calcifications; useful for tumor staging.	Risk of secondary neoplasms due to ionizing radiation; low sensitivity for detecting optic nerve invasion.
OCT	Identification of submillimetric tumors (<10µm, retinal layers, and retinal vasculature without the need for intravenous contrast.	Limited ability to differentiate active from inactive tumors; dependent on media clarity; limited field of view.
MRI	Assessment of tumor invasion of the choroid, sclera, and optic nerve; evaluation of extraocular extension and intracranial involvement.	High cost; longer acquisition time.

CT: Computed Tomography, OCT: Optical Coherence Tomography; MRI: Magnetic resonance imaging.

2. Materials and Methods

2.1 Objectives

The primary objective of this study is to analyze and evaluate the scientific evidence regarding emerging imaging strategies used for assessing tumor extent, high-risk features and tumor characterization in pediatric patients with retinoblastoma. The specific objectives are to compare conventional diagnostic techniques with current imaging modalities, assess their validity as reference standards (gold standard), and determine the circumstances in which emerging techniques may provide complementary or superior information compared to existing diagnostic methods.

2.2 Inclusion criteria

Studies evaluating imaging methods used for the diagnosis of retinoblastoma in the pediatric population aged 0-10 years and published between January 2020 and May 2025 were included if available in full text in English or Spanish.

Eligible study designs included observational, retrospective, and prospective studies, as well as clinical studies and systematic reviews with primary data. All articles included were required to describe the imaging technique used for diagnosis and/or follow-up, along with their parameters and outcomes.

2.3 Exclusion criteria

Articles were excluded if they focused exclusively on genetic or molecular aspects without clinical diagnosis application. Studies involving other ocular tumors, adult patients, animal models, or *in vitro* designs were also excluded.

Additionally, articles that addressed only treatment or prognosis without focusing on the diagnosis of retinoblastoma were not considered.

2.4 Study design

A systematic review was conducted based on literature searches in databases including PubMed, ScienceDirect, SciELO, and the free search engine Google Scholar. These sources enabled the retrieval of scientific articles, systematic reviews, and clinical studies published in English and Spanish over the past five years, applying an *open access* filter.

The search strategy included terms in both Spanish and English related to "retinoblastoma", "diagnosis", "early detection", "screening", "ultrasonography", "ultrasound", "magnetic resonance imaging", "MRI", "fundoscopy", "fluorescein angiography", "computed tomography", "CT", "optical coherence tomography," "OCT," and "optical coherence tomography angiography" (OCTA). Medical Subject Headings (MeSH, DeCS), free-text terms, and controlled vocabulary were combined using Boolean Operators (AND, OR).

Search results were exported to Mendeley Reference Manager for reference management and duplicate removal, facilitating the systematic review process and study selection. Each search was documented in a shared spreadsheet to ensure organized data collection by all team members and to maintain real-time consistency and traceability of the information.

2.4.1 Study population and sample

A total of 308 records were identified through systematic research. After removing duplicated and applying initial screening filters, 43 articles were selected for full-text review. Four independent reviewers applied the predefined eligibility criteria, resulting in the exclusion of 26 studies. At the end, 17 studies were included in this systematic review.

The included studies were subsequently categorized according to their thematic focus as follows:

- 9 studies focused on advanced magnetic resonance imaging techniques.
- 4 studies addressed the role of optical coherence tomography, fluorescein angiography, and optical coherence tomography angiography.
- 2 comparative studies of computed tomography versus magnetic resonance imaging.
- 2 studies combining ocular ultrasonography, computed tomography, and magnetic resonance imaging.

2.4.2 Data collection

A comprehensive data extraction process was conducted for the 17 studies. The following variables were collected: author and year of publication, study design, population/sample characteristics, imaging techniques, main findings, and conclusions.

Additionally, quantitative outcomes related to the diagnostic performance of each imaging modality—such as sensitivity, specificity, and diagnostic accuracy—were included. Each variable was systematically coded in a shared spreadsheet, allowing for validation and resolution by consensus among the reviewers.

The quality of the data extracted was assessed prior to the development of the results tables, following the PRISMA 2020 guidelines. The last electronic search was conducted on December 2, 2025.

2.4.3 Variables analyzed

The clinical variables used to evaluate the effectiveness of different imaging techniques across the included studies were optic nerve invasion (particularly postlaminar invasion), other high-risk histopathological features (including choroidal invasion, anterior chamber involvement, and scleral invasion), tumor activity parameters, and findings related to staging and local tumor extension.

Additionally, when available, quantitative variables related to diagnostic performance—such as sensitivity, specificity, and diagnostic accuracy—were extracted. Other parameters included apparent diffusion coefficient (ADC) values, radiomics model characteristics, and measures of association.

Finally, the overall risk of bias for each study was assessed using the QUADAS-2 tool, to interpret the results in light of their methodological quality.

2.4.4 Methods of synthesis

A structured narrative synthesis was conducted based on the previously extracted quantitative and qualitative variables. Studies were first organized according to the predominant imaging modality and, within each group, according to the primary diagnostic outcome.

For studies reporting measures of diagnostic accuracy, ranges of sensitivity, specificity, and diagnostic accuracy were described comparatively for each outcome and imaging modality. In more descriptive studies, findings were integrated by highlighting the potential clinical role of these techniques in tumor characterization, detection of recurrence, and monitoring of therapeutic response, as well as their main limitations. The overall interpretation of the evidence was conducted in light of the risk of bias assessed using QUADS-2, assigning greater weight to studies with a low overall risk of bias and considering findings from emerging techniques or higher-risk studies as exploratory evidence.

3. Results

3.1 Publication bias

The review identified a moderate risk of publication bias, primarily due to the fact that most included studies reported positive findings regarding the utility of imaging techniques, whereas reports with negative or inconclusive results were limited.

In addition, a substantial proportion of the available literature consisted of case series, retrospective studies, and reports from specialized ocular oncology centers, which may limit generalizability and favor the publication of studies involving advanced diagnostic systems.

Methodological heterogeneity across studies—particularly in the definition of the reference standard, small sample sizes, and the lack of standardized diagnostic protocols—also increases the risk of bias. Another relevant factor is the overrepresentation of studies conducted in settings with greater availability of magnetic resonance imaging (MRI), which may lead to an underestimation of techniques used in resource-limited environments.

Although a comprehensive search strategy was applied across four databases, it is possible that this review did not capture studies from the gray literature or those published in non-indexed journals. Therefore, the findings should be interpreted with caution, particularly regarding the reported magnitude of the diagnostic benefit of certain imaging modalities in retinoblastoma.

3.2 Methodological assessment of certainty

The methodological assessment of certainty was based on the technique–utility matrix presented in Table 2, which summarizes the diagnostic utility and limitations of emerging imaging techniques used in retinoblastoma, according to the synthesis of the included studies.

High-resolution magnetic resonance imaging (MRI) and its advanced sequences (including ADC mapping and radiomics models), portable optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), and microvascular flow imaging (MFI) assess different anatomical and pathophysiological components of the tumor. This variability influences the type of outcomes that each modality can evaluate with greater precision.

Table 2. Emerging imaging techniques for the diagnosis of retinoblastoma

Emerging imaging techniques	Utility	Limitations
High-resolution MRI [13,14]	Detection of postlaminar optic nerve invasion (PLONI), choroidal invasion, and extra-scleral extension	False negatives in focal choroidal invasion (<3mm). Limited detection of prelaminar optic nerve, ciliary body and scleral invasion.
MRI with ADC mapping [15]	Tumor grading, local staging, detection of recurrence, and evaluation of metastatic disease.	Susceptible to artifacts and image distortion. Limited number of studies available.
MRI with radiomics model [16]	Improved prediction of PLONI compared to conventional MRI.	Limited number of studies available.
Portable OCT [17]	Direct visualization of the retina; closer follow-up; early detection of tumor recurrence.	Difficulty in scanning peripheral lesions and evaluating advanced disease; longer anesthesia time required.
OCTA [18]	Assessment of intrinsic tumor vascularity, residual vascular changes, and vascular dilation in response to treatment; monitoring of tumor recurrence.	Limited field of view; inability to capture peripheral lesions; difficulty imaging large lesions.
Microvascular Flow Imaging (MFI) [19]	Visualization of small-caliber vessels and tumor microcirculation; evaluation of treatment response.	Lack of standardized quantitative vascular indices.

PLONI: postlaminar optic nerve invasion; ADC: apparent diffusion coefficient; MFI: microvascular flow imaging; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography.

3.3 Summary of findings

This systematic review presents the summary of the 17 included studies (Table 3).

Table 3. Summary of findings

No.	Author/ Year	Title	Objective	Results
1.	Kheir WJ et al. 2025 [20]	High-risk features in retinoblastoma: the association between histopathology and MRI	To evaluate retinoblastoma characteristics based on MRI findings.	MRI allows high-specificity identification of postlaminar optic nerve invasion (PLONI), associated with high-risk histopathological features.
2.	Onishi et al. 2024 [21]	Outcomes of five cases of retinoblastoma with optic nerve invasion on imaging	To evaluate which imaging techniques best detect optic nerve invasion in retinoblastoma.	B-scan ultrasonography is more useful for early diagnosis; MRI demonstrates greater efficacy in detecting optic nerve invasion compared to CT.
3.	Woldeyohannes A.M. et al. 2024 [22]	Retinoblastoma in Ethiopian Children: Imaging Findings and Staging	To evaluate imaging patterns and staging of retinoblastoma.	MRI is more sensitive for soft tissue evaluation and spatial resolution, whereas CT is more specific for detecting calcifications.

No.	Author/ Year	Title	Objective	Results
4.	Zhao, Jianshe et al. 2024 [23]	Multimodal imaging for the differential diagnosis and efficacy evaluation of intraocular retinoblastoma in children with selective ophthalmic artery infusion	To evaluate the clinical efficacy of imaging techniques in retinoblastoma.	MRI alone allows for a comprehensive evaluation of patients with retinoblastoma, thereby reducing radiation exposure in children by limiting the use of CT.
5.	Spadoni V.S. et al. 2024 [15]	Role of apparent diffusion map in the evaluation of retinoblastoma	To analyze the association between MRI and histopathological differentiation.	ADC values on MRI may serve as biomarkers for tumor differentiation and for predicting the risk of optic nerve invasion.
6.	M de Bloeme C.M. et al. 2024 [24]	Optic nerve thickening on high-spatial-resolution MRI predicts early-stage post laminar optic nerve invasion in retinoblastoma	To evaluate the diagnostic accuracy of optic nerve thickening on MRI.	A predictive model combining MRI features demonstrates high sensitivity and specificity for detecting postlaminar optic nerve invasion (PLONI).
7.	Ramasubramanian, Riemann et al. 2024 [19]	Microvascular flow ultrasound imaging for retinoblastoma	To present MFI findings for the characterization of tumor vasculature in retinoblastoma.	MFI enables reliable visualization of tumor microvascularization and demonstrates a more extensive vascular pattern compared to color Doppler or fluorescein angiography. However, it remains a subjective technique due to the lack of quantitative data.
8.	Chiranthan, Madhu et al. 2023 [25]	Can Enhancement Pattern in Normal-Sized Optic Nerves on Magnetic Resonance Imaging Better Predict Tumor Invasion in retinoblastoma Eyes?	To evaluate in greater detail MRI findings related to optic nerve invasion.	MRI enhancement patterns may predict optic nerve invasion on histopathology and could be useful for guiding therapeutic decision-making.
9.	Q. Dias, Margarida, et al. 2023 [17]	Optical Coherence Tomography (OCT) in retinoblastoma Management: Experience of the Portuguese National Reference Center	To review the role of OCT in retinoblastoma.	Handheld OCT allows direct visualization of the retina and can facilitate early detection of tumor recurrence, enabling earlier and less aggressive local treatment, potentially preserving vision.
10.	Deike-Hofmann. et al. 2022 [26]	Anterior chamber enhancement predicts optic nerve infiltration in retinoblastoma	To evaluate the proposed imaging biomarker for optic nerve infiltration.	Optic nerve invasion may be predicted by anterior chamber enhancement following intravenous administration of gadolinium contrast on MRI.

No.	Author/ Year	Title	Objective	Results
11.	Orman G., Huisman T.A.G. 2022 [27]	A descriptive neuroimaging study of retinoblastoma in children: magnetic resonance imaging features	To evaluate and provide a detailed description of the neuroimaging features of retinoblastoma.	MRI enables the differentiation of specific imaging characteristics between unilateral and bilateral lesions.
12.	Surukrattanaskul S. et al. 2022 [28]	Correlation between clinical presentations, radiological findings and high-risk histopathological features of primary enucleated eyes with advanced retinoblastoma at Queen Sirikit National Institute of Child Health: 5 years result	To evaluate the correlation between clinical presentation, radiological findings, and high-risk histopathological features in primarily enucleated eyes.	Radiological evaluation should include ocular ultrasonography and brain and orbital MRI. MRI is the most effective imaging modality for detecting postlaminar optic nerve invasion (PLONI).
13.	Fernández JP et al. 2021 [18]	Optical Coherence Tomography Angiography Microvascular Variations in Pre- and Posttreatment of retinoblastoma Tumors	To characterize microvascular variations using a portable optical coherence tomography angiography (OCTA) system.	Fluorescein angiography can evaluate vascular changes; however, OCTA provides a noninvasive and sensitive technique for assessing intrinsic tumor vasculature and the surrounding retinal microvasculature.
14.	Li et al. 2022 [16]	MRI-based radiomics model can improve the predictive performance of postlaminar optic nerve invasion in retinoblastoma	To develop and validate an MRI-based radiomics model for predicting optic nerve invasion in retinoblastoma.	The MRI-based radiomics model outperforms conventional visual assessment in predicting postlaminar optic nerve invasion (PLONI).
15.	Abusayf, Mohammed M et al. 2020 [13]	Histopathological assessment of optic nerve invasion guided by radiological findings in enucleated globes with retinoblastoma	To correlate optic nerve invasion detected by MRI with the level of histopathologically confirmed invasion.	MRI is an effective modality for detecting postlaminar optic nerve invasion (PLONI), with high sensitivity, specificity, and diagnostic accuracy, although its sensitivity is lower for assessing prelaminar and laminar optic nerve invasion.
16.	Nadiarnykh, Oleg et al. 2020 [29]	Optical coherence tomography (OCT) to image active and inactive retinoblastomas as well as retinomas	To provide an overview of OCT images of active and inactive retinoblastoma tumors.	OCT does not reliably distinguish between active and inactive retinoblastomas; however, it complements other imaging modalities and is useful for evaluating regression patterns and tumor follow-up.

No.	Author/ Year	Title	Objective	Results
17.	Habib Y.S. et al. 2020 [14]	High Resolution MR Imaging guidelines in retinoblastoma: prospective study correlated with histopathological results	To evaluate the diagnostic utility and MRI indices.	High-resolution MRI demonstrates strong concordance with histopathological findings, particularly for detecting postlaminar optic nerve invasion (PLONI) and choroidal involvement.

MRI: magnetic resonance imaging; CT: computed tomography; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography; MFI: microvascular flow imaging; PLONI: postlaminar optic nerve invasion.

3.4 Study selection

In accordance with the PRISMA 2020 guidelines, a systematic search was conducted across three databases—PubMed, ScienceDirect, and SciELO. Google Scholar was used as a complementary source to identify studies not indexed in the primary databases. A total of 308 records were identified.

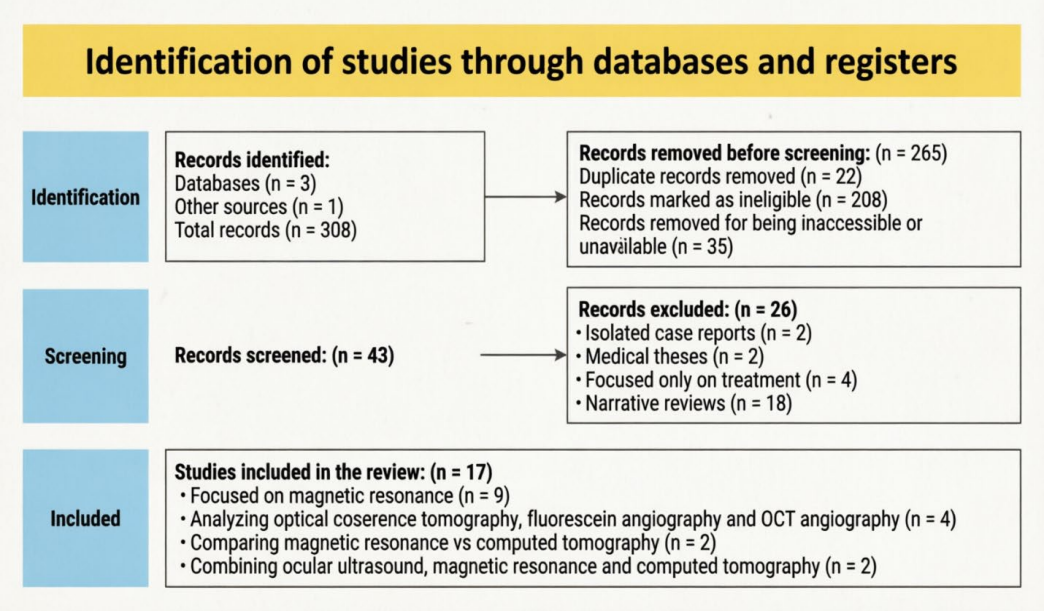
Following initial screening, 22 duplicates were removed, 208 records were excluded as ineligible, and 35 were inaccessible or unavailable. A total of 43 articles were assessed for full-text eligibility, of which 26 were excluded: 2 were isolated case reports, 2 were medical theses, 4 focused exclusively on treatment, and 18 were narrative reviews (Figure 1).

Ultimately, 17 studies were included in the systematic review. Study selection was performed independently by four reviewers using predefined criteria, with discrepancies resolved by consensus.

The included studies were categorized into four thematic groups: studies focused on magnetic resonance imaging (n = 9); studies analyzing optical coherence tomography, fluorescein angiography, and optical coherence tomography angiography (n = 4); comparative studies of magnetic resonance imaging versus computed tomography (n = 2); and studies combining ocular ultrasonography, computed tomography, and magnetic resonance imaging (n = 2).

Regarding the geographic origin of the studies, a location bias was observed, with a predominance of publications from Europe and Asia and limited or no representation from Latin America. This may limit the ability to assess variability in the reported findings.

Figure 1. Flow diagram of study identification through databases and registers



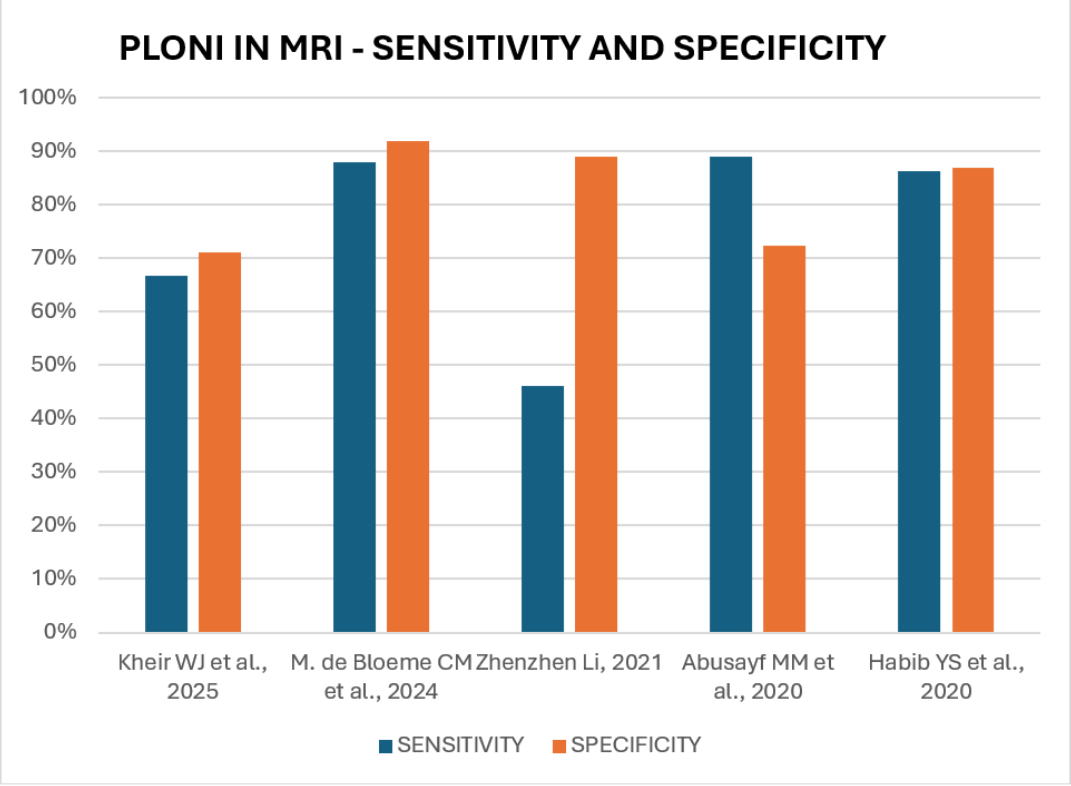
Source: Authors' own elaboration based on the PRISMA 2020 flow diagram.

3.5 Study characteristics

The main characteristics of the 17 included studies are systematically summarized in Table 3. The larger studies primarily focused on the evaluation of high-resolution magnetic resonance imaging (MRI) and its correlation with high-risk histopathological features, such as postlaminar optic nerve invasion (PLONI), massive choroidal invasion, and extraocular extension. In contrast, smaller case series were oriented toward emerging imaging techniques, including optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), and microvascular flow imaging (MFI).

MRI—either high-resolution or incorporating advanced sequences—was the predominant imaging modality and was used in most of the studies, either as the primary technique or in combination with other modalities. The comparative figure (Figure 2) presents the reported sensitivity and specificity for PLONI across the studies analyzed in retinoblastoma.

Figure 2. Sensibility and specificity for the detection of PLONI using MRI



Computed tomography (CT) and B-scan ultrasonography were primarily used in multimodal studies focused on initial diagnosis and staging. In these studies, CT and ultrasonography were either compared with MRI or used as complementary techniques.

Studies evaluating portable OCT and OCTA were conducted in smaller series, focusing on retinal characterization, assessment of tumor activity, post-treatment regression, and microvascular changes. However, in most cases, formal measures of sensitivity and specificity against a histopathological reference standard were not available. Microvascular flow imaging (MFI) was explored in a descriptive study as a tool for visualizing tumor microvasculature.

To provide a broader overview, eight studies were included in Table 4, presenting quantitative measures of diagnostic performance such as sensitivity, specificity, diagnostic accuracy, and other indicators related to optic nerve invasion and extraocular extension. Notably, the majority of these studies evaluated MRI, reflecting a greater availability of quantitative data for this modality compared to other imaging techniques.

Although heterogeneity in imaging protocols was observed, most studies employed MRI performed on 1.5 to 3.0 Tesla systems, consistently including T1- and T2-weighted sequences—typically with fat

suppression—along with intravenous contrast enhancement and, in several cases, diffusion-weighted imaging (DWI) with ADC mapping. These elements help define a minimum set of technical parameters that can be reproduced in clinical practice for the evaluation of retinoblastoma.

Table 4. Quantitative results of the study

N.	Author/Year	Study design	Sample	Techniques evaluated	Quantitative results
1.	Kheir WJ et al., 2025 [20]	Prospective Study	44 patients (48 eyes)	High-resolution MRI (3T sequences: T1-3D and T2).	**Postlaminar optic nerve invasion:** sensitivity (66.7%) and specificity (71.1%). **Massive choroidal invasion:** sensitivity (45.5%) and specificity (75.7%). **Anterior chamber invasion:** accuracy (79.2%). **Scleral invasion:** accuracy (62.5%).
2.	Zhao J et al., 2024 [23]	Retrospective Study	256 patients	CT and MRI (3.0 T sequences: T1, T2, DWI and T1 with contrast: modified Dixon). Comparative CT in a subpopulation.	**CT:** Diagnostic accuracy of 96.96%. **MRI:** Diagnostic accuracy of 84.84%.
3.	Spadoni VS et al., 2024 [15]	Retrospective Study	8 patients	MRI with diffusion maps (ADC) (1.5 T, sequences: T1 pre- and post-contrast, high-resolution T2).	**Optic nerve invasion:** Diagnostic accuracy 100%. Sensitivity 66.6% and specificity 80%. **ADC:** 0.520×10^{3} mm^2/s (poorly differentiated tumors), 0.774×10^{3} mm^2/s (well-**differentiated tumors).**
4.	M. de Bloeme CM et al., 2024 [24]	Retrospective Study	124 patients	High-resolution MRI (sequences: high-resolution 3D T2, and T1 with contrast).	**Postlaminar optic nerve invasion:** sensitivity of 88% and specificity of 92%.
5.	Surukrattanaskul S et al., 2022 [28]	Retrospective Study	33 eyes	Ultrasound, MRI (1.5 T), and CT.	**MRI: Optic nerve invasion:** Sensitivity (75%) and specificity (54%).

N.	Author/Year	Study design	Sample	Techniques evaluated	Quantitative results
6.	Li et al. 2022 [16]	Prospective Study	124 patients	MRI (1.5–3.0 T with T1, T2, and contrast-enhanced T1 sequences with fat suppression).	**Postlaminar optic nerve invasion:** **Radiomics:** sensitivity of 81.1% (training); 82.4% (validation). **Radiologists:** sensitivity of 43.2% (training) and 52.9% (validation).
7.	Abusayf MM et al., 2020 [13]	Prospective Study	38 patients	MRI (3.0 T orbital and cerebral with T1, T2 fat-suppressed sequences, T1 with contrast, DWI, and high-resolution 3D sequence).	**Postlaminar optic nerve invasion:** accuracy (63.3%), sensitivity (88.9%), specificity (72.4%). **Prelaminar optic nerve invasion:** sensitivity (0.0%). **Laminar optic nerve invasion:** sensitivity (42,9%).
8.	Habib YS et al., 2020 [14]	Prospective Study	57 patients (58 eyes)	High-resolution 3.0 T MRI with T1, T2 fat-suppressed sequences, DWI, and ADC maps.	**Choroidal invasion:** accuracy (86.2%), sensitivity (95.2%), specificity (60%). **Prelaminar optic nerve invasion:** accuracy (75.8%), sensitivity (58.8%), specificity (82.9%). **Postlaminar optic nerve invasion:** accuracy (86.2%), sensitivity (85.2%), specificity (87%).

3.6 Certainty of evidence

The overall certainty of the evidence was assessed by one reviewer, considering the risk of bias (QUADAS – 2), consistency of results, and precision of estimates. For optic nerve invasion evaluated by MRI, the certainty was classified as moderate: several prospective and retrospective studies, with histopathological correlation, show relatively consistent sensitivity and specificity values.

For other high-risk histopathological factors (massive choroidal invasion, anterior chamber involvement, scleral or extraocular extension), the certainty is low to moderate. There are few studies, with limited sample sizes and heterogeneity in outcome definitions and imaging protocols, which reduce the precision and applicability of results.

Regarding emerging techniques focused on tumor activity and treatment response (OCT, OCTA, MFI, diffusion mapping, and radiomic models), the certainty of evidence is low. These consist of small, observational series, generally lacking a histopathological gold standard or formal accuracy metrics; therefore, their findings should be considered exploratory. Evidence for CT and ultrasound is also of low certainty: although they confirm their utility for detecting calcifications and intraocular masses, most studies are descriptive and lack systematic analysis of sensitivity and specificity.

Table 5. Risk of bias as assessed by QUADAS-2

Study (author,year)	Consecutive/ Representative patients	No selection bias	Index test clearly described	Appropriate reference standard	Same standard for all	Appropriate time interval between index test & reference standard	All patients included	Overall risk of bias
Kheir et al., 2025 [20]	Low	Low	Low	Low	Low	Low	Low	Low
Onishi et al., 2024 [21]	High	High	Low	Moderate	Moderate	Low	Low	High
Abebe / Woldeyohannes et al., 2024 [22]	Low	Low	Low	Moderate	Low	Low	Low	Low
Zhao et al., 2024 [23]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Spadoni et al., 2024 [15]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
de Bloeme et al., 2024 [24]	Low	Low	Low	Low	Low	Low	Low	Low
Ramasubramanian et al., 2024 [19]	Low	Low	Low	Moderate	Low	Low	Low	Low
Chiranthan (Meel) et al., 2023 [25]	Low	Low	Low	Low	Low	Low	Low	Low
Dias et al., 2023 [17]	Low	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Deike-Hofmann et al., 2022 [26]	Low	Low	Low	Low	Low	Low	Low	Low
Orman & Huisman, 2022 [27]	Low	Moderate	Low	Low	Low	Low	Low	Low
Surukrattanaskul et al., 2022 [28]	Low	Low	Low	Low	Low	Low	Low	Low
Fernández et al., 2021 [18]	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Abusayf et al., 2020 [13]	Low	Low	Low	Low	Low	Low	Low	Low
Nadiarnykh et al., 2020 [29]	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
Habib et al., 2020 [14]	Low	Moderate	Low	Low	Low	Low	Low	Low
Li et al., 2022 [16]	Low	Moderate	Low	Low	Low	Low	Low	Low

4. Discussion

The findings of this review indicate that MRI, particularly high-resolution MRI, remains the most widely used imaging modality for evaluating tumor invasion in retinoblastoma, although its diagnostic performance varies significantly across studies. The sensitivity for detecting postlaminar optic nerve invasion (PLONI) ranges from 66% to 88%, while specificity ranges from 71% to 92%. These figures align with historical reports describing MRI as a reliable, yet not infallible, diagnostic tool. Studies incorporating high-resolution MRI, apparent diffusion coefficient (ADC) mapping, and radiomic models suggest a potential improvement in predictive accuracy for PLONI and other high-risk factors; however, these findings are based on small case series and require external validation.

Recent studies have attempted to integrate advanced sequences into MRI protocols, such as ADC maps and radiomic models. For instance, the analysis by Zhenzhen Li et al. demonstrates that the radiomic model appears to outperform conventional visual radiological assessment, suggesting significant potential for improving the early detection of PLONI [16]. Furthermore, while ADC mapping has also yielded promising results, the high-resolution MRI guidelines proposed by Habib et al. [14] emphasize the need for further studies utilizing optimized sequences to enhance image quality. This is particularly important as these techniques remain susceptible to artifacts and geometric distortions, which may compromise diagnostic accuracy.

In contrast, more traditional techniques such as CT demonstrated good diagnostic accuracy but have clear limitations in identifying optic nerve invasion. This was evidenced in the study by Onishi et al. [22], where CT failed to detect invasion in 2 out of 5 cases, with the use of ionizing radiation highlighted as an additional drawback. The same study demonstrated the initial utility of B-mode ultrasound for identifying intraocular masses (5/5) but noted its limited capacity to evaluate deeper structures or extraocular involvement. Consequently, while ultrasound remains a valuable tool for early diagnosis, it is less useful for detailed tumor characterization and long-term follow-up [21].

New techniques continue to be investigated to improve retinoblastoma staging and comprehensive evaluation. Portable OCT and OCT angiography (OCTA), according to the available literature, could offer a non-invasive and more sensitive alternative for analyzing both the tumor and its vasculature, while also facilitating the monitoring of tumor recurrence [18]. A study on MFI highlights that tumor feeding vessels are better visualized compared to fluorescein angiography (FA), which could prove useful for assessing therapeutic response [19]. These tools are promising; however, the scarcity of studies evaluating their clinical effectiveness limits the strength of the available evidence in our analysis. Overall, these emerging techniques appear particularly useful for detailed tumor characterization and monitoring treatment response, rather than replacing MRI for assessing tumor extension and high-risk factors.

The use of imaging modalities in children with retinoblastoma requires diligent bioethical consideration due to increased pediatric radiosensitivity and the cumulative risk of late effects. Guided by the ALARA (As Low As Reasonably Achievable) radiation protection principle, computed tomography should be reserved for clinically justified scenarios, such as detecting intraocular calcifications when other modalities are unavailable or yield incomplete results, evaluating orbital bone involvement, or in emergency settings with limited resources where MRI cannot be promptly performed. In routine clinical practice, non-ionizing modalities such as MRI and ocular ultrasound should be prioritized. Optimizing low-dose pediatric protocols, avoiding unnecessary examinations, and obtaining informed consent from parents or guardians are essential for ethical and responsible diagnostic practice. These considerations must also account for technological access disparities across different healthcare settings.

One of the most relevant limitations of this review is the substantial heterogeneity among the included studies with respect to design, sample size, outcome definitions, and imaging protocols. This precluded the conduct of a formal meta-analysis and necessitated a structured qualitative synthesis within the framework of a systematic review. Such heterogeneity also impacts the certainty of the evidence. For MRI, certainty was rated as moderate, with relatively consistent results but based on selected samples. Most studies originated from tertiary referral centers and relied on enucleated eyes; consequently, the evidence is more representative of advanced disease rather than early-stage retinoblastoma and may not be fully generalizable to other clinical settings.

Regarding emerging techniques, the certainty of evidence is low due to small sample sizes and the absence of a uniform histopathological gold standard. Furthermore, the pool of available studies from the past five years with open-access data was limited, potentially excluding relevant publications. This gap is particularly evident for research conducted in Latin America, underscoring the need to generate local evidence on the

diagnostic performance of these techniques across diverse healthcare contexts. Therefore, findings should be interpreted with caution and always in conjunction with comprehensive clinical assessment.

5. Conclusion

In children with retinoblastoma, high-resolution MRI is the imaging modality that offers the highest accuracy, sensitivity, and specificity for evaluating optic nerve invasion and other high-risk histopathological factors. The incorporation of advanced MRI sequences, such as diffusion mapping and radiomic models, has yielded significant findings, although these approaches remain under active investigation. Ocular ultrasound continues to be useful for the initial detection of intraocular masses and calcifications but plays a limited role in the detailed assessment of tumor extension. Meanwhile, the use of CT has declined due to concerns regarding ionizing radiation exposure.

Emerging techniques such as OCT, OCTA, and MFI show promising results for tumor characterization and follow-up and could prove valuable in assessing therapeutic response. Nevertheless, current evidence remains insufficient to formulate definitive recommendations. Prospective, multicenter studies with standardized imaging protocols are needed to confirm these findings and to more precisely define the role of each imaging modality within the diagnostic algorithm for retinoblastoma.

5.1 Limitations of the study

One of our most relevant limitations is the substantial heterogeneity among the included studies, particularly in terms of design, sample size, outcome definitions, and imaging protocols. This prevented the performance of a formal meta-analysis and required a structured qualitative synthesis within the framework of a systematic review. Such heterogeneity also affects the certainty of the evidence. Additionally, the pool of available studies from the past five years with open access to information was limited and may have excluded important research, a gap that is especially evident in Latin America. This highlights the need to generate local evidence on the performance of these techniques across different contexts. Hence, findings should be interpreted with caution and in conjunction with clinical assessment.

6. Abbreviations

RB: Retinoblastoma

MRI: Magnetic Resonance Imaging

CT: Computed Tomography

OCT: Optical Coherence Tomography

OCTA: Optical Coherence Tomography

Angiography MFI: Microvascular Flow Imaging

PLONI: Postlaminar Optic Nerve Invasion

ADC: Apparent Diffusion Coefficient

7. Administrative information

7.1 Author contributions

Sara Walsh: Conceptualization, Methodology, Investigation, Project Administration, Writing – Original Draft, Writing – Review & Editing

Ariana Veloz: Conceptualization, Methodology, Investigation, Visualization (Tables & Figures), Writing – Review & Editing

Bruno García: Conceptualization, Investigation, Software, Formal Analysis, Critical Revision of the Manuscript for Important intellectual content, Writing - Review & Editing.

Christian Chaucalá: Conceptualization, Investigation, Validation, Visualization, Methodology, Writing – Review & Editing

7.2 Conflict of interest

None.

7.3 Funding

None.

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