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LITERATURE REVIEW

Dissemination of Retinoblastoma Post-Enucleation: Histopathological Risk Factors Review

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Abstract

Introduction: Examining the histopathological markers indicative of high risk in retinoblastoma is imperative for evaluating the potential for post-enucleation recurrence and metastatic spread. **Purpose:** This article seeks to elucidate diverse definitions of high-risk histopathological features in advanced retinoblastoma, which confer susceptibility to recurrence and metastasis following enucleation. **Review:** Reducing mortality rates associated with retinoblastoma poses a significant clinical challenge. It is well-established that post-laminar optic nerve invasion, extensive choroidal invasion, and scleral invasion are key features commonly observed in advanced retinoblastoma cases requiring enucleation. **Conclusion:** The presence of these features in advanced retinoblastoma necessitates adjunctive therapeutic interventions to reduce the risk of orbital recurrence or metastatic spread, thereby enhancing patient survival rates.

Keywords: retinoblastoma; high-risk histopathological features; enucleation; tumor recurrence; metastasis

Introduction

Retinoblastoma, a perilous retinal malignancy, typically manifests in under 5-year-old children, affecting 1 in 18.000 live births. Despite its rarity, early detection is crucial to pre-empt the spread or metastasis of this treatable intraocular childhood cancer. Retinoblastoma survival rates vary globally, reaching 95% in developed countries with specialized centers, however, remaining comparatively lower in developing nations. The overarching treatment goals for retinoblastoma focus on preserving life, the globe, and vision.[1]

The neuroretina comprises small basophilic cells, known as retinoblasts, exhibiting expansive hyperchromatic nuclei and scant cytoplasm. It manifests through two distinct growth patterns: endophytic infiltration into the vitreous, disseminating tumor cells throughout the ocular structures, and exophytic growth, which involves extension into the subretinal space, often resulting in retinal detachment. Clinical presentations commonly include leukocoria, strabismus, and proptosis, with occasional resemblance to orbital pseudo-cellulitis due to the progressive nature of the disease. The presence of extraocular or systemic metastasis markedly worsens the overall prognosis.[2]

The international classification of retinoblastoma (ICRB) effectively predicts the outcome of intravenous chemotherapy for intraocular retinoblastoma. By categorizing intraocular retinoblastoma into Groups A to E, the ICRB system demonstrates high ocular salvage rates for Groups A, B, and C (above 90%). In contrast, advanced Groups D and E show rates below 50%, identifying Group E as a high-risk category requiring primary enucleation.[3] Enucleation, which entails the removal of the entire globe while preserving periorbital structures, involves cutting the optic nerve as extensively as possible. Some patients may experience extraocular recurrence or metastasis after enucleation, mainly when the central nervous system exhibits high-risk histopathological features.[4]

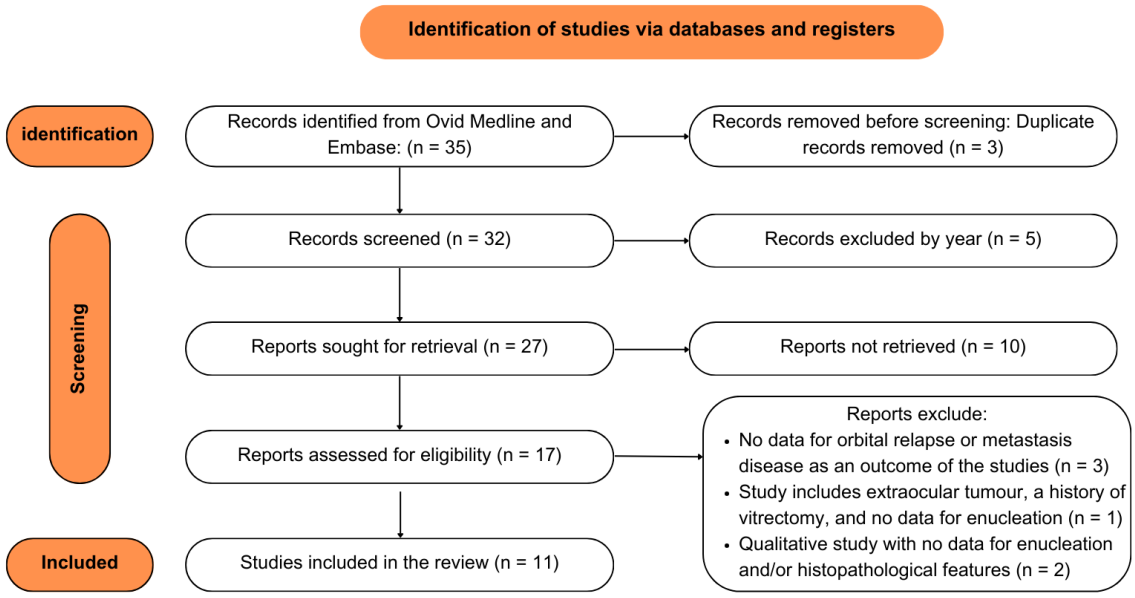

Figure 1. Scheme of systematic review process and analysis.

Pathological examination plays a vital role in surgical settings by elucidating cellular characteristics, identifying high-risk features, guiding decisions on adjuvant therapies, and predicting prognosis and recurrence risk. Regrettably, a lack of consensus among healthcare professionals regarding the definition of high-risk histopathological features in retinoblastoma results in disparate approaches to standard treatments for adjuvant therapy and subsequent outcomes.[5]

This review comprehensively examines the histopathological characteristics linked to extraocular recurrence in advanced retinoblastoma. Analyzing diverse studies over the past decade consolidates the current understanding of histopathological observations in instances of extraocular tumor recurrence. Despite not being a recent study, it highlights crucial elements in diagnosing and managing retinoblastoma.

Review and discussion

A systematic literature search used Ovid MEDLINE (1966-July 2023) and EMBASE (1947-July 2023). The search strategy employed keywords such as "retinoblastoma," "enucleation," and "orbital relapse," utilizing both accessible text terms and medical subject headings, with Boolean operators "OR" and "AND" to combine or exclude keywords as necessary. The retrieved references were imported into EndNote, and duplicate articles were eliminated. Inclusion criteria encompassed studies involving human participants with advanced retinoblastoma, written in English and published from 2014 onwards. Exclusion criteria were articles with overt extraocular disease or metastasis identified at the time of enucleation, prior history of ocular surgery or invasive procedures, and insufficient data on histopathological features, orbital relapse, or metastatic disease outcomes. Additionally, case reports were excluded due to their heterogeneous nature, limited evidence level, inability to establish causality, and inadequate data availability.

The literature examination across two databases yielded 35 articles (Figure 1). Subsequent removals included three duplicates and five publications before 2014. Based on titles and abstracts, screening narrowed the selection to 27 related studies addressing the research questions under investigation. Ten articles not aligning with the specified criteria were subsequently excluded. Upon meticulous analysis of the remaining 17 articles, five were further omitted from this review due to the absence of essential data about histopathological characteristics, orbital relapse, and metastatic occurrences.

Table 1 compiled the characteristics of patients observed across all studies on retinoblastoma. Notably, the age of presentation varied across the studies. Retinoblastoma, a rare tumor primarily affecting children under the age of five, displayed varying mean ages in this review. Patients' youngest and oldest mean ages were 18 and 37.4 months, respectively. Notably, the average age of diagnosis for retinoblastoma appeared to be higher in developing countries, such as Jordan, Argentina, India, and Pakistan.

In Table 2, all included studies identified massive choroidal invasion and post-laminar optic nerve invasion as high-risk histopathological features. Furthermore, seven studies classified invasion of the optic nerve resection margin as an additional high-risk feature.[6],[7],[8],[9],[10],[11],[12] However, three studies did not explicitly designate scleral invasion as a high-risk feature.[13],[14],[15] While scleral invasion was not explicitly mentioned in the definition of high-risk histopathological features, it was considered high-

Table 1. Demography of patients and disease characteristics.

Study (year)	Country	Number of treated patients	Gender		Mean age at diagnosis (month)	Laterality	
			M	F		Unilateral	Bilateral
Yousef (2014)	Jordan	49	27	22	30	30	19
Brennan (2015)	USA	203	104	99	20	146	57
Mendoza (2015)	USA	266	147	119	18	231	35
Laurent (2016)	Argentina	96	46	50	26	70	26
Ye (2016)	China	53	35	18	24	53	
Fabian (2017)	UK	40	22	18	23	37	3
Chevez-Barios (2019)	USA	321	169	152	24	321	
Kaliki (2020)	India	616	352	264	34	516	100
Kaliki (2022)	India	32	14	18	30	20	12
Shaheen (2022)	Pakistan	113	65	48	37.4	113	
Mohammad (2023)	Jordan	118	62	56	22.5	59	59

Black = The author excludes this group from the study population.

Table 2. High-risk histopathology features in retinoblastoma.

Study (year)	Histopathological risk stratification		Definition of high-risk histopathological features					Orbital relapse	Metastasis
	Low-risk	High-risk	Massive choroidal	PLONI	Sclera	Anterior segments	Optic nerve resection margin		
Yousef (2014)	17	33						-	-
Brennan (2015)	148	59						-	4 (6.8%)
Mendoza (2015)	190	76						-	11 (14.5%)
Laurent (2016)	N/A	84						-	4 (4.8%)
Ye (2016)	N/A	53						-	1 (1.9%)
Fabian (2017)	54	10						-	-
Chevez-Barios (2019)	216	94						3 (3.2%)	4 (4.2%)
Kaliki (2020)	379	237						1 (0.4%)	21 (8.9%)
Kaliki (2022)	9	23						-	-
Shaheen (2022)	30	83						1 (1.2%)	11 (13.2%)
Mohammad (2023)	78	43						-	7 (16.3%)

Black = The author does not categorize the histopathological features as high-risk in the study; Blue = The histopathological characteristics regarded as high-risk in the population.

risk when combined with other features. Interestingly, four of the literature studies did not consider anterior segment involvement a high-risk histopathological feature.[10],[13],[15],[16]

The studies consistently identified massive choroidal invasion and post-laminar optic nerve invasion as the predominant high-risk histopathological features observed in enucleated eyes, followed by invasion to the anterior segment and sclera. A single eye may exhibit multiple histopathological features, amplifying the risk of metastasis and disease severity. Remarkably, the combination of optic nerve resection line invasion with other features escalated the risk of central nervous system metastasis and mortality.[10] A study conducted by Yousef et al.[12] revealed that 34% of enucleated eyes exhibited no high-risk histopathological features. Among eyes with identified high-risk features, 18% displayed massive choroidal invasion, while 14% demonstrated post-laminar optic nerve invasion.[12] Invasion to the anterior chamber and ciliary body were observed in 14% and 6% of cases, respectively.[12] Interestingly, there were no instances of scleral invasion, either alone or in conjunction with invasion to the optic nerve resection margin.[12]

No metastasis and mortality were observed in patients with high-risk histopathological features who received adjuvant chemotherapy during the period time of follow-up for 40 months[12], 78.6 months[7], and 34 months[8].

In a study conducted by Brennan et al.[6], metastatic disease was identified in four patients, one of whom exhibited metastasis at multiple sites, including the liver, bone marrow, and liver, six months after primary enucleation. Similarly, metastasis was reported in a study by Mendoza et al.[14], where 11 patients experienced metastasis, primarily affecting the central nervous system, bone, or liver. Among these cases, six out of eleven patients with metastasis presented with poorly differentiated cells and high-risk histopathological features, two displayed poorly differentiated cells without high-risk histopathological features, and three exhibited moderately differentiated cells with high-risk histopathological features.[14] Mortality ensued in seven patients characterized by poorly or moderately differentiated cells and high-risk histopathological features.[14] While in Laurent et al.[10] found four patients who had metastatic cerebrospinal fluid receiving post-enucleation adjuvant chemotherapy. Despite receiving adjuvant chemotherapy, three patients with metastatic disease submitted to their condition: two patients died after primary enucleation, and one patient died after secondary enucleation.[10]

Research conducted by Ye et al.[16] found that within the group receiving three cycles of treatment, one mortality was noted from metastatic after nine months post-enucleation. Conversely, there were no instances of metastasis or mortality related to the tumor among those who received six cycles of chemotherapy. The difference between the two groups was insignificant in disease-free and overall survival rates ($p = 0.35$), which may be attributed to the limited participant size.[16] Chevez-Barios et al.[13] identified four metastasis cases: one with extensive choroidal invasion and three with invasion in the post-laminar optic nerve and significant choroidal and scleral involvement. Among these patients, three fatalities occurred due to metastasis to the central nervous system or unspecified causes.[13]

Kaliki et al.[8] reported mortality in 22 patients with high-risk retinoblastoma despite all individuals receiving adjuvant chemotherapy. Notably, one patient exhibited no high-risk histopathological features; however, mortality ensued due to non-compliance with treatment, resulting in extraocular tumor progression.[8] High-risk histopathological features contributing to mortality included post-laminar optic nerve invasion combined with optic nerve resection line involvement in ten patients, post-laminar optic nerve invasion without optic nerve resection line involvement in nine patients, and massive choroidal invasion in seventeen patients. Importantly, individual eyes may harbor multiple histopathological features, compounding the risk of metastasis and mortality.[8]

Shaheen et al.[11] reported that 12 patients experienced disease recurrence: metastatic manifestations in 11 patients (seven intracranial, three leptomeningeal, and one with pineal blastoma and spinal metastasis) and one with orbital recurrence. Notably, mortality occurred in four patients possessing high-risk histopathological characteristics attributed to sepsis. Three out of ten patients declined further treatment, while seven patients discontinued therapies prematurely. The research delineated outcomes based on histopathological risk stratification, revealing fewer relapses in the low-risk group compared to the high-risk cohort. Additionally, a higher incidence of orbital and metastatic relapses was observed in the high-risk category, with statistically significant differences ($p < 0.05$).[11]

A study by Mohammad et al.[15] discovered that seven patients exhibited metastasis in the central nervous system, lymph nodes, or bone marrow, with some patients manifesting metastasis in multiple locations. All patients with metastases died because of their illness: three from the primary enucleation group (IIRC group E) and four from the secondary enucleation group (one from IIRC group D and three from IIRC group E).[15] Notably, the study found no statistically significant correlation regarding metastasis between primary and secondary enucleation ($p = 0.44$)[15], and no instances of orbital recurrence were observed.

In developing countries, the diagnosis of retinoblastoma often occurs at advanced stages, leading to a higher prevalence of extraocular dissemination and subsequently reduced survival rates compared to developed countries.[17] In this study, most participants underwent primary enucleation and indicative of advanced-stage retinoblastomas which is categorized within ICRB Groups D and E. Based on the globe salvage rate, Zhao et al.[18] described it as 90% in Groups A-C but diminishes to 47% for Group D. Notably, 53% of Group D eyes and all Group E eyes can manifest more than one high-risk histopathological features, indicating that the primary enucleation is the most suitable therapeutic approach.[18],[21]

High-risk histopathological features in retinoblastoma are associated with the advanced stage of the disease. All authors in this review considered the most common high-risk histopathological features as massive choroidal and post-laminar optic nerve invasion, invasion to the sclera, anterior chamber, and optic nerve resection margin. Kaliki et al.[8] reported in their study that there was a discrepancy between experts worldwide regarding the understanding of high-risk histopathological features. The study's primary findings reported that the

most acceptable features to define high-risk cases in retinoblastoma were invasion to the post-laminar optic nerve, optic nerve transection, scleral tissue, and massive choroidal.[5],[22]

The extent of optic nerve invasion represents a pivotal determinant in the prognosis of retinoblastoma. Specifically, post-laminar optic nerve invasion, whether with or without involvement of the optic nerve resection margin, is designated as high-risk due to its association with an increased propensity for metastasis to the central nervous system. This assertion is substantiated by a study conducted by Shields et al.[19], which demonstrated a statistically significant correlation between the incidence of metastases and the presence of invasion to the post-laminar or resection line of the optic nerve in patients with retinoblastoma.[19] Furthermore, Chevez-Barrios et al.[20] conducted an animal study to investigate invasion and metastasis patterns, revealing that brain metastasis could ensue from direct extension along the optic nerve. Tumor cells can infiltrate the optic nerve and disseminate into the circulating subarachnoid fluid, facilitating secondary metastasis, even in cases where tumor cells remain undetected at the optic nerve resection line. Moreover, tumor cells may traverse the circulation of subarachnoid fluid to reach the spinal cord, distant cerebral locales, and the contralateral optic nerve.[20]

Massive choroidal invasion is defined as tumor invasion to more than 50% of the thickness of choroid layers with a diameter > 3 mm.[13],[23] Retinoblastoma with massive choroidal invasion has a metastasis pattern that occurs through hematogenous dissemination, potentially spreading to distant organs such as lungs, bones, brains, and others. Some studies considered that the hematogenous spreading of tumors from choroidal invasion presents a lower risk of mortality compared to direct invasion of the central nervous system.[6],[24]

Not all research papers in this study identified scleral invasion as a high-risk factor in retinoblastoma. Mendoza et al.[14] describe it as high-risk only if the tumor co-existed and extended from the choroid. If the tumor moves from the choroid to the sclera, it can reach the brain through specific spaces or directly from the optic nerve.[13] The manifestation of scleral invasion often involves optic nerve and choroidal invasion, indicating a more advanced disease stage. Although scleral invasions are perceived as high-risk, they often signify residual disease following initial treatment, requiring a more aggressive treatment.[5],[25] An area around an optic nerve is rich in vessels and penetrates the sclera to nourish the choroid and optic nerve. We assumed that tumor spreading to the central nervous system could occur from direct invasion through the optic nerve to the meninges or spread from the choroid. Nevertheless, we contend that both transmission pathways substantially contribute to metastasis and mortality compared to other features.

Seven studies considered an invasion of the anterior segment a high-risk feature (70%). Based on our understanding, several academic publications do not provide a detailed explanation of anterior segment invasion as an independent factor for high-risk histopathological features in retinoblastoma. Recent advances in retinoblastoma treatment have led to decreased enucleation rates, with more advanced diseases being successfully treated with eye-conserving techniques. Therefore, clinicians are now observing the invasion of anterior segments of the eyes with helpful vision, a previously rare condition.[5],[26] A higher incidence of advanced intraocular disease at diagnosis was associated with massive choroidal invasion and post-laminar optic nerve invasion in eyes with primary enucleation. Meanwhile, ciliary body and scleral invasion were the most common features found in secondary enucleation.[6] High-risk histopathological features are significantly associated with a prolonged enucleation time.

This review offers insights into histopathological factors and orbital relapse in advanced retinoblastoma. However, it has limitations due to a lack of long-term data and detailed outcome evaluations in the studies examined. Most studies focus on specific histopathological findings without tracking changes over time, making it hard to determine their impact on disease recurrence. Moreover, the lack of comprehensive outcome measures, such as survival rates and treatment responses, diminishes its practical utility in informing treatment decisions for advanced retinoblastoma. Future research should incorporate longitudinal data and comprehensive outcome assessments to rectify these deficiencies. This approach is crucial for elucidating the disease's trajectory and refining treatment modalities to enhance patient outcomes.

Conclusion

This review provides an overview of histopathological features associated with extraocular recurrence in advanced retinoblastoma. The dissemination of retinoblastoma after enucleation is influenced by various high-risk histopathological features, including invasion of the massive choroid, post-laminar optic nerve, and scleral. These features contribute to the advanced stage of the disease and challenges for effective management. Understanding these high-risk features is crucial for treatment decisions and improving patient outcomes, though further research is needed to address gaps in long-term data and comprehensive outcome evaluations.

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