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Review Article

Periocular basal cell carcinoma: A comprehensive narrative review on pathogenesis, diagnosis, and management

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Abstract

Basal cell carcinoma (BCC) is the most common malignancy affecting the eyelid and periocular region, comprising over 80% of all eyelid tumors. While BCC rarely metastasizes, its potential for local invasion into critical ocular structures can result in significant morbidity, including vision loss, disfigurement, and functional impairment. Given the anatomical complexity of the periocular area, early diagnosis and precise intervention are essential.

This narrative review aims to provide a comprehensive and ophthalmology-specific overview of periocular BCC, encompassing its epidemiology, pathogenesis, histopathology, diagnostic strategies, and management options. The review also highlights current challenges and proposes future directions in improving care for this increasingly common malignancy.

A literature search was conducted using PubMed, Scopus, and Google Scholar for English-language articles published between January 2010 and April 2024. Keywords included "basal cell carcinoma," "eyelid tumor," "periocular BCC," "Mohs surgery," "Hedgehog pathway," and "vismodegib." Approximately 80 peer-reviewed articles were included based on clinical and scientific relevance.

Nodular BCC is the most prevalent histological subtype in the periocular region, followed by infiltrative and morpheaform types, which have higher recurrence risks. Diagnosis is often delayed due to resemblance to benign lesions. Mohs micrographic surgery offers >99% cure rates for high-risk cases. For advanced or unresectable cases, systemic therapies such as Hedgehog pathway inhibitors and immunotherapy provide emerging treatment options.

Periocular BCC exemplifies a low-mortality but high-morbidity malignancy where early detection, multidisciplinary collaboration, and subtype-specific management can significantly impact visual outcomes and quality of life. Future efforts should focus on diagnostic innovation, outcome measurement, and global awareness.

Keywords: Basal cell carcinoma, Hedgehog signaling, Mohs surgery, vismodegib, dermoscopy, miRNA, quality of life

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1. Introduction

Basal cell carcinoma (BCC) is the most prevalent cutaneous malignancy worldwide, accounting for 80–90% of non-melanoma skin cancers (NMSC). Though it exhibits minimal metastatic potential, BCC can be locally aggressive, particularly in cosmetically and functionally sensitive regions such as the periocular area. In this context, it constitutes the most common eyelid malignancy, representing over 85% of all eyelid tumors.[1-5]

The periocular region, including the lower eyelid and medial canthus, is especially vulnerable to ultraviolet (UV) radiation due to its anatomic exposure. UVB-induced DNA damage, particularly to tumor suppressor genes such as TP53 and PTCH1, contributes significantly to BCC pathogenesis. Additional risk factors include fair skin phenotype, increasing age, chronic sun exposure, prior radiation, immunosuppression, and genetic conditions such as Gorlin syndrome. In darker-skinned populations, the incidence is lower, but late presentation and underdiagnosis are more common.[6,7]

BCC subtypes such as nodular, infiltrative, and morpheaform are frequently encountered in the periocular region and differ significantly in their biological behavior and

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risk of recurrence. Morpheaform and infiltrative subtypes are particularly challenging due to their indistinct clinical margins and deep tissue invasion, often necessitating advanced surgical techniques.[1,8]

Despite its clinical significance, BCC is frequently underreported in cancer registries due to its low mortality. This limits accurate global estimation of disease burden, especially for ocular variants. Moreover, early lesions often mimic benign conditions such as chalazion, blepharitis, or seborrheic keratosis, delaying diagnosis and increasing the likelihood of extensive surgery.[9]

Given the functional, aesthetic, and reconstructive complexity of periocular BCC management, a multidisciplinary approach involving ophthalmology, dermatology, oncology, and reconstructive surgery is often required. Early recognition and appropriate histopathologic evaluation are critical for optimal outcomes.[10]

This narrative review aims to comprehensively explore the epidemiology, etiopathogenesis, clinical presentation, histological subtypes, diagnostic modalities, and management strategies of BCC of the eye, with particular focus on the periocular region. Emphasis is placed on early detection, histopathological correlation, margin-controlled surgical techniques, and recent advances in systemic therapies. In doing so, this review highlights current challenges and future directions in delivering equitable and effective care for periocular BCC.

2. Methodology

This narrative review was conducted to synthesize current knowledge on periocular basal cell carcinoma (BCC), focusing on its pathogenesis, clinical presentation, diagnostic strategies, and treatment options. The literature search was performed using three electronic databases: PubMed, Scopus, and Google Scholar for articles published between January 2010 and April 2024.

Search terms and Medical Subject Headings (MeSH) included combinations of: "basal cell carcinoma," "eyelid tumor," "periocular BCC," "ocular adnexal neoplasm," "Mohs surgery," "Hedgehog signaling pathway," "non-melanoma skin cancer," "vismodegib," and "immunotherapy for BCC." Boolean operators (AND/OR) were used to optimize results.

After removing duplicates, studies were screened by title and abstract, followed by full-text assessment to ensure relevance and quality. Studies were selected based on clinical applicability, scientific merit, and alignment with the review's scope.

2.1. Inclusion criteria

1. Articles published in English
2. Peer-reviewed original research, clinical trials, reviews, meta-analyses, and consensus guidelines
3. Studies focusing specifically on BCC involving the eyelid, periocular skin, orbit, or ocular adnexa

2.2. Exclusion criteria

1. Case reports involving fewer than 10 patients
2. Editorials, commentaries, conference abstracts, and non-peer-reviewed sources
3. Articles lacking relevance to the clinical or histopathological features of ocular BCC

Approximately 80 articles were selected based on relevance, recency, and quality. Titles and abstracts were first screened, followed by full-text review to ensure eligibility. In addition, a snowballing approach was employed to identify relevant references from the bibliographies of key articles.

Due to the narrative nature of this review, no formal evidence grading or risk-of-bias assessment (e.g., PRISMA or GRADE) was performed. While every effort was made to include a broad and representative sample of the literature, the potential for selection bias is acknowledged.

2.3. Histopathology of periocular basal cell carcinoma

Basal cell carcinoma (BCC) of the eye typically arises from the basal layer of the epidermis or from adnexal appendages such as hair follicles and sebaceous units. It demonstrates distinct histopathological patterns that correlate with clinical behavior and recurrence risk.[1,11]

The most common subtype in the periocular region is nodular BCC, accounting for approximately 60–70% of cases. It is characterized by nests and lobules of basaloid cells with peripheral palisading and retraction artifact within the surrounding stroma. These tumors often exhibit a well-demarcated growth pattern, making them more amenable to complete surgical excision.[1,12]

Aggressive subtypes such as infiltrative, micronodular, and morpheaform (sclerosing) BCCs are associated with deeper tissue invasion, poorly defined borders, and a higher recurrence rate. In these subtypes, tumor strands and islands infiltrate between collagen bundles in the dermis, often eluding complete removal during standard excision. The morpheaform subtype appears histologically as thin cords of basaloid cells surrounded by dense fibrous stroma, contributing to its insidious spread and diagnostic difficulty.[1,13]

Superficial BCC, while more common on the trunk, may occasionally present near the brow or lateral canthus and is typified by basaloid cell nests attached to the undersurface of the epidermis in a horizontal growth pattern. Pigmented BCC, seen more frequently in individuals with darker skin tones, contains melanin-laden basaloid cells and

melanophages and may be clinically confused with melanoma.[1,14]

Histologic grading based on subtype is a critical factor in determining prognosis and guiding the extent of surgical margins. Rare cases may exhibit perineural invasion or vascular involvement, which are considered high-risk features necessitating aggressive management.

Immunohistochemical markers such as Ber-EP4, Bcl-2, and PHLDA-1 assist in differentiating BCC from morphologically similar adnexal tumors or squamous cell carcinoma. These markers are particularly useful in assessing deep margins during Mohs surgery or when frozen sections are inconclusive.[15,16]

The clinical relevance of each histologic subtype is summarized in **Table 1**, and their relative frequency in periocular presentations is visualized in **Figure 1**.

This histopathological classification not only aids in diagnosis but also directs treatment planning, particularly with regard to surgical margins, follow-up, and recurrence risk.

2.4. Diagnostic approach to periocular basal cell carcinoma

Early and accurate diagnosis of periocular BCC is crucial to prevent vision-threatening complications and preserve ocular function. The disease often presents as a slowly enlarging, non-healing lesion near the eyelid margin or canthus. Classic features include a pearly appearance, telangiectasia, rolled edges, central ulceration, and loss of eyelashes (madarosis). However, clinical diagnosis can be challenging, particularly in the early stages.

A significant diagnostic pitfall is the resemblance of BCC to benign conditions such as chalazion, blepharitis, seborrheic keratosis, or even skin tags. This similarity often leads to delays in specialist referral and appropriate biopsy, allowing for further local spread of the tumor. This underscores the importance of high clinical suspicion, especially in lesions near the medial canthus where deeper invasion and orbital extension are more common.[10,17]

Dermoscopy serves as a valuable non-invasive diagnostic adjunct. Key dermoscopic features of periocular BCC include:

1. Arborizing vessels
2. Blue-gray ovoid nests
3. Ulceration or crusting
4. Shiny white areas and leaf-like structures

Histopathological confirmation via biopsy remains the gold standard. The type of biopsy depends on tumor size and location:

1. Punch biopsy is adequate for small, well-demarcated lesions.
2. Incisional or shave biopsy is preferred for larger or ill-defined lesions, especially in the medial canthus.
3. In cases where functional structures may be at risk, initial diagnostic incisional biopsy is often prudent to avoid overtreatment.

When deep invasion or orbital extension is suspected—especially in recurrent or medial canthal tumors—imaging is warranted:

1. High-resolution CT scan is useful for assessing bony involvement.
2. MRI provides superior soft tissue detail for orbital invasion.
3. Optical coherence tomography (OCT) or ultrasound biomicroscopy (UBM) may assist in evaluating superficial extent and guiding excision margins in selected cases.

Intraoperative frozen section control or Mohs micrographic surgery (MMS) offers precise margin assessment and is particularly valuable in functionally critical areas around the eye where tissue preservation is vital.

The diagnostic process is summarized in **Chart 1**, which outlines a practical stepwise approach to periocular BCC evaluation.

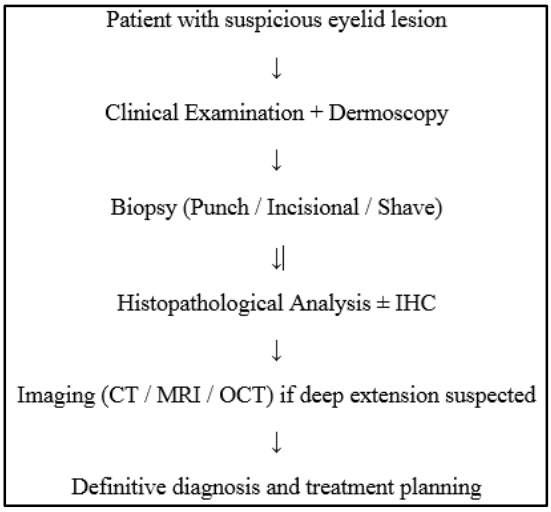

Chart 1: Diagnostic workflow for periocular basal cell carcinoma

This stepwise approach enables timely diagnosis, accurate tumor subtyping, and optimal treatment strategy selection, which is essential in preserving ocular and adnexal function while minimizing morbidity.

2.5. Management of periocular basal cell carcinoma

The primary goal in managing periocular BCC is complete tumor eradication while preserving eyelid function, cosmesis,

and ocular protection. Treatment strategies vary based on tumor subtype, location, recurrence risk, and patient-specific factors such as age and comorbidities.[3,10]

Mohs micrographic surgery is the treatment of choice for high-risk, recurrent, and medial canthus tumors due to its superior tissue preservation and margin control. Cure rates and recurrence risks of various treatment modalities are compared in Table 2, and visually represented in **Figure 2**.

2.5.1. Mohs micrographic surgery

Mohs surgery remains the gold standard for high-risk periocular BCCs, especially those involving the medial canthus, recurrent lesions, and aggressive histologic subtypes such as infiltrative and morpheaform BCC. It offers the highest cure rates (>99%) and the advantage of intraoperative margin control with maximal tissue conservation.[18,19]

2.5.2. Standard surgical excision[20]

Standard excision with predefined clinical margins is commonly used where Mohs is unavailable. Recommended margins are:

1. 3–4 mm for low-risk, well-defined lesions
2. 5–6 mm for high-risk or ill-defined lesions

Reconstruction following excision depends on defect size and location and may involve techniques such as:

1. Hughes tarsoconjunctival flap
2. Cutler-Beard flap
3. Mustardé cheek rotation flap

Close histopathologic margin assessment is necessary to reduce recurrence.

2.5.3. Non-surgical management[21,22]

Non-surgical treatments are reserved for select low-risk or non-surgical candidates, though their use in periocular BCC is limited due to risk of ocular irritation and inadequate tissue penetration.

1. Topical therapies: Imiquimod or 5-fluorouracil (5-FU) may be used in superficial BCC but are rarely appropriate periocularly.
2. Photodynamic therapy (PDT): Suitable for superficial lesions on the trunk or face but less effective near the eyes.
3. Radiation therapy: Useful in elderly patients or those unfit for surgery, though it carries long-term risks such as telangiectasia, skin atrophy, and eyelash loss.

2.5.4. Systemic therapy[23,24]

For advanced, recurrent, or inoperable BCC, especially those extending into the orbit or medial structures, targeted molecular therapy is indicated:

1. Hedgehog pathway inhibitors (HHIs)
   a. Vismodegib and Sonidegib are FDA-approved for advanced BCC.
   b. Target SMO in the Hedgehog signaling pathway.
   c. Side effects include dysgeusia, alopecia, fatigue, and cramps.
   d. Resistance may occur due to SMO mutations or downstream pathway activation.
2. Immunotherapy
   a. Cemiplimab, an anti-PD-1 antibody, is approved for HHI-resistant or metastatic BCC.
   b. Its role in periocular BCC is emerging and under investigation.

2.5.5. Follow-up and recurrence

Due to high recurrence risk, especially in the medial canthus and aggressive histologies, long-term follow-up is essential.

Recommended follow-up schedule:

1. Every 3–4 months for the first year
2. Biannually for the next 2–3 years
3. Annually thereafter in low-risk patients

An individualized approach based on histological subtype, lesion location, and patient comorbidities is essential for optimal outcomes. Multidisciplinary management involving oculoplastic surgeons, dermatologists, and oncologists is often required in complex or advanced cases.

Table 1: Histological subtypes of periocular BCC: Clinical behavior and recurrence risk

Subtype	Estimated Frequency	Growth Pattern	Aggressiveness	Recurrence Risk
Nodular	60–70%	Well-demarcated nests	Low	Low
Infiltrative	10–15%	Strands infiltrating stroma	High	Moderate to High
Morpheaform	5–10%	Thin cords in dense stroma	High	High
Micronodular	<5%	Small deep tumor islands	High	High
Superficial	<5% (periocular)	Horizontal, epidermal nests	Low	Moderate
Pigmented	Variable (by race)	Pigmented basaloid nests	Variable	Variable

Table 2: Treatment modalities for periocular bcc: indications, efficacy, and limitations

Treatment Modality	Indications	Cure Rate	Recurrence Risk	Key Notes
Mohs Surgery	High-risk, medial canthus, recurrent, infiltrative	>99%	<5%	Preferred for tissue preservation and margin control
Standard Excision	Low to moderate-risk lesions	~90–95%	10–15%	Requires predefined margins; reconstruction needed
Radiation Therapy	Inoperable or elderly patients	85–90%	Up to 15%	Cosmetic drawbacks; risk of lash loss
Topical Therapy	Superficial BCC (non-periocular)	70–85%	Moderate	Not suitable for periocular region
Hedgehog Inhibitors	Advanced/inoperable BCC	Variable (50–60% response)	Moderate to high	Used in HHI-eligible patients
Cemiplimab	HHI-resistant/metastatic BCC	Emerging data	Not well defined	Reserved for refractory cases

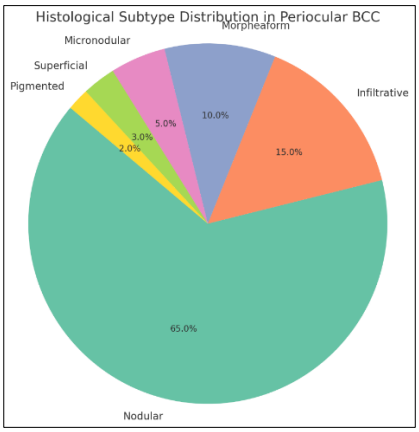

Figure 1: Pie chart showing the distribution of histopathological subtypes of periocular BCC based on estimated literature data.

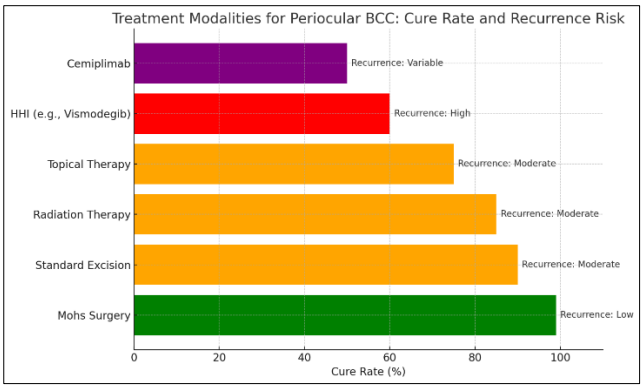

Figure 2: Cure rates and recurrence risks for periocular bcc treatments (Horizontal bar chart comparing treatment efficacy: Mohs >99%, Excision ~90%, etc. Recurrence risk color-coded.)

3. Discussion

Periocular basal cell carcinoma (BCC) represents a unique clinical entity within cutaneous oncology due to the anatomical complexity, aesthetic sensitivity, and vital functional roles of the periorbital region. While BCC is rarely life-threatening, its local aggressiveness can result in significant ocular morbidity, functional disruption, and disfigurement, particularly if diagnosis or treatment is delayed. The current review consolidates a broad spectrum of data concerning epidemiology, diagnosis, histopathology, and management strategies for periocular BCC, offering critical insights for clinicians across dermatology, ophthalmology, and oncology.[1,10]

Nodular BCC remains the predominant histological subtype in the periocular region, as consistently shown in population-based studies. However, the rising prevalence of more aggressive subtypes—such as morpheaform and infiltrative BCC—poses a greater risk of recurrence and necessitates more extensive surgical intervention.[1,14] As shown in Table 1 and Figure 1, subtype plays a pivotal role in guiding treatment decisions and prognostication.

A major clinical challenge continues to be the misidentification of early BCC as benign conditions such as chalazion or blepharitis, particularly in primary care settings. This leads to diagnostic delays and larger tumor sizes at presentation. Incorporating dermoscopy and prompt biopsy, as outlined in Flowchart 1, can significantly enhance early detection. Furthermore, a higher index of suspicion should be maintained for lesions in the medial canthus, where deep tissue infiltration and orbital extension are more likely.[1,25]

Management of periocular BCC requires a balance between oncological control and preservation of eyelid function and appearance. Mohs micrographic surgery is favored due to its superior margin control and high cure rates, especially for recurrent, ill-defined, or high-risk subtypes (**Figure 2**). However, access to Mohs-trained surgeons remains a limitation in many regions, leading to increased reliance on standard excision techniques or, in some cases, radiation therapy—particularly in elderly or inoperable patients.[10,18]

Systemic therapies, including Hedgehog pathway inhibitors (HHIs) such as vismodegib and sonidegib, have

expanded options for patients with advanced, metastatic, or unresectable BCC. Despite their efficacy, side effects and the emergence of resistance limit long-term use. Cemiplimab, an anti-PD-1 immune checkpoint inhibitor, offers a promising alternative for HHI-resistant cases, although further real-world data are needed.[23]

Another underexplored domain is patient-reported outcomes. Few studies have investigated the psychological, functional, and cosmetic impact of treatment for periocular BCC.[19-21] The lack of standardized tools for evaluating long-term quality of life post-reconstruction is a significant gap in the literature.

Additionally, disparities in access to specialized care contribute to varied outcomes globally. In rural or underserved regions, limited dermatologic and oculoplastic expertise often delays diagnosis and restricts treatment options. Innovations such as AI-assisted dermoscopic screening and teleophthalmology may help address this inequity.

Ultimately, this review reinforces the necessity of a multidisciplinary approach to periocular BCC. Collaboration among dermatologists, oculoplastic surgeons, oncologists, and pathologists is essential to achieving optimal outcomes. Clinicians must remain vigilant in early detection, subtype-based risk stratification, and tailored treatment planning, especially in cosmetically and functionally sensitive zones.

Future studies should aim to validate prognostic biomarkers, standardize follow-up protocols, and incorporate patient-centered outcome metrics to guide evolving management paradigms for periocular BCC.

4. Limitations

This review is narrative in design and lacks systematic data synthesis or meta-analysis. Selection bias may be present due to the non-quantitative inclusion of articles. Only English-language studies were reviewed, which may limit generalizability. Additionally, the lack of patient-reported outcome measures in the literature limits assessment of psychosocial burden and long-term functional impact, particularly after periocular reconstruction.

5. Future Directions

Future research on periocular BCC should prioritize:

1. Development and validation of AI-based teledermatology tools for early screening, especially in rural or underserved populations.
2. Large-scale, prospective studies evaluating functional and cosmetic outcomes post-reconstruction.
3. Exploration of patient-centered surgical outcome measures to assess the holistic impact of treatment.
4. Identification of molecular biomarkers predictive of recurrence or resistance to systemic therapies.
5. Expanded global cancer registries to better reflect the true epidemiological burden of ocular BCC.

Innovations in imaging, personalized therapies, and health equity will shape the next generation of care for patients with periocular BCC.

6. Conclusion

Basal cell carcinoma (BCC) of the eye, particularly in the periocular region, represents the most common malignant tumor of the eyelid and poses unique clinical challenges. Although metastasis is rare, the potential for local invasion, recurrence, and cosmetic and functional disfigurement makes early diagnosis and individualized management essential. Mohs micrographic surgery remains the preferred treatment modality for high-risk cases, offering tissue preservation and low recurrence.

BCC of the eye exemplifies a malignancy where early detection and precise intervention can significantly impact vision preservation, aesthetics, and quality of life. A multidisciplinary and patient-centered approach, combining surgical precision with reconstructive planning and long-term surveillance, is key to optimizing clinical outcomes. As incidence continues to rise, greater emphasis must be placed on public awareness, clinician education, and research into advanced therapeutic strategies.

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9. Conflict of Interest

There are no conflicts of interest

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