Peer Review File

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Reviewer A: This is a comprehensive review on the current treatment modalities for periocular basal cell carcinoma (BCC). The authors summarized not only the traditional and standard therapies, but also the recent progress of pathogenesis, diagnosis, therapeutics, and precautions. The manuscript was well written. I have only one minor comment:

Comment 1: Can the authors add a section describing the current staging of BCC, for example the 8th TNM classification?

Reply 1: I am so grateful to the reviewer for the positive and valuable comments! We fully agree that the current staging of BCC should be listed due to its important role in the clinical practice. Therefore, we added a section entitled TNM clinically staging BCC of eyelid skin, marked in red as follows.

- Clinical TNM staging of eyelid BCC

Accurate staging of a skin cancer is fundamental for optimal patient management. Cancer stage, termed tumor-node-metastasis (TNM) stage or stage group, takes account of tumor characteristics (T, by physical examination), regional spread to lymph node(s) (N, by physical examination), and metastasis of distant organs (M, by physical examination and imaging). The regional lymph nodes involve the preauricular, submandibular, and cervical lymph nodes. The latest 8th edition TNM classification system of malignant tumors (TNM8) was published in 2017 by the Union for International Cancer Control, which formed the foundation for handling and reporting skin cancer cases (34).

The latest 8th edition TNM classification system of non-melanoma eyelid skin cancers (NMSC, typically including the basal cell, squamous cell, and sebaceous carcinoma) are displayed in Table 1. As for T (primary tumor), T0 indicates no evidence of primary tumor, and Tis carcinoma in situ. T1-T3 categories are stratified at ≤ 20 mm, > 20 to 40 mm and > 40 mm in maximum tumor dimensions, respectively. Subdivisions of a and b are defined as with or without tarsal plate or eyelid margin invasion, and c is deemed the involvement of full thickness of eyelid. Furthermore, T4 is defined by the invasion of adjacent ocular, orbital, or facial structures. If the eyelid BCC invades ocular or intraorbital structures, the subdivision of T4a is defined. T4b is deemed by the presence of bony walls of orbit erosion, paranasal sinuses extension, or lacrimal sac/nasolacrimal duct or brain invasion.

With regard to N (regional lymph nodes), Nx indicates unevaluable regional lymph nodes, N0 no evidence of lymph node involvement, N1 metastasis in a single ipsilateral regional node with a greatest dimension of 3 cm or less, and N2 metastasis in a single ipsilateral regional node with a greatest dimension of more than 3 cm or in bilateral or contralateral lymph nodes. For M (distant metastasis), M0 is defined by no distant metastasis, and M1 distant metastasis.

The above mentioned TNM system has been applied to describe and record the anatomical extent of tumor. Stage and prognostic groups are adopted to ensure, as far as possible, the homogeneity of each group with regard of survival and the distinction of these groups in respect of the survival rates by condensing these TNM categories into groups (Table 2). In general, carcinoma in situ is designated as stage 0; location at the eyelid as stages I and II; extension to regional lymph nodes as stage III; and distant metastasis as stage IV.

In addition, the prognostic factors for survival for eyelid NMSC are divided in to essential, additional, and new and promising categories according to the ninth edition of the UICC Manual of Clinical Oncology (35). In essential factors, worse prognosis is indicated by the presence of orbit or sinus invasion, immunosuppression of host, preauricular and/or cervical lymph node involvement, or systemic metastasis at presentation. In additional factors, eyelid BCC and SCC have a better prognosis than sebaceous tumors, and the nodular BCC has a better prognosis than morpheaform ones. With regard to new and promising factors, improvements in local control relate to less systemic recurrence.
(Pages 14 - 17, lines 203 – 248, in TNM clinically staging BCC of eyelid skin section)

- Table legends

Table 1 The latest 8th edition TNM classification system of non-melanoma eyelid skin cancers
Table 2 The latest 8th edition stage and prognostic groups of non-melanoma eyelid skin cancers
(Page 64, lines 971 – 976, in Table legends section)

- Table 1 The latest 8th edition TNM classification system of non-melanoma eyelid skin cancers

Categories	Subdivisions	Maximum Tumor/ Lymph Node Dimensions	Notes

T (Primary Tumor)	T1	≤ 20 mm	T1-T3a/b: with/without tarsal plate or eyelid margin invasion; T1-T3c: involvement of full thickness of eyelid T4a: ocular or intraorbital structures invasion; T4b: bony walls of orbit erosion, paranasal sinuses extension, or lacrimal sac/nasolacrimal duct or brain invasion
	T2	> 20 to 40 mm	
	T3	> 40 mm	
	T4	Any size, but adjacent ocular, orbital, or facial structures invasion	
N (Regional lymph nodes)	Nx	Unevaluable regional lymph nodes	The preauricular, submandibular, and cervical lymph nodes
	N0	No evidence of lymph node involvemen	
	N1	A single ipsilateral regional node ≤ 3 cm	
	N2	A single ipsilateral regional node > 3 cm or in bilateral or contralateral lymph nodes	
M (Distance metastasis)	M0	No distant metastasis	/
	M1	Distant metastasis	/

Adapted from JD. B, MK. G, CH. W. Union for International Cancer Control. TNM Classification of Malignant Tumours Eighth Edition: Oxford: Wiley Blackwell; 2017.

- Table 2 The latest 8th edition stage and prognostic groups of non-melanoma eyelid skin cancers

Stages	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2a	N0	M0
IIA	T2b, T2c, T3	N0	M0
IIB	T4	N0	M0
IIIA	Any T	N1	M0
IIIB	Any T	N2	M0
IV	Any T	Any N	M1

Adapted from JD. B, MK. G, CH. W. Union for International Cancer Control. TNM Classification of Malignant Tumours Eighth Edition: Oxford: Wiley Blackwell; 2017.
(in the Tables document)

Reviewer B: In this paper, Authors reviewed recent research progress of pathogenesis, diagnosis, therapeutics and precaution of periocular BCCs. There are a few points to note below.

Comment 1: The description "Basal cell carcinoma (BCC) is by far the most common human cancer" is not appropriate. We can only say it most common in skin cancer.

Reply 1: Thank you so much for your kind correction. I fully agree with you that it is

too arbitrary to claim that “Basal cell carcinoma (BCC) is by far the most common human cancer”, therefore, we have changed this sentence, marked in red as follows.

- Basal cell carcinoma (BCC) is by far the most common human skin cancer. (Page 3, line 31, in Abstract section)
- Basal cell carcinoma (BCC) is by far the most common human skin cancer. (Page 5, line 56, in Introduction section)

Comment 2: In the classification of pathogenesis, author should add "Epigenetic changes".

Reply 2: Thank you very much for your careful review and professional comments. We fully agree and have added “Epigenetic changes” section in the main text, marked in red as follows.

- Epigenetic changes

Heritable genomic modifications in eukaryotic cells may be produced without alterations in the genomic DNA sequence, which is known as epigenetics. Epigenetic alterations are mainly comprised of CpG Island Methylation (CIM), histone methylation and acetylation, and gene regulations mediated by miRNAs. DNA methylation is one of the most essential mechanisms for regulating gene expression (18). Heitzer et al. presented the PTCH promoter to be hypermethylated in a few cases and proposed that this methylation might only play a minor part in BCC carcinogenesis (23), while Goldberg et al. found the hypomethylated FHIT promoter (24). Darr et al. investigated metastatic BCCs in comparison to the non-metastatic ones and found hypomethylation at MYCL2(25). Furthermore, among of the extensive modifications of histone N-terminal tail regions, methylation and acetylation are the most well-studied ones. EZH2, a histone methyltransferase, was found upregulated in aggressive BCCs, while H3K27me3 and 5hmC were indicated to be upregulated in more benign phenotypes (26). The upregulated levels of different genes might be applied to discriminate BCCs from benign skin diseases. In addition, mature miRNAs may target specific mRNAs and degrade them or inhibit their translation into proteins. A number of potential miRNA markers for BCCs have been investigated in numerous studies. Various upregulated miRNAs were identified, e.g., Hsa-miR-223-3p and Hsa-miR-197-3p, among others (27). miR-203 is specifically expressed in the epidermis and create an inhibitory loop of miR-203 c-JUN (18, 28). It was found downregulated in BCC cases, and its therapeutic potential for BCCs has been demonstrated (29).

(Pages 10 - 11, lines 136 – 158, in Epigenetic changes section)

Comment 3: Authors have not described diagnosis and precaution of BCC

individually. These two parts have been described partly during the treatment part. Since this paper mainly focused on treatment, authors may not emphasize these two parts in abstract and introduction, unless describe these two parts individually.

Reply 3: We are so grateful for your professional comments. We fully agree with you that the emphasis of this review is mainly on treatment, therefore, we have changed the sentences in abstract and introduction sections, marked in red as follows.

- In this paper, we review recent research progress of pathogenesis, clinical presentation, and therapeutics of periocular BCCs.
  (Page 3, lines 41 – 43, in Abstract section)
- Therefore, we review recent research progress of pathogenesis, clinical presentation, and therapeutics of periocular BCCs.
  (Page 6, lines 77 – 78, in Introduction section)