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REVIEW

Basal cell carcinoma cytology revisited – a modern perspective on an old technique

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ABSTRACT
Basal cell carcinoma is the most frequently occurring cancer in humans. In light of its vast prevalence, this disease causes a substantial burden on the quality of life of patients. Histopathologic examination is currently the gold standard for diagnostic confirmation and a requisite for therapeutic planning. Cytology possesses several advantages compared to biopsy. This is namely due to its minimal invasiveness, absence of scarring, improved aesthetic outcome, cost-effectiveness, and procedural simplicity. This review focused on contemporary evidence on basal cell carcinoma cytology to provide a comprehensive description of the technique with practical insights for specific clinical scenarios. This review also aimed to delineate and discuss evidence gaps and potential novel applications of this technique in the context of recent advances in cytopathology, dermatosurgery, molecular targeted therapy, and precision medicine *(Tab. 2, Ref. 43)*. Text in PDF *www.elis.sk*
KEY WORDS: basal cell carcinoma, cytology, Papanicolaou test, May-Grunwald Giemsa.

Introduction

Basal cell carcinoma (BCC) is the most frequently occurring cancer in humans (1). While very rarely metastasizing, this slow-growing, locally invasive malignancy has significant consequences for quality of life in terms of functional and esthetic morbidity. The etiology of BCC is believed to be directly associated with the integrated effects of genetic predisposition, exposure to ultraviolet radiation, and additional risk factors (e.g., immunosuppression). The diagnosis of BCC is in most cases established clinically, although the accuracy of clinical examination can be improved with dermoscopy. If a high-risk subtype of BCC is clinically suspected, a biopsy is indicated to guide the subsequent therapeutic decision-making process (2).

Initially introduced by Arnault Tzanck in 1947, dermatological cytology was used for the diagnosis of blistering disorders (3). Although currently considered archaic, BCC cytodiagnosis can still be recommended for initial rapid assessment and confirmation of a clinically diagnosed case of BCC. Subtype classification of high-risk BCC is requisite for therapeutic planning; however, standard cytomorphological criteria used in clinical practice do not provide additional prognostic value. As a consequence, histopathological confirmation is mandatory (4). Based on the available evidence, conventional cytology can be considered a reliable noninvasive method for the diagnostic confirmation of BCC, but due to the above-mentioned limitations, it remains largely unnoticed by the diagnostic recommendations. In this review, the authors aim to provide an up-to-date, comprehensive description of the technique with practical insights for specific clinical scenarios. The authors also aim to discuss the emerging concepts and recent advances that are expected to broaden the future applications of this method in the field of neoplastic dermatology. This review narratively synthesizes evidence gaps where no research has been conducted to date.

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Description of the technique

To our knowledge, the most commonly described sample collection technique is scrape cytology. With this technique, the tissue is obtained by scraping the tumor or scratching a part of the lesion off, both performed with a scalpel blade (5, 6). Imprint smear cytology is a useful alternative for easily exfoliating ulcerated lesions. The sample is collected by placing the glass slide against the ulcerated part of the lesion. Imprint smears can also be used in the intraoperative assessment of margin control. This is performed by taking an imprint from the cut surface of the biopsy specimen. Compared to scraping, the imprint samples possess less pronounced cellularity. The advantage of this technique is a lower degree of erythrocyte contamination (6). When performing imprint cytology (with the exception of its intraoperative modification), the lesions must be selected based on the presence of ulceration. A single study conducted by Fernández-Guarino et al directly evaluated the comparative efficiency of these techniques. The authors reported higher accuracy of scraping and scratching compared to imprinting, with a slight superiority of the scratch technique ($p < 0.05$), although the description of the lesion selection process was not included in the methods section (6).

Limited reports describe the use of fine-needle aspiration cytology (FNAC) in palpable lesions (7, 8). In this technique, a

Tab. 1. Cytomorphological features of the main differential diagnoses.

Lesion type	Described cytomorphological features	Sources
BCC	In the uniform small basaloid cells of pigmented BCC, the cells contain pigment granules Clusters of cells are highly cohesive The marginal palisading of nuclei on the periphery of clusters Uniform, small, oval, hyperchromatic nucleus Evenly dispersed, finely dotted chromatin High nuclear-cytoplasmic ratio	(15, 16)
Well-differentiated squamous cell carcinoma	Cells with abundant smooth cytoplasm filled with keratin Dyscohesive cells	(6)
Poorly differentiated squamous cell carcinoma	Large clusters of elongated cells Large nuclei with coarse chromatin texture and prominent nucleoli	
Basaloid squamous cell carcinoma	Cohesive fragments as well as single, small, round to spindle-shaped cells with scant cytoplasm Hyperchromatic nuclei with fine granular chromatin and inconspicuous nucleoli Nuclear moulding single keratinized cells	(17)
Actinic keratosis	Atypical squamous cells with ragged edges Single cells with keratinization Loosely cohesive cell groups Cytological features may be analogous to those of squamous cell carcinoma	(6)
Seborrheic keratosis	Exfoliated superficial large polygonal squamous cells Small, round, basaloid cells Horn cysts	(6)
Paget disease	Round-to-ovoid Paget cells, isolated or in clusters Vacuolated cytoplasms Eccentric nuclei, dense chromatin, and inconspicuous nucleoli High nuclear-cytoplasmic ratio	(18, 19)
Pilomatrixoma	Clusters of basaloid cells Eccentric, round-to-oval vesicular nuclei Calcium deposits Mild to moderate amounts of ill-defined cytoplasm "naked nuclei" "Ghost cells" with pale, eosinophilic cytoplasm Multinucleated giant cells Inflammatory background	(20, 21, 22, 23)
Cutaneous Merkel cell carcinoma	Discrete, small, round, dyscohesive basaloid cells Monomorphic, large, round-to-oval nuclei with small, inconspicuous nucleoli Fine chromatin and deep blue scanty cytoplasm (MGG) Cytokeratin 20 and chromogranin positivity (Immunocytochemistry)	(24)
Trichoepithelioma	Branching, tightly cohesive thick cell groups of basaloid cells Moderate cellularity, rounded fragments Individual cells are larger and have more cytoplasm than that of BCC	(25)

Source: adapted by the authors according to various sources of literature (6, 15–25).

24-gauge needle can be used with subsequent withdrawal of the needle alone, without suction (9). The use of negative pressure aspiration with a puncture gun and a 21-gauge needle was also described (10). Due to the possible presence of necrosis in the center of a nodular lesion, a peripheral needle insertion point is preferred (11). Owing to low tissue yield, the FNAC technique is not suitable for the superficial variant of basal cell carcinoma (10).

Regardless of the collection method used, the obtained sample is then spread on the slide in a thin layer and fixed with alcohol-based fixatives for the Papanicolaou stain (PAP) or air-dried for May–Grünwald–Giemsa (MGG). A careful approach enables the visualization of undamaged cell clusters (5, 6). PAP and MGG are currently the best described staining methods recommended by the British Society of Cytopathology (12). MGG offers an advantage in its simplicity. The high intensity of background staining that veils the cellular details is a downside of this method. PAP produces polychromatic differential staining, enhancing the contrast between the nucleus, cytoplasm, and background. Due to its propensity to stain keratin orange to pink, depending on the degree of keratinization, it enables an accurate differentiation between keratinizing and non-keratinizing cells (13, 14). A study performed by Christensen et al discovered no significant differences in sensitivity and specificity between the two staining methods, although limited evidence demonstrates the inferiority of PAP compared to MGG (6, 15).

Standard cytomorphological criteria for the diagnosis of BCC include the presence of highly cohesive clusters of uniform small basaloid cells with very little cytoplasm. A small, oval, hyperchromatic nucleus with evenly dispersed, finely dotted chromatin and a high nuclear-cytoplasmic ratio is characteristic. Sometimes one to two distinct nucleoli are present. A marginal palisading of nuclei on the periphery of clusters is typically present. The above-described cytomorphology of BCC was reported across several studies (5, 15, 16). The cytomorphological analysis provides a distinct per-

Tab. 2. Characteristic cytomorphological features of superficial and non-superficial BCC.

Superficial BCC	Sensitivity	Non-Superficial BCC	Sensitivity
Moderate cellularity of basal cells	55.17%	High cellularity of basal cells	74.55%
Groups of basal cells with distribution as large clusters, medium clusters, and small clusters	100% (33.8%, 34.3%, and 31.9%, respectively)	Groups of basal cells with distribution as large clusters, small clusters, and medium clusters	98.18% (46.81%, 30.45%, and 22.69% respectively)
The presence of basal cell sheets	62.07%	The presence of basal cell sheets	60.00%
Mild grade of basal cell atypia	86.21%	Basal cells with a moderate to severe grade of atypia	52.73%, and 10.91%
Presence of dehiscence	11,33 %	Presence of dehiscence	34.55%
Moderate grade of squamous cellularity	41.38%	Low grade of squamous cellularity, absence of squamous cells	32.73% and 25,5%
High proportion of isolated cells	82.76%	High proportion of isolated cells	65.45%
Presence of palisade cells and clear sebaceous cells	68.97% and 44.83%, respectively	Presence of palisade cells	56.36%
Absence of mucin	93.10%	Absence of mucin and absence of clear cells	74.55% and 98.18%, respectively
More than 10 groups of stromal fragments	37.93%	Less than 5 groups of stromal fragments	38,18 %

Source: data from "Use of Cytology in the Diagnosis of Basal Cell Carcinoma Subtypes", by Pasquali, P. et al., 2020, J Clin Med, 9, p. 612 (5).

spective on the differential diagnosis of BCC. Owing to their macromorphological and dermoscopic similarities, the main differential diagnoses belong mostly to the spectrum of keratinocyte cutaneous neoplasms, with some exceptions (e.g., pilomatrixoma, cutaneous Merkel cell carcinoma, trichoepithelioma) (Tab. 1). The differentiation of malignant versus benign basal cells is exceedingly difficult, and therefore it is important to keep in mind that basaloid cells rarely appear in cytological samples under physiological conditions (6). When present, they are strong indications for BCC and other very rare, mostly adnexal skin tumors (15–25).

When applying standard cytomorphological criteria, pooled data from the latest meta-analysis demonstrated 97.5 % sensitivity and 90.1 % specificity of this technique (5). The diagnostic performance of BCC cytology is currently also limited by its low yield in therapeutic decision-making. The establishment of a treatment plan is determined by the pathologic features of biopsy specimens that can aid the differentiation between low- and high-risk BCC (17). A study by Pasquali et al aimed to identify cytomorphological features characteristic of superficial and non-superficial BCC. The main findings of this study are described in Table 2. Further studies are needed to establish the role of cytology in BCC subtype classification (5).

The role of cytology in monitoring treatment response in BCC

With the advent of nonsurgical treatment modalities for BCC, the ability to monitor the treatment response with noninvasive skin imaging techniques has become very desirable. Clearance rates for nonsurgical modalities are known to be inferior to those of excisional surgery for BCCs (17). Consequently, monitoring treatment response is necessary. Dermoscopy, reflectance confocal microscopy (RCM), and optical coherence tomography (OCT) are currently used for this purpose. Recent meta-analysis suggests that RCM is the most sensitive method for detecting persistent disease after nonsurgical treatment. On the other hand, OCT offers the best specificity. The availability of both of these techniques is, in most cases, limited to highly specialized academic centers. Dermoscopy, although cost-effective and readily available, is associated with a certain proportion of false-negative lesions (26). Cytology demonstrates high sensitivity and specificity for BCC differentiation. Thus, its addition to clinical and dermoscopic monitoring could improve the diagnostic accuracy of nonsurgical treatment response monitoring.

In terms of post-excisional monitoring, most guidelines recommend follow-up every 6 to 12 months, even though the formation of scar tissue renders the detection of recurrent BCC difficult on the clinical, dermoscopic, as well as histopathological levels (27). A lack of consensus prevails regarding the management of incompletely excised BCCs. The clinician must decide whether a re-excision or a "wait and see" approach with diligent follow-up is appropriate. We hypothesize that cytology follow-up examination of high-risk and incompletely excised BCCs could potentially increase the rate of early detection of recurring lesions due to its ability to analyze individual malignant cells rather than more complex morphological features, which can be altered by the formation of scar tissue. To the best of our knowledge, no study has been conducted to investigate the role of cytology follow-up in the management of BCC, and therefore, this could be an interesting new area of research to explore.

Imprint cytology and dermatosurgery

The role of intraoperative margin evaluation techniques in reducing the risk of recurrence of BCC is well established. The gold-standard procedure for high-risk non-melanoma skin cancers is Mohs micrographic surgery (MMS) (28, 29). Compared to traditional surgical excision, MMS is more effective in terms of quality-adjusted life years and recurrence rates (30). Although undeniably effective, this technique is not widely available due to the high technical requirements as well as the need for specialized medical personnel. Limited evidence shows a potential role for intraoperative imprint cytology in achieving margin control (29, 31, 32). Imprint smears require a short processing time, providing the surgeon with information to guide on-table decisions. If proven effective, this technique may represent a technically undemanding and cost-effective alternative for resource-limited settings where MMS may not be readily available.

BCC and immunocytochemistry

A potential diagnostic pitfall of cytology that can, in rare instances, lead to serious consequences is the failure to correctly diagnose basaloid squamous cell carcinoma (bSCC) or cutaneous Merkel cell carcinoma (MCC), although these entities are exceedingly rare compared to BCC (33). Both bSCC and MCC are BCC mimics at the clinical, dermoscopic, as well as cytomorphological levels (34, 35). Limited evidence shows a potential future role for immunocytochemistry in distinguishing these highly aggressive neoplasms from other tumors with basaloid cytomorphology. The candidate stains are derived mostly from previous immunohistochemical studies. For MCC, anti-cytokeratin 20 and chromogranin positivity are characteristic. In the case of bSCC, the use of anti-AE1/AE3 cytokeratin antibodies provides the most consistent results (24, 36). With the currently used cytomorphological criteria, we are not able to estimate the risk profile of BCC, which is essential for therapeutic decision-making. This is an important limitation because the main objective of performing a cytological examination is to avoid the need for surgical intervention. A study by Shamsi Meymandi et al, evaluating the role of immunohistochemistry in differentiation between high- and low-risk BCC, demonstrated an association between P53 positivity and high-risk BCC types (micronodular, morpheaform, infiltrative, and basosquamous types) (37). Based on these preliminary results, we hypothesize that not only immunohistochemistry but also immunocytochemistry with markers such as P53 may potentially play a future role in the prognostic evaluation of BCC.

Liquid-based cytology and genetic testing

Liquid-based cytology (LBC) represents an important advancement in the field of cytodiagnostics. Primarily used for cervical cytology, LBC also demonstrated its efficiency in the analysis of non-gynecological samples. The technique of LBC provides some key advantages compared to standard specimens. Uniform cell distribution across the slide surface with less cell overlap and reduced blood contamination ensures improved visualization of individual cells. The unique characteristics of LBC samples may have some important implications for overcoming one of the main limitations of standard cytology, namely the inability to classify subtypes of BCC. The diagnostic performance of cytology in detecting the discriminative features of superficial and non-superficial BCC (e.g., grade of cellular atypia) could potentially be increased with the use of LBC (5). Additionally, LBC enables multiple specimen preparation. Multiple samples can then be used for immunohistochemical and genetic examinations (38). The use of LBC in BCC cytodiagnosis is an interesting research gap. To date, no published research on this topic is available.

In recent years, recognition of the main mechanisms involved in the molecular pathophysiology of BCC has enabled rapid advancements in the field of targeted therapy. Sonidegib and vismodegib are hedgehog pathway inhibitors (HhIs), currently indicated for metastatic, locally advanced, or recurrent BCC, as well as Gorlin syndrome and non-Gorlin syndrome related multiple basal cell carcinomas. Despite proven efficiency, mutations in the target molecule SMO render more than 50 % of tumors resistant to HhIs, and more than 20 % of initial responders develop resistance as a result of acquired SMO mutations (39). Pre-treatment genetic testing is also recommended to exclude tumors caused by mutations downstream of the drug's target SMO (e.g., the germline SUFU mutation). This approach enables the identification of patients who might not benefit from HhIs due to resistance (40). Cytopathology offers excellent benefits in regard to personalized targeted treatment with its minimally invasive nature, high diagnostic value, formalin-free samples, and high DNA yield for molecular testing (41). It also offers considerable benefits in the sampling of small or multiple lesions and/or lesions unsuitable for surgical procedures. In other cancers, cytology material proved to be equivalent to histopathology samples in determining mutations by various molecular genetic methods, including next-generation sequencing (42, 43). Despite multiple advantages, the use of cytology in molecular genetic analysis of BCC lesions was not described in the scientific literature.

Conclusion

Based on the current evidence, conventional cytology can be recommended as a rapid and reliable noninvasive method for the diagnostic confirmation of clinically suspected BCC. Although present-day cytology cannot replace histologic examination, innovative research is being conducted with the aim of breaching the current limitations of the technique. Recent technological advances have opened a broad range of potential novel applications of cytology in the management of BCC. The focus of future research should not only be centered around the role of cytology as an alternative to histopathology but also around the potential innovative applications of this technique for solving emerging challenges in BCC management.

Learning points

- Conventional cytology can be recommended as a rapid and reliable noninvasive method for the diagnostic confirmation of clinically suspected BCC.
- Present-day cytology cannot replace histologic examination.
- Recent technological advances have opened a broad range of potential novel applications of cytology in the management of BCC.
- Understanding the evidence gaps in BCC cytodiagnosis can direct future research.

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