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REFLECTANCE CONFOCAL MICROSCOPY AND OPTICAL COHERENCE TOMOGRAPHY AS ADDITIONAL NON-INVASIVE TOOLS IN BASAL CELL CARCINOMA DIAGNOSIS

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ABSTRACT

Aims: Basal Cell Carcinoma (BCC) is the most common malignant tumor worldwide with a significantly growing incidence rate over the past years, and a variety of new, innovative diagnostic methods have been introduced to its diagnosis process in recent decades. In this research, we would like to focus on reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) with particular emphasis on their role in BCC diagnosis. Our goal is to introduce and describe these imaging techniques and evaluate their diagnostic accuracy.

Methods: The literature review was conducted using the PubMed database. Publications from 2004–2025 were searched combining following phrases: „basal cell carcinoma”, „BCC”, „diagnosis”, „optical coherence tomography”, „OCT”, „reflectance confocal microscopy”, „RCM”, „diagnostic methods”, „BCC characteristics”, „BCC features”. The literature review included various types of publications such as narrative and systematic reviews, randomized controlled trials (RCTs), cohort studies, meta-analyses, and expert consensus papers.

Results: RCM demonstrates excellent diagnostic performance in BCC detection, with sensitivity and specificity reaching up to 100%, and enables non-invasive visualization of critical histological features. Its imaging depth is limited to approximately 250–300 μm . OCT provides deeper imaging (up to 2 mm), with a sensitivity of 92.4% and a specificity of 86.9%, and may contribute to distinguishing BCC subtypes.

Conclusions: OCT allows for deeper tissue penetration, however, RCM provides superior image resolution compared to OCT. Like RCM, the reliability of OCT interpretation depends heavily on clinician experience, and there is currently no official training curriculum. However, artificial intelligence models are being introduced to assist in image analysis and reduce inter-observer variability. Despite the growing use of non-invasive techniques in BCC diagnosis, skin biopsy with histopathological analysis remains the definitive diagnostic gold standard.

Keywords: BCC, Basal Cell Carcinoma, Diagnosis, Optical Coherence Tomography, Reflectance Confocal Microscopy, Non-melanoma Skin Cancers

INTRODUCTION

EPIDEMIOLOGY

Non-melanoma skin cancers (NMSCs) are the most common malignant tumors in the world [1]. NMSCs occur in around 2 million people worldwide each year and their incidence has been significantly growing over the years [2]. According to the Polish National Cancer Registry, the NMSC incidence rate in Poland also increased considerably during the last couple of years. In 2011, there were 11,439 new confirmed cases and in 2022, that number grew to 15,716 cases. It is estimated that this trend will persist in the future [3][4]. Basal cell carcinoma (BCC) is the most frequently diagnosed NMSC and represents 75-80% of all NMSC cases [2]. The Risk of developing BCC in a lifetime is approximately 30% [5]. BCC appears most often in fair-skinned people over the age of 50 with a predominance for the male sex [6].

ETIOLOGY AND RISK FACTORS

The main but also modifiable risk factor for BCC is ultraviolet (UV) exposure, especially sunburns in childhood, occupational sun exposure, or usage of sunbeds [7][8]. UVB radiation plays a much bigger role in developing BCC than UVA radiation. UVB directly damages DNA and RNA, causing characteristic transition mutation, while UVA induces photooxidative stress [9][10]. BCC may develop more frequently at a much younger age in patients with genetic predisposition syndromes like xeroderma pigmentosum, basal cell naevus syndrome known as Gorlin syndrome, Bazex syndrome, and albinism [11][10][12]. Apart from inherited syndromes mentioned above, several tumor suppressor genes and proto-oncogenes are associated with BCC pathogenesis. Most commonly observed in sporadic BCC is excessive activation of the Hedgehog (HH) signalling pathway by inactivation of PTCH1 receptor in 90% of cases, or by activation of SMO receptor in 10% of cases. The tumor protein 53 (TP53) gene and members of the RAS proto-oncogene family also contribute to BCC development [2][13][14][15][16]. Other risk factors are a family history of skin cancer, Fitzpatrick skin types I and II, a light eye color, blonde or red hair, and freckles. Immunosuppression, both in patients after organ transplantation or HIV-positive patients, photosensitizing medication such as tetracyclines, hydrochlorothiazide or statins, ionizing radiation, and exposure to arsenic or polycyclic aromatic hydrocarbons may lead to the development of BCC [6][13][15][17]. BCC may also appear in scars, ulcers, non-healing fistulae, burns, and lesions of chronic inflammation [5][15].

CLINICAL PRESENTATION

There are many subtypes of BCC, some of the most recognised include: nodular (the most common), superficial, morphea-like (sclerosing), fibroepithelial, infiltrative, and micronodular [18][10][19]. Different subtypes may occur simultaneously within the same neoplasm [10][19]. The vast majority of lesions are amelanotic, but some of them can contain various amounts of melanin [9][18]. BCC location and presentation vary depending on subtype. Nodular BCC can be found mainly on the face and neck, particularly nose, cheeks, forehead, and eyelids, while superficial BCC usually appears on shoulders, back, and chest [18][14][10]. Usually, the reason for patients' concerns and seeking medical attention is a growing, non-healing lesion that may bleed recurrently [9]. The most common presentation of BCC is shiny, pink/pinkish cream colored, scaly papule/nodule with telangiectasia. Often it shows a central recess [14][18].

BCC is characterised by a low mortality rate, however, it can cause significant destruction of surrounding tissues, which can lead to an insufficient cosmetic effect [20][6][10]. The main challenge of BCC treatment are recurrences of lesions. Long-term risk of reappearance is approximately 46% over a 10-year period, therefore identifying determinants of tumor recurrence is important [10]. The risk factors of recurrence are: older age, multiple BCC lesions, localisation on the H area of the face, aggressive histological characteristics, larger size of the tumor (>2cm), and prior recurrence of BCC [10][21].

TREATMENT

The choice of BCC treatment method is multidimensional and depends on age, tumor type, location, size, recurrence, comorbidity, and the patient's preference [10][18]. The most effective method is surgical removal of the lesion, which carries the lowest risk of recurrence. It is also considered a standard, first-line therapy for BCC. In case of high-risk tumors, micrographically controlled surgery shall be performed [11][21]. Superficial, low-risk lesions can be treated by photodynamic therapy, topical therapies with 5-fluorouracil or 5% Imiquimod, and destructive approaches as electrodesiccation and curettage (EDC) or cryosurgery [11][21][18]. Radiotherapy is an alternative if surgery is contraindicated, especially among elderly patients [21][18]. Another, more recent therapy includes Hedgehog Inhibitors (HHIs) (vismodegib and sonidegib) that are dedicated for patients with advanced or metastatic BCC that cannot be treated with standard therapy [18][21][11].

DIAGNOSIS

The first step in diagnosing BCC is clinical examination, which is usually followed by a dermoscopy evaluation of suspicious lesions. The gold standard for making a final diagnosis is a skin biopsy with histopathological analysis, which identifies the exact subtype of BCC and is crucial for choosing an optimal treatment plan [22][10]. Although dermoscopy has enhanced the accuracy of skin cancers identification and reduced the number of benign tumors

being excised, incorrect diagnosis still occurs [23]. Furthermore, while managing patients with multiple suspicious lesions, skin biopsy may not be the best option. Fortunately, in the past decades, many novel non-invasive imaging methods improving BCC diagnosis have been developed. These additional diagnostic tools include reflectance confocal microscopy (RCM), optical coherence tomography (OCT), high-frequency ultrasound (HFUS), Raman spectroscopy, fluorescence polarization, and some others [22][24].

Although these new techniques are becoming more and more popular and provide additional details for the diagnostic process of skin cancers, they are still poorly understood and not used in daily practice. In this research, we would like to focus on reflectance confocal microscopy and optical coherence tomography with particular emphasis on their role in BCC diagnosis. Our goal is to introduce and describe these imaging techniques and evaluate their diagnostic accuracy.

METHODS

The literature review was conducted using the PubMed database. Publications from 2004–2025 were searched combining the following phrases: „basal cell carcinoma“, „BCC“, „diagnosis“, „optical coherence tomography“, „OCT“, „reflectance confocal microscopy“, „RCM“, „diagnostic methods“, „BCC characteristics“, „BCC features“. The literature review included various types of publications such as narrative and systematic reviews, randomized controlled trials (RCTs), cohort studies, meta-analyses, and expert consensus papers.

CONTENT OF THE REVIEW

REFLECTANCE CONFOCAL MICROSCOPY

One of the new diagnostic tools that can improve the detection of BCC lesions is reflectance confocal microscopy (RCM). RCM is an innovative, non-invasive imaging technique that provides real-time in vivo evaluation of different skin layers with almost histological resolution in horizontal, grayscale, and optical sections without the need to perform a biopsy [25][26][27].

The mechanism of RCM includes a single point illumination by using a near-infrared laser source with a specific wavelength. Then the light passes through the skin to illuminate a point inside the tissue and is reflected back from the selected focal point to enter the detector through a special pinhole, which finally generates 2D horizontal images of scanned tissue. Due to significant differences in reflectivity of the examined tissue, contrast in RCM images may be observed, and structures with a higher reflective index occur as white areas [24][7]. RCM image depth is however limited to superficial dermis, up to 250-300 μm , and therefore evaluation of tumor depth margins and invasion is not always possible [28][26][7].

The RCM features for diagnosing skin tumors are relatively easy to learn, and the results may be repeatable, which allows other clinicians to achieve similar results [29]. Unfortunately, the BCC confocal criteria used in various studies differed significantly. The most frequently listed RCM criteria that enforce diagnosis of BCC are tumor islands, peri-tumorals clefting, polarization of nuclei, and increased vascularization with enlarged and thickened blood vessels/with thickened walls. Other RCM findings in BCC include dark silhouettes, dendritic structures, peri-tumoral collagen bundles, epidermal streaming, ulceration or erosion, inflammatory infiltrate, keratinocyte atypia, peripheral palisading, cauliflower architecture and many more [24][30][31][23][32][33][34][35][36][37][38][28][7]. This method can also be used to repeatedly monitor BCC progression and to provide surveillance of the recurrence of BCC [28][39]. RCM seems to be promising also in subtyping BCC [40][34]. When it comes to differentiation of BCC subtypes via RCM, nodular BCC has an additional enhanced vascular density, big tumor islands and peritumoral collagen bundles, whereas aggressive BCC subtypes are characterized by hyporeflective areas, and superficial BCC is diagnosed by features such as epithelial chords attached to the epidermis [7][38]. Furthermore, due to the high reflective index of keratin and even higher for melanin and melanosomes, RCM has proven its efficacy in differentiating nonmelanocytic skin tumors from malignant melanocytic neoplasms, for example, pigmented BCC from primary melanoma [41][6][24][42]. Because of the RCM capabilities mentioned above, this innovative technique has the potential to expedite the process of making treatment decisions by decreasing the amount of time spent waiting for biopsy results and also reduce the number of unnecessary biopsies on benign lesions that seemed suspicious earlier. [26].

The sensitivity and specificity of this diagnostic method vary significantly according to different studies. As stated by meta-analyses from 2019, sensitivity and specificity of RCM for the diagnosis of BCC stand at 92% and 93%, with sensitivity ranging between 73% and 100%, and specificity ranging between 38% and 100% [43]. Combining dermoscopy with RCM may enhance the diagnostic efficacy of BCC. Sensitivity and specificity of these methods used together showed higher rates compared with dermoscopy or RCM alone [44][45].

Moreover, RCM may be a helpful tool during therapeutic procedures made on BCC lesions and result in a higher efficacy of these procedures, thereby reducing the number of additional medical interventions and overall cost associated with them. Preoperative assessment of the tumor margins may optimize surgical treatment, enabling better functional and aesthetic outcomes [46][25][47][48]. In a randomized controlled trial conducted by Kaduch et al. (2017), 100% of patients diagnosed with BCC via RCM had tumor-free margins compared to 94% of patients

diagnosed by a punch biopsy. In this study, 95 patients were randomized to the RCM "one-stop-shop", which consisted of BCC diagnosis and subtyping via RCM with subsequent direct surgical excision or to standard care, which consisted of BCC histopathological analysis and subtyping made by a punch biopsy and followed by planned excision. Providing an RCM "one-stop shop" strategy improved tumor-free margins in BCC management [49]. A prospective study made by Navarrete-Dechent et al. (2019) showed that use of RCM immediately after initial laser ablation of lesions can detect subclinical persistent tumors, prompting additional laser passes. Nine patients with a sum of 22 lesions were treated with laser ablation with the addition of RCM imaging on first pass post-ablation sites. In five cases, residual tumor was identified and once more treated with laser. The follow-up period lasted from 22 to 32 months and no recurrences were found [50]. RCM can also be used to guide Mohs micrographic surgery by improving the precision of BCC margin assessment [51][47].

Limitations of RCM include limited depth penetration, small field of view, greyscale images, interpretation dependent on the operator's experience, lack of standardized imaging protocols, and interpretation criteria. Additionally, RCM is related to high equipment costs [26][47][28]. The amount of experience of RCM users has an impact on the sensitivity and specificity of this method, even when the same diagnostic criteria are being applied [43].

In the past few years, some deep learning - based artificial intelligence models have been introduced to automatically identify BCC in RCM images. This diagnostic approach may optimize BCC diagnosis in the future because of its objectivity and independence from RCM users' experience, but further large-scale studies are still required to achieve better diagnostic efficacy of automated interpretation of RCM images [52][53].

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a non-invasive diagnostic method widely applied in various medical fields such as gastroenterology, ophthalmology, dentistry and dermatology. [54][55][56]. Since 1997, OCT has been used in order to visualize sub-surface micromorphology of the skin [56][57]. This method can be a great support in dermatological offices during the diagnosis of BCC [58].

OCT allows us to receive real-time cross-section, two- or three-dimensional images of tissues with different optical properties thanks to interferometric techniques that use near-infrared light waves [54][55][59]. The technology is similar to ultrasound, but instead of sound, OCT uses light waves that provide higher image resolution from 3 to 15 μm and moderate penetration depth from 0.4 to 2 mm [60][61]. Visualization of single cells is not available [59]. It complements RCM in imaging of nonmelanoma skin cancers [56].

To establish an accurate diagnosis and discrimination between BCC from clinical BCC mimics like actinic keratosis, amelanotic melanoma or sebaceous hyperplasia, specialists can search for structures typical of BCC visualized on OCT [62]. The significant characteristics are grey/dark lobular structures with a hyperreflective peritumoral stroma and peripheral dark rimming [62][57]. Other possible features are destruction of layering, epidermal disarray, or dilated vessels [59]. The subtype classification depends additionally on lobular structure type, dominant vascular pattern, and the stretching effect of the stroma among investigated lesions [62]. The discrimination of the subtype of the BCC is significant because it determines the possible treatment methods, non-invasive for superficial BCC and excision of the lesion in case of non-superficial BCC [63]. In the study of Kelly A E Sinx et al. (2020), scientists pointed to significant specificity of OCT (78.3%) to detect superficial BCC compared to clinical examination (47.8%) [63]. According to Adan et al. (2021), discrimination of superficial BCC from non-superficial BCC by using individual features visible in OCT is efficient. Researchers presented that in 44% of cases, biopsy was not needed to determine the subtype [64].

Most studies point out morphological aspects typical of BCC seen in OCT, but some investigate other attributes. In the study of Yücel et al. (2016), scientists focused on optical density and signal attenuation of BCC lesions in two groups of patients. They reported that among the first group with BCC showing disrupted dermo-epidermal junction, the optical density was lower ($P = 0.002$) and attenuation measurements were higher ($P = 0.012$) compared to healthy skin. In contrast to the first group, the second one with classic nodular BCC lesions showed attenuation measurements significantly lower ($P = 0.017$) than in healthy skin [60].

Numerous studies reveal the dominance of OCT over dermoscopy and clinical examination regarding the diagnostic capabilities of BCC lesions. Sensitivity level of diagnostic accuracy of OCT may vary between particular studies, but remains superior to values obtained by traditional noninvasive methods. In the meta-analysis of Yi-Quan Xiong et al. (2018), researchers reported the sensitivity of 92.4% and specificity of 86.9% for diagnosis of BCC with the use of OCT, meanwhile for dermoscopy 83.2% and 85.8% respectively [65]. Some other studies have also shown the dominance of OCT over clinical examination and dermoscopy in terms of sensitivity and specificity for diagnosis of BCC [63][66].

OCT can increase diagnostic certainty of BCC, which could potentially reduce the number of diagnostic biopsies. According to Markowitz et. al. (2015), thanks to OCT 36% of overall biopsies could be prevented by sending high assurance BCC lesions directly to surgical treatment [67].

OCT is also taken into account during the treatment process of BCC. It performs better than dermoscopy to determine the tumor-free margins during therapeutic excision of lesions. Therefore, OCT may help to reach a

“one-stop-shop method”, which aims to remove the entire tumor in one surgery, decreasing overall procedure costs. In the study of Carvalho et al. (2017), eight out of ten BCC were removed entirely in a single excision when OCT was used to determine the margins of the tumors [68][47][69].

The interpretation of OCT images comes with challenges and can be supported by artificial intelligence approaches [70][71]. Researchers are creating models that use machine learning and algorithms to detect the epidermal layer to automate and improve the diagnostic accuracy of BCC [70][72][71].

Despite the potential for major improvements in patient comfort, post-treatment monitoring, and diagnostic accuracy of BCC, OCT is still poorly understood by many dermatologists [70]. Another limitation of OCT is the dependence of effectiveness on the interpreter's experience and subjectivity. In the cohort study of Wolswijk et al. (2023), the sensitivity of BCC indication was notably higher for the expert (82.2%) than for the novice assessor (71.8%) [73]. So far, there is no official OCT training curriculum, but experts agree that practice should include both acquiring and interpreting OCT images [57].

DISCUSSION

BCC is the most common malignant tumor worldwide with a dynamically growing incidence rate over the years, and a variety of novel, innovative diagnostic methods as OCT and RCM have been introduced to improve its diagnosis in recent decades.

RCM is a highly sensitive and specific method in BCC diagnosis, which makes it a reliable tool in clinical practice. This novel technique can also be used in the preoperative detection of BCC margins, providing higher efficacy of surgical treatment or in other therapeutic procedures like laser ablation. However, there are no standardized RCM criteria for BCC diagnosis and its diagnostic accuracy depends a lot on the experience of its user. OCT is a promising non-invasive technology with great sensitivity and specificity for BCC detection. Thanks to its speed of use and moderate penetration depth, OCT outperforms RCM, which is more time-consuming and superficial. However, RCM provides better image resolution than OCT.

Due to the high recurrence rate of primary BCC, OCT and RCM may be of value in monitoring and early diagnosing among patients with risk factors. With the use of these techniques, practitioners can detect skin cancers more quickly and accurately without the need for invasive biopsies and make prompt therapeutic decisions. When the dermoscopy image is inconclusive, additional non-invasive methods may also help avoid unnecessary biopsies of benign skin lesions and improve patients’ satisfaction [22][24]. To facilitate the practical understanding of both techniques, Table 1 summarizes the key comparative features, advantages, and limitations of Reflectance Confocal Microscopy and Optical Coherence Tomography in the context of BCC diagnosis.

Table 1. Comparison of Reflectance Confocal Microscopy (RCM) and Optical Coherence Tomography (OCT) in BCC Diagnosis

Parameter	Reflectance Confocal Microscopy (RCM)	Optical Coherence Tomography (OCT)
Imaging depth	~250–300 µm (superficial dermis)	0.4–2 mm (upper and mid dermis)
Resolution	High (quasi-histological)	Moderate (3–15 µm)
Visualization	Horizontal optical sections, grayscale	Vertical cross-sections, grayscale
Sensitivity	73–100% (average ~92%)	~92.4%
Specificity	38–100% (average ~93%)	~86.9%
Operator dependency	High – interpretation depends on training	Moderate – interpretation requires training
Learning curve	Steep – no standardized curriculum	Moderate – no official curriculum
Time required per lesion	Longer (~10–15 minutes)	Shorter (~2–5 minutes)
Cost of equipment	High	High

Portability	Limited (mainly bench-top)	Some portable units exist
Use in margin assessment	Yes – effective for preoperative mapping	Yes – assists surgical planning
AI integration	Deep learning models under development	Machine learning aids interpretation
Main limitations	Shallow depth, grayscale only, expertise required	Lower resolution, limited cellular detail
Clinical utility	Subtype ID, recurrence monitoring, surgery guidance	Subtype discrimination, surgical decision support

CONCLUSIONS

Although these new non-invasive techniques are being widely applied to the BCC diagnosis and provide valuable additional information supporting clinicians in the diagnostic process, skin biopsy with histopathological analysis still remains a gold standard for making a definitive diagnosis of BCC. Further large-scale, high-quality studies are needed to standardize imaging protocols and to establish specific interpretation criteria of BCC in order to thoroughly investigate the diagnostic accuracy of OCT and RCM. The widespread use of these non-invasive diagnostic methods in the dermatological daily clinical practice in the future will be determined by their affordability, the possibility of unequivocal interpretation of the imaging results and their reproducibility.

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