Non-Invasive Tools for Improving Diagnosis of Non-Melanoma Skin Cancer: A Review

M Amjadi, B Coventry, J Greenwood AM

Citation

M Amjadi, B Coventry, J Greenwood AM. *Non-Invasive Tools for Improving Diagnosis of Non-Melanoma Skin Cancer: A Review*. The Internet Journal of Plastic Surgery. 2010 Volume 7 Number 2.

Abstract

Background Non-melanoma skin cancers (NMSC) are the most common cancers diagnosed in the western world. *The need for surgical treatment of such lesions is on the increase. The fact that the majority of such lesions appear on aesthetically sensitive areas of head and neck means that a non-invasive method of diagnosis has the potential to both eliminate the need for tissue biopsy, as well as act as an adjunct to surgery to ensure minimal healthy tissue is sacrificed. MethodsA review of all literature using databases of Pubmed and Medline was carried out. All the titles and abstracts of all articles found were searched and relevant articles were selected. A further review of all the references mentioned in the selected studies was carried out and all relevant articles were added to the database. All selected articles were reviewed and categorised into groups based on the technique or the technology being investigated. ResultsThe minimally-invasive techniques currently under use or under investigation are: dermoscopy, high frequency ultrasound (HFUS), optical coherence tomography (OCT), and confocal microscopy including both fluorescence confocal scanning microscopy (FCSM) and reflectance confocal microscopy (RCM) ConclusionsBased on this review RCM is the only device that has shown any promise in delivering a non-invasive real-time in vivo image of the skin and its structures that is comparable in resolution to histology, has reasonable inter-operator reliability, and therefore has the potential for use in conjunction to surgery. To date, trials in its use however have been limited. Neville JA, Welch E, Leffell DJ. Management of nonmelanomaskin cancer in 2007. Nat Clin Pract Oncol 2007;4:462–9*

INTRODUCTION

Non-melanoma skin cancers (NMSC) are the most common cancers diagnosed in the western world [1] . The continuing rise in the incidence of NMSC will translate to greater need for surgical interventions. This paper has aimed to review the current literature regarding non-invasive methods of investigation of skin lesions. Non-invasive diagnostic tools have received increased attention for diagnosis, screening and management of NMSC. Several modalities are commercially available. Most of these devices are still limited to use in tertiary referral centres and research facilities.

The gold standard for diagnosis of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and solar keratosis (SK) is biopsy and histological examination. However, multiple lesions occur in areas of chronic sun damage, such that in the majority of cases lesions occur in the context of 'field cancerisation'. Here, the diagnosis is often made clinically without confirmation by histology, since repeated and multiple biopsies may not be practical or feasible. Since skin biopsy alters the original skin morphology due to iatrogenic trauma, inflammation and scarring, non-invasive methods allowing in vivo study of the skin are of great advantage.

The development of topical treatment modalities including Imiquimod, diclofenac, salicylates, Hyaluronic acid, 5-Fluorouracil and ALA-photodynamic therapy, have changed the management of NMSC. Topical treatment of lesions often does not incorporate histological diagnosis. As topical treatments are only indicated for superficial and 'low-risk' lesions [1] , with further development of these treatment modalities the need for non-invasive diagnostic methods will likely increase.

In the past ten to fifteen years, a number of non-invasive diagnostic tools have been developed and been investigated for their applicability for screening, diagnosis and management of skin cancer. These modalities allow the examination of large affected areas and offer the potential for non-invasive monitoring of topical treatment modalities in NMSC. Technologies vary considerably with regard to

their penetration depth, resolution and clinical applicability, and a number of studies have evaluated their diagnostic accuracy and sensitivity and specificity rates. While dermoscopy is widely used in the clinical setting, the application of others often remains limited to specialized cancer centres and research facilities.

A review of all literature using databases of Pubmed and Medline, searching for keywords of 'noninvasive' or 'non-invasive' or 'minimally-invasive', and 'skin' was carried out. All the titles and abstracts of articles found were searched and relevant articles were selected. A further review of all the references mentioned in the selected studies was carried out and all relevant articles were added to the database. All selected articles were reviewed and categorised into groups based on the technique or the technology being investigated.

DERMOSCOPY

Dermoscopy uses horizontal pattern analysis for diagnosis by inspecting the skin with a hand-held lens using cross polarized light. The magnification reached by dermoscopy ranges from 6 to 100 fold, depending on the device. Penetration depth reaches the level of the papillary dermis [2]. It is used widely in dermatological practice for the differentiation of melanocytic lesions, and sensitivity and specificity rates of 73%–96% and 73–100% have been reported for detection of melanoma [3]. With respect to NMSC, studies have focused on the differentiation of pigmented BCC and SK against melanoma whereby dermoscopy may aid in the differential diagnosis [4]. Case reports have described dermoscopic features of facial non-pigmented SK and the dermoscopic differentiation of superficial BCC and SCC in situ [5]. Dermoscopy adds another dimension to clinical diagnosis due to better magnification and its use can increase accurate diagnosis of lesions of most types by surgeons and other clinicians.

HIGH FREQUENCY ULTRASOUND

HFUS uses ultrasound of frequencies between 20–100 MHZ to evaluate skin morphology. Images are obtained in vertical sections with penetration and resolution varying with the respective frequencies. 20 MHZ ultrasound has a penetration depth of 3.8 mm with an axial resolution of 39 μm and a lateral resolution of 210 μm. Newer devices employing 100 MHZ yield a resolution of 9.9 μm and 84 μm, yet have a decreased penetration of 1.1 mm [6]. While routine ultrasonography is widely used clinically for evaluation of cutaneous, adipose, lymphatic, and deeper tissues, and has been used for preoperative assessment of skin tumours, HFUS has not yet been established for NMSC diagnosis outside investigational settings [7]. Advantages of high frequency ultrasound include the deep penetration, whereby measurements of tumour thickness may be obtained on vertical images. However, the resolution does not reach the cellular level and histological subtypes of skin tumours may not be distinguished [8]. Use of fine ultrasound probes through hollow bevel-tipped needles is currently being investigated experimentally.

OPTICAL COHERENCE TOMOGRAPHY

OCT is an imaging technique based on interferiometry. The principle is comparable to ultrasound, but instead of longitudinal ultrasound waves, infrared-light is used, yielding an axial and lateral resolution of approximately 15 μm [9] and a penetration depth of 500–1000 μm [10]. The images obtained by OCT are 2 dimensional, cross-sectional and have a lateral dimension of 4 to 6 mm. It has previously been shown that by using OCT the layers of the skin as well as adnexal structures and blood vessels can reliably be visualized [11]. However, no cellular or subcellular details may be seen. The basement membrane cannot be distinguished, such that early tumour invasion cannot reliably be determined [12]. Preliminary studies have described the features of NMSC, including BCC and SK and suggest that this technique may aid in the evaluation of NMSC [13]. In a recent study [14] OCT features in NMSC were identifiable, but SK and BCC could not be differentiated. OCT diagnosis was shown to be less accurate than clinical diagnosis, but high accuracy in distinguishing lesions from normal skin was obtained, crucial for delineating tumour borders.

FLUORESCENCE CONFOCAL SCANNING MICROSCOPY

Confocal microscopy is based on the detection of exogenous or endogenous contrast within the tissue. Both fluorescence and reflectance mode confocal laser microscopy have been evaluated for their clinical and investigational application in dermatology [15]. The principle of FCSM is the excitation and detection of fluorophores by scanning conjugated horizontal planes within the tissue using a laser light source. Exogenous fluorophores are injected using a hypodermic syringe and image contrast is achieved by differential-distribution and accumulation in the intercellular and intracellular compartment. The commercially available FCSM (OptiScan Ltd., Melbourne, Australia) employs an Argon-ion Laser (488 nm) for tissue illumination and

excitation, while emitted fluorescence is used to visualize the morphological details [21 22] . FCSM images are oriented horizontally with a lateral resolution of 0.5 to 1 μm and an axial resolution of 3–5 μm, at 488 nm, the penetration depth reaches 200 to 250 μm (level of the papillary dermis). FCSM enables the visualization of cellular and sub-cellular structures in vivo, with a resolution which is comparable to routine histology sections. However, injection of fluorescence dye is needed, which removes the technique from the realm of 'non-invasive' cathegory. Another limitation relates to the innate instability associated with handheld devices [16] .

REFLECTANCE CONFOCAL MICROSCOPY

RCM is based on the reflectance, scattering and absorption of monochromatic light by endogenous chromophores such as melanin, haemoglobin and other cellular microstructures. Images have a resolution at the cellular level comparable to routine histology [17] .

In the past decade, advances have been made in imaging human skin by RCM in vivo. The main investigational effort, however, lies in the evaluation of melanocytic lesions and high sensitivity and specificity rates have been described. Repeated imaging can be performed, and the motion-artefacts of life imaging are overcome by stabilizing the objective lens with an adhesive ring device on the skin surface.

Of note is the disadvantage of studies that have used RCM in diagnosis of NMSC. The most cited studies regarding the use of RCM in diagnosis of BCC have been conducted by a single group [18] . These studies all appear to use a study [19] conducted in 2002, which had used 8 lesions in 5 patients, as a sentinel study for creating the diagnostic criteria for BCC, and measuring sensitivity and specificity levels, as the basis of reference for all future studies of the group [20 21] . This introduces possible questions of bias in the integrity of such studies, as well as issues regarding possible statistical power of a study conducted on 5 patients. Studies that have been performed outside of this group, which continue to use the original group's results as a point of reference, have never been as extensive, or as clear in demonstrating the benefits of RCM [22] . Apart from the studies conducted by that group, there is a lack of studies on the human skin performed by means of RCM.

The main limitation of the RCM technique is the failure to visualize the depth invasion of skin tumours due to its relatively shallow penetration on horizontal sections and inability to evaluate lesions with significant hyperkeratosis. RCM therefore, does not permit an evaluation of the basement membrane on horizontal sections, thus early invasion of SK and progression to invasive SCC cannot be determined. RCM may allow therapeutic monitoring of patients with SK, where previously only clinical evaluation was employed to assess efficacy with the potential to detect sub-clinical or residual disease. Thus patients receiving non-invasive therapy, e.g. patients with SK or BCC treated with Imiquimod may be evaluated using RCM permitting a systematic morphologic description of defined skin sites as treatment progresses [23] , although these studies have used the criteria of BCC diagnosis that were developed by the same group of researchers as mentioned above.

SUMMARY

Clearly, non-invasive methods of diagnosis on NMSC would provide major clinical and economic benefits for surgeons and the community and represent a significant step forward. A number of non-invasive diagnostic methods are currently being evaluated for their clinical applicability for NMSC diagnosis. The obvious advantages of non-invasive diagnostic tools are the lack of tissue processing or staining, the possibility of examining tissue in its native state, thus permitting repeated imaging or monitoring of selected skin sites over time. While dermoscopy is routinely used for evaluation of BCC, its role for SK may be limited to pigmented SK due to its unspecific features. HFUS presently remains an investigational device, requiring further clinical studies to evaluate its applicability in skin tumour management. OCT, while only used in specialized skin cancer centres, appears to have the potential for clinical applicability and evaluation of NMSC. For HFUS and OCT comparable systematic studies are lacking, and future investigations will have to determine their role in clinical dermatology. While the use of non-invasive imaging devices may aid in the diagnosis and management of NMSC, there are several limitations. Both HFUS and OCT lack the appropriate resolution. Further improvement of the described technologies may overcome these problems in the future. Our group and others are currently studying the potential role of RCM in improving in vivo diagnosis and better assessment of surgical margins for NMSC.

References

1. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. Arch Dermatol 2009; 145(12):1431-8
2. Marghoob AA, Swindle LD, Moricz C et al. Instruments

and new technologies for the in vivo diagnosis of melanoma. J Am Acad Dermatol 2003; 49:777–97
3. Kittler H, Pehamberger H, Wolff K et al. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002 3:159–65
4. Katz BJ, Oliviero M, Rabinovitz H. Dermoscopy and its impact on skin cancer diagnostics. J Drugs Dermatol 2010; 9(2):129-30.
5. Felder S, Rabinovitz H, Oliviero M et al. Dermoscopic differentiation of a superficial basal cell carcinoma and squamous cell carcinoma in situ. J Dermatol Surg 2006; 32:423–5
6. Vogt M, Ermert H. High Resolution Ultrasound In: Bioengineering of the Skin. Skin, Skin imaging and Analysis; second edition, KP Wilhelm, P Elsner, E Berardesca, H Maibach (eds.). Informa Healthcare USA Inc, NY, USA, 2007; pp. 17–29
7. Lassau N, Spatz A, Avril MF et al. Value of high frequency US for the preoperative assessment of skin tumors. Radiographics 1997; 17:1559–65
8. Wortsman X, Wortsman J. Clinical usefulness of variable-frequency ultrasound in localized lesions of the skin. Journal of the American Academy of Dermatology 2010; 62:247-256
9. Welzel J, Bruhns m, Wolff H. Optical coherence tomography in contact dermatitis and psoriasis. Arch Dermatol Res 2003; 295:50–5
10. Gambichler T, Orlikov A, Vasa R et al. In vivo optical coherence tomography of basal cell carcinoma. J Dermatol Sci 2007; 45:167–73
11. Welzel J, Lankenau E, Birngruber R et al. Optical coherence tomography of the human skin. J Am Acad Dermatol 1997; 37:958–63
12.
13. Olmedo JM, Warschaw KE, Schmitt JM et al. Optical coherence tomography for the characterization of basal cell carcinoma in vivo: a pilot study. J Am Acad Dermatol 2006; 55:408–12
14. Mogensen M, Joergensen TM, Nurnberg BM, Morsy HA, Thomsen JB, Thrane L, Jemec GBE. Assessment of Optical Coherence Tomography Imaging in the Diagnosis of Non-Melanoma Skin Cancer and Benign Lesions Versus Normal Skin: Observer-Blinded Evaluation by Dermatologists and Pathologists. Dermatologic Surgery 2010; 35:965-972
15. Swindle L, Freeman M, Jones B, Thomas S. Fluorescence confocal microscopy of normal human skin and skin lesions in vivo. Skin Res Technol 2003b; 9:167
16. Paoli J, Smedh M, Ericson MB. Multiphoton Laser Scanning Microscopy—A Novel Diagnostic Method for Superficial Skin Cancers. Seminars in Cutaneous Medicine and Surgery 2009; 28:190-195
17. Selkin B, Rajadhyaksha M, González S, Langley RG. In vivo confocal microscopy in dermatology. Dermatol Clin 2001; 19:369–77
18. Rajadhyaksha M, González S, Zavislan JM, Anderson RR, Webb RH. In vivo confocal scanning laser microscopy of human skin II: advances in instrumentation and comparison with histology. J Invest Dermatol 1999; 113:293-303
19. González S, Tannous Z. Real-time, in vivo confocal reflectance microscopy of basal cell carcinoma. J Am Acad Dermatol 2002; 47:869-874
20. Goldgeier M, Fox C, Zavislan J, Harris D, González S. Noninvasive imaging, treatment, and microscopic confirmation of clearance of basal cell carcinoma. J Dermatol Surg. 2003; 29:205-210
21. Nehal, KS, Gareau D, Rajadhyaksha M. Skin Imaging With Reflectance Confocal Microscopy. Semin Cutan Med Surg 2008; 27:37-43
22. Calzavara-Pinton P, Longo C, Venturini M, Sala R and Pellacani G. Reflectance Confocal Microscopy for In Vivo Skin Imaging. Photochemistry and Photobiology 2008; 84:1421–1430
23. Marra D, Torres A, Schanbacher CF, González S. Detection of residual basal cell carcinoma by in vivo confocal microscopy. Dermatol Surg 2005; 31:538–41

Author Information

Mahyar Amjadi, BMBS, BDS, FRACDS
Royal Adelaide Hospital

Brendon J Coventry, MBBS, PhD, FRACS
Royal Adelaide Hospital

John E Greenwood AM, MBChB, MD, FRACS
Royal Adelaide Hospital