Nevisense: improving the accuracy of diagnosing melanoma

“...whenever an alteration can be defined histologically, a corresponding alteration in the impedance spectrum can be found!”

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Nevisense is based on Electrical Impedance Spectroscopy (EIS). Spectroscopy is used in various forms: for example, acoustical spectroscopy (sound or ultrasound), for ECG or EEG (a bandwidth is needed to convey accurate shape in the time domain), EIS (tissue composition and structure) or optical (visible or infrared to detect and quantify specific molecules). It is well known that much useful clinical information can be obtained by various forms of spectroscopy. The first researchers to detect a difference between healthy and cancerous tissue in the electrical domain were Fricke and Morse [1] who studied breast cancer. However, their findings can be attributed to differences in water content, and were not specific to cancer. Not until Schwan [2] explained how different tissue properties show up in different frequency ranges did it become clear that the frequency range is critical for relating tissue characteristics to features of an electrical impedance spectrum. Tissue characteristics corresponding to what histopathologists see in

a microscope are found in the so called β -dispersion range of alternating electrical current, that is, from about 1 kHz to several MHz.

Evolution of the Nevisense method

Dr Ollmar began as early as 1989 to study induced reactions in the oral mucosa, and this investigation was later extended to skin reactions. The first studies focusing on skin were published by Ollmar and Emtestam [3]. Much of the ground breaking work was done by Dr Ingrid Nicander who presented her PhD thesis in 1998 with the title Electrical impedance related to experimentally induced changes of human skin and oral mucosa. Her thesis includes a seminal work where patterns in EIS are related to histological classification [4]. The relationship between histological features and EIS features lead to a tentative generalization: whenever an alteration can be defined histologically, a corresponding alteration in the impedance spectrum can be found! This seemed to work well in a

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laboratory context when inducing various toxic or allergic reactions, but could it be put to use in a clinical context for differential diagnostics?

The company SciBase AB (Stockholm, Sweden) was founded in 1998 to explore this possibility. Early versions of the now named Nevisense device were used for research purposes by the cosmetic industry and researchers to characterize the skin barrier and the oral mucosa, and their elicited reactions. However, it became clear that a more important challenge would be skin cancer, and in particular, malignant melanoma. SciBase received funding from investors and a Swedish research foundation for the exploration of this potential application. Important results can be found in the PhD thesis presented by Peter Åberg in 2004: Skin cancer as seen by electrical impedance. It was found that the classical electrode system composed by flat gold electrodes on a ceramic substrate suffered from reduced signal to noise ratio while trying to extract tissue properties from below the intact stratum corneum. The ability to investigate the skin below the skin's surface is an important requirement to detect malignant melanoma at early stages of development, while not an issue for reactions or diseases where the stratum corneum has been degraded. To circumvent this problem, an entirely new electrode design featuring tiny spikes that penetrate into the stratum corneum was developed and tested [5–7].

The publication of Dr Åberg's thesis provided proof of principle that the technology could detect skin cancer, including malignant melanoma. This attracted investors to finance the continued development and design of Nevisense aiming for a clinically useful diagnostic decision support tool. Even though promising results had been obtained, the key question was whether it

was good enough to actually help a clinician decide whether to remove a suspect lesion or not.

To answer this question, large multicenter clinical studies had to be performed, where the studied lesions would have to represent a wide spectrum of malignant melanomas and other lesions where there was a clinical suspicion of melanoma. Statistical analysis would need to show a high sensitivity in detecting melanoma, without having to remove too many suspicious but benign suspect lesions. In clinical practice, even though around 95% of excised lesions turn out to be harmless, malignant melanomas are still regularly missed both by the physician and the histopathologist [8]. To further develop the system and the classification algorithms used to assess suspect lesions, EIS data from international multicentre studies were analyzed to provide the final evidence. Some of this work was part of a PhD thesis presented by Ulrik Birgersson 2012: Electrical impedance of human skin and tissue alterations: mathematical modeling and measurements. A number of improvements were implemented in a stepwise fashion: all electronics were re-engineered, a touch screen was added to facilitate stand-alone measurements without a connected PC, the electrode system was redesigned to better capture malignancies at different skin depths and the classification algorithms were fine-tuned [9–11].

Other methods

An unfamiliar spot is often discovered by the patient who then consults a doctor for a medical opinion. Visual assessment of suspicious lesions will likely always be the first step of diagnosis. In primary care, the medical opinion would be based on the ABCD rule, sometimes enhanced by dermatoscopy. In a dermatology

Figure 1. From prototype to medical device.

Figure 2. Patient flow including Nevisense for enhanced accuracy.

GP: General practitioner; MM: Malignant melanoma.

clinic, the specialist may have access to digital dermatoscopy with basic image analysis. Some clinics are equipped with more advanced optical instrumentation like confocal microscopy, Raman spectroscopy, multispectral imaging or the nonoptical EIS [9–11].

Early detection of melanoma is vital for treatment outcome and survival, and a sensitivity of <95% would not be clinically acceptable. It is easy for any method to achieve 100% sensitivity by deeming every lesion positive. This approach entails zero specificity, no discrimination at all. In general over 90% of all excised lesions are excised just to be safe to make sure no melanoma is missed, while only about 3–5% of all suspicious lesions excised turn out to be melanomas.

For an often-lethal disease like malignant melanoma, sensitivity is the first priority, and requiring a sensitivity of at least 95% yields a very low specificity for most methods. A combination of methods might increase both sensitivity and specificity by utilizing different types of information, for example, image analysis, optical spectroscopy and EIS. A recent paper describes a combination of near IR spectroscopy with impedance spectroscopy in an implementation differing from that of Nevisense, and reports very high values of sensitivity and specificity. However, no melanoma was included in that study [12], and basal cell carcinoma was used to represent malignant skin tumors.

Given a minimum sensitivity requirement of at least 95%, no other detection method has demonstrated specificity above 10% in large

clinical studies of malignant melanomas. In the Nevisense pivotal study [11], great care was taken to include a wide range of melanoma types at different stages of development to be representative of a realistic clinical spread. In view of this, the Nevisense observed specificity of 34% was a very promising result, especially since this was achieved at an observed sensitivity of 97%.

Introduction of a new clinical tool

Nevisense was developed according to European regulatory requirements as an adjunct tool for the detection of melanoma, and is duly CE marked as a medical device. Figure 1 shows early work with a prototype device under PC control (left), and the Nevisense stand alone product in clinical use about 10 years later (right). It was introduced onto the European market after publication of the article in *Skin Research & Technology* in 2013 [10]. The pivotal study validating the technique was published in the *British Journal of Dermatology* in 2014 [11]. This was the largest study of its type ever done, and it is the basis for an application to the US FDA for approval in the US market. The acceptance of a new adjunct tool is, of course, dependent on evidence from large clinical studies that show it adds clinical value. However, acceptance also depends on economic factors related to reimbursement systems. These vary between different countries and insurance systems, and have to be handled in each region. Figure 2 shows where Nevisense is intended to enhance accuracy in melanoma management.

In conclusion, the goal of this product is to find more melanomas in the clinic, and at the same time reduce the number of false positive diagnostic decisions. The outcome of the third clinical study [11], the largest in its kind ever published, strongly suggests that the goal has been achieved.

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