Issues in Emerging Health Technologies

Optical Scanners for Melanoma Detection

Summary

✓ The key to a melanoma cure is early detection before the cancer has spread beyond the epidermal skin layer.

✓ Several novel, hand-held, automated optical scanning devices have been developed to aid care providers in early diagnosis. These technologies quickly and non-invasively permit visualization deeper into the skin to detect evidence of malignant change.

✓ Approved for marketing in Canada and/or the United States (US) are the devices Aura, MelaFind, and the SIMSYS-MoleMate Skin Imaging System.

✓ The reference standard is visual examination of skin lesions, followed by biopsy and histopathologic analysis, although inter-rater agreement among dermatopathologists varies. Dermoscopy provides additional visual information, increasing diagnostic accuracy, but is not widely used and is time-consuming.

✓ Optical scanners have favourable sensitivity rates (i.e., they identify most melanomas) but show low specificity, meaning that many skin lesions are mislabelled as suspicious and proceed to unnecessary biopsy.

The Technology

Melanoma is a cancer that begins in melanocytes, which are deep epidermal cells that produce the pigment melanin. In Canada, melanoma is the seventh most common cancer, with about 6,000 new cases estimated in 2013 (3,300 men and 2,700 women) and an age-standardized incidence rate of 13.4 per 100,000 people (15.1 for men and 12.2 for women). Based on 2007 estimates, the lifetime probability of dying from the disease is 1 in 287 men and 1 in 420 women. If melanoma is detected at an early stage (less than 1 mm deep), the 5-year survival rate is 93 to 97%; however, the survival rate drops to 10% to 20% with advanced disease. To enable early detection while avoiding unnecessary biopsies, there is a need for accurate diagnostic devices that can differentiate benign skin lesions from malignant ones. Several non-invasive, automated, hand-held optical scanners have been developed to help dermatologists determine whether a skin biopsy is indicated. Three devices that have been approved in Canada and the US are discussed here.

- Aura (Verisante Technology, Inc., Vancouver, British Columbia, Canada) uses near-infrared laser light (Raman spectroscopy) to measure vibrational modes of biomolecules and distinguish malignant from benign skin lesions. The hardware includes a diode laser, a fibre and fibre-bundle delivery system, a hand-held Raman probe, a spectrograph, a camera detector, and a computer. A 785 nm laser beam is delivered to the probe, and the signal from the skin is transmitted to the spectrometer for spectral analysis.

- MelaFind (MELA Sciences, Inc., Irvington, New York, US) uses an illuminator that shines light of 10 wavelengths, a lens system that creates images of the light scattered back from the lesions, and a light sensor to assess tissue up to 2.5 mm beneath the skin’s surface. Information from the device is transmitted into image analysis algorithms using a skin disorder database. A treatment suggestion is provided; i.e., MelaFind positive (high degree of morphological disorganization) or MelaFind negative (low degree of morphological disorganization).

- SIMSYS-MoleMate Skin Imaging System (MedX Health, Inc., Hamilton, Ontario, Canada) uses a hand-held scanner and computer software to provide images that demonstrate a lesion’s vascular composition and pigment network. The technology employs spectrophotometric intracutaneous analysis (SIAscopy) — a light-based imaging system capable of producing rapid images of melanin, blood, and collagen to a skin depth of 2 mm. The MoleMate proprietary software provides dermatoscopic images; dermal and epidermal pathological characteristics; and the ability to catalogue, monitor, and compare lesions over time.
Melanoma risk factors include severe blistering sunburn, ultraviolet light exposure (sunlight and tanning lamps or beds), presence of numerous moles (> 50), positive family or personal history, and immune suppression. Risk is higher for people with light- versus dark-coloured skin. 

Compared to other cancers, a younger population is affected by melanoma, accounting for 22 years of lost life due to invasive disease. Unlike many cancers, the age-standardized incidence rates of melanoma have increased annually from 1998 to 2007 (by 1.4% in men and 1.5% in women) and the lifetime risk of developing invasive melanoma has increased from 1 in 500 people in 1930 to 1 in 74 in 2000. 

Current Practice

Tumor depth is the most important prognostic factor for melanoma. Early detection when lesions are more superficial may improve survival; however, early recognition can be a challenge. Trained dermatologists can recognize advanced melanoma by visual inspection using the ABCDE criteria (Asymmetry, Border irregularity, Colour variegation, Diameter > 6 mm, Evolution), but, in the early stages, melanomas often mimic benign lesions. Hence, most melanomas in North America are > 6 mm in diameter (the size of a pencil eraser) when diagnosed. 

For those at increased risk, such as people with many nevi (sharply circumscribed lesions of the skin) or a tendency to develop atypical nevi, early detection relies on thorough yearly examinations by physicians, supplemented by monthly self-exams by patients. There is no evidence to support general population screening for melanoma. 

The reference standard for melanoma diagnosis is visual examination of skin lesions by a dermatologist, followed by biopsy and histopathology analysis, although intrarater agreement among dermatopathologists is not 100%. For example, a study testing dermatopathologist agreement across 1,250 samples revealed a kappa value of 0.8 for melanoma versus non-melanoma and 0.62 for malignant versus borderline versus benign melanocytic lesions. 

About half of all melanomas are first identified by the patient. Clinical guidelines suggest that a mole exhibiting a significant change in shape or colour, or causing itching or burning, should undergo complete (not partial) excision. This is possible if the lesion is small. If not — for example, for cosmetic or functional reasons — then incisional or punch biopsies are indicated focusing on areas with pigmentation variation or nodular components. Further, if a patient expresses concern about a particular lesion, it is recommended that reassurance be provided only if a lesion is highly unlikely to be melanoma; otherwise, repeat observation after one to two months is considered essential. Photography (single lesion or total body) may be used to capture baseline images with repeat photography several months later.
A useful dermatologic tool is dermoscopy, which involves 10x microscopy and polarized light and/or a liquid medium to allow for a non-invasive, detailed examination of the structures of a pigmented lesion. Sequential dermoscopy may be used to track changes in lesions over time and has been shown to decrease rates of excision of benign lesions. However, the utility of dermoscopy varies with experience, many dermatologists are not trained in its use, and it can be time-consuming, particularly when used for multiple lesions.

### Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), the University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and February 14, 2014. Regular alerts were established to update the search until March 6, 2014.

Citations were selected for inclusion if they evaluated the use of optical scanners for the detection of melanoma. Devices currently approved for marketing in Canada or the US were considered.

### The Evidence

**Aura**

One study of Aura was identified from the University of British Columbia and the BC Cancer Agency, where the device was developed. Research funding was provided by a number of sources including the device manufacturer. Adults were enrolled if they had lesions that were of clinical interest or possible skin cancers. Excluded were lesions that were very small (< 1 mm across); inaccessible to the probe; infected; or previously biopsied, excised, or traumatized. For the analysis, Raman spectral measurements were taken from skin lesions that caused concern; i.e., malignancies and premalignancies that required treatment plus benign conditions that can visually mimic skin cancer. The final classification of lesions was established through clinical evaluation by an experienced dermatologist (without dermoscopy) and/or by histopathologic analysis if a skin biopsy was performed after device use. Biopsy was carried out for all possibly malignant lesions; all lesions classified as cancerous at the end of the study were confirmed as such through biopsy, and approximately 30% of premalignant and benign lesions were also biopsied. Included in the analysis were 518 lesions from 453 subjects (sex distribution approximately equal, median age 61 years). Of these, 313 lesions (60%) underwent subsequent treatment, including 44 melanomas.

The system’s diagnostic performance was tested according to the ability to discriminate melanoma from benign pigmented skin lesions that are similar in appearance. Results showed that, for melanoma versus benign pigmented lesions, as sensitivity increased from 90% to 99%, specificity fell from 58% to 15%. Across the sensitivity span of 90% to 99%, positive predictive values (PPVs) ranged from 30% to 15%, and negative predictive values (NPVs) from 98% to 99%. The authors concluded that their results supported the use of Raman spectroscopy to guide skin cancer diagnosis, including differentiation of melanoma from benign pigmented skin lesions, and that this technology had the potential to reduce the number of unnecessary skin biopsies.

**MelaFind**

One published study on the MelaFind device was identified. The industry-funded, multi-centre, prospective, blinded trial (NCT00434057) was conducted at seven US centres in 2007 to 2008. Enrolled were 1,383 patients scheduled for the excision of 1,831 pigmented skin lesions. Exclusions included small or large lesions (< 2 mm or > 22 mm); lesions near the eye or on palmar, plantar, or mucosal surfaces; sites that were not device-accessible; and previous biopsy, excision, scarring, or tattoo in the area. Melanoma risk factors, ABCDE, and patient’s concern were recorded, as were pre-biopsy diagnoses by examining dermatologists. MelaFind images, standard clinical photographs, and a dermoscopic image were acquired for each lesion. Histologic specimens evaluated by two independent dermatopathologists served as the reference standards (a third served as adjudicator, as needed). As the objective was to see how MelaFind performed in situations of uncertainty, lesions with a pre-biopsy diagnosis of melanoma were excluded. Regarding binding, clinicians did not receive the results of the MelaFind device, and information from MelaFind was not used in diagnosis or treatment.
Of the evaluable lesions, about 8% were melanomas; most were spreading superficial melanomas, a form that can be difficult to differentiate from benign lesions. Compared with histopathologic evaluation, MelaFind displayed 98% sensitivity (125 of 127 lesions) and 9% specificity, versus 4% specificity for the clinical examination alone (P = 0.02). PPV for MelaFind was 9% and NPV was 99%. Sensitivity for clinicians could not be calculated, as the melanomas they missed would only be identified via long-term follow-up; however, a separate study (39 dermatologists, 50 lesions of which 25 were melanomas) revealed about 78% sensitivity for clinicians.\textsuperscript{8,39-42} A similar study from Sweden reported 71% sensitivity for clinicians.\textsuperscript{43}

**SIMSYS-MoleMate**

A randomized controlled trial (RCT) of SIMSYS-MoleMate was conducted at 15 primary care sites in Eastern England, enrolling 1,297 patients with 1,580 lesions. This study was funded by the School for Primary Care Research of the National Institute for Health Research. Patients were assessed by trained clinicians via best practice (clinical history, naked eye examination, seven-point checklist), alone or with the MoleMate system.\textsuperscript{44} There was little difference between groups in numbers of histologically confirmed melanomas, appropriateness of referral, proportion of benign lesions appropriately managed in primary care, and percentage agreement with an expert decision (based on clinical examination alone) to biopsy or monitor. The authors stated that adding MoleMate to best practice resulted in lower agreement with expert assessment that the lesion was benign and led to a higher proportion of referrals (30% versus 22%, P = 0.001). Further, they expressed concern that “the novel technology provided false reassurance, as the systematic application of best practice guidelines ultimately proved more accurate.”\textsuperscript{44}

**Adverse Effects**

No adverse effects of device use are described aside from the potential harms which may follow false-negative and false-positive results. False-negatives can lead to delays in diagnosis and treatment, and possibly increased morbidity and mortality, whereas false-positives can lead to unnecessary invasive procedures.

**Administration and Cost**

**Aura**

The probe is lightly placed on the lesion for about one second. Spectral measurements are taken in duplicate by separately measuring each lesion and then measuring normal-appearing surrounding skin, usually within 5 cm of the lesion. Larger and non-homogeneous lesions are measured several times. The information is processed by the computer, and separation of benign from malignant lesions is possible according to the Receiver Operating Characteristics (ROC).\textsuperscript{5} Proponents list Aura’s advantages over competitors as rapid scan time (1 second), a small probe for hard-to-reach lesions, use for skin cancers aside from melanomas, and less extensive user training.\textsuperscript{5,45} The device selling price in Canada will be $65,000 including all necessary software, although it is also available for long-term monthly lease, plus $10 for each disposable tip that touches a patient.\textsuperscript{7,16} There are no additional costs for operation. A service contract after the one year warranty period is available for $5,000 per year. (Anna Trinh, Verisante Technology, Inc., Vancouver: personal communication, 2014 Mar 4).

**MelaFind**

After hair is removed and the skin is prepared with alcohol, the device lightly touches the lesion for several seconds. Findings are analyzed in less than a minute including comparison with 10,000 archived images. Provided are images of the lesion from each of 10 wavelengths plus information about the level of three-dimensional morphological disorganization; i.e., “high disorganization” or “low disorganization.”\textsuperscript{26,46} The device may be purchased for US$128,000, which includes operational software packages and upgrades, as well as device training and practice integration support. (Natalie Tucker, MELA Sciences, Irvington, NY: personal communication, 2014 Mar 5). Alternatively, the two-year cost of leasing the device, including training cost, is US$7,500 to $10,000 in the US and Germany. There is a $50 fee for each use to “unlock” the system.\textsuperscript{32,34,47-49} Consumables include products to assist in the data capture such as cleaning and coupling agents, and patient data cards. (Natalie Tucker, MELA Sciences, Irvington, NY: personal communication, 2014 Mar 5).

**SIMSYS-MoleMate**

Detailed descriptions of the SIMSYS-MoleMate administration procedure were not available, although manufacturer information indicates that scans are
performed “in seconds,” and that the device can be used to detect skin cancers other than melanomas. The cost of SIMSYS-MoleMate is C$4,000 to $5,000 for the scanner alone and $5,000 to $6,000 with mole mapping.12 An economic evaluation was performed alongside the United Kingdom (UK)-based RCT of SIMSYS-MoleMate.50 Results showed that over a lifetime horizon, the MoleMate system would cost an extra £18 over best practice alone and yield an extra 0.01 quality-adjusted life-years (QALYs) per patient examined. The incremental cost-effectiveness ratio was £1,896 per QALY gained, with a 66% probability of being below £30,000 per QALY gained; i.e., the upper limit of acceptable QALY value in the UK.

Concurrent Developments

There is great interest in detection of early melanomas, particularly using non-invasive optical technologies.2,4,5,12 Nevisense (SciBase, Sweden) is marketed to aid in the detection of melanomas and is currently available only in the Nordic countries, Germany, and Australia, although application for FDA approval may be underway.52,53 VivoSight (Michelson Diagnostics, UK) is an optical scanner with FDA approval and a CE mark,54 but marketing materials only describe its use for non-melanoma skin lesions.55 Many additional technologies are being explored such as confocal laser scanning microscopy, epidermal genetic information retrieval, electrical impedance spectroscopy, optical coherence tomography, reflex transmission imaging, high resolution ultrasound, and melanoma-sniffing dogs.3,29

Rate of Technology Diffusion

Uptake and diffusion of optical scanning devices may be slow for several reasons: multiple types of devices based on different technologies are available, which may lead to a lack of clinical agreement as to which specific device to adopt; marketing approval is not universal; purchase or leasing costs are high compared to other diagnostic aids; health payer coverage is not widely offered, whereas biopsy costs are fully funded; and dermatologists may not see the added value versus their own experience with the adjunctive use of dermoscopy and photography.47 Until costs fall, there may be limited uptake of the technology other than in institutional settings.

Implementation Issues

The devices varied with respect to manufacturers’ suggestions regarding use beyond trained dermatologists. Based on marketing materials, both Aura and MoleMate could be suitable for primary care providers,6,12 whereas MelaFind is recommended for use by dermatologists only.11 Place in therapy also varies. For example, the manufacturer of MelaFind states that the device is to be used to aid dermatologists in their decision to perform a biopsy and is not to be used to make or confirm a melanoma diagnosis,11 whereas the other two manufacturers do not emphasize this point.

An issue for all of the reviewed devices is that the technology (with present specificity and sensitivity values) has high negative predictive value but low positive predictive value. This means that many biopsies of benign lesions will still occur, although possibly fewer than with clinical examination alone. Crucially, the evidence base for all three devices is limited, with one key trial for each. Thus far it is not clear how the devices will perform in a non-research setting, or what their optimal place is in diagnosis. Multi-centre confirmatory studies will be helpful in this respect. A combination of the various technologies available for optical screening of melanoma in the same device could produce the greatest diagnostic utility.

References


Cite as: Foerster V. Optical scanners for melanoma detection [Issues in emerging health technologies, Issue 123]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014.

A clinical expert in dermatology was consulted by CADTH in preparing this report.

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ISSN: 1488-6324 (online)