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RESEARCH ARTICLE

Thermal Product Sensor: A potentially new diagnostic tool in the detection of skin malignancy

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ABSTRACT

Skin cancer is one of the most common cancers in the world. Skin cancer is currently a global public health problem that is escalating. In the UK, the incidence of malignant melanoma has increased from 837 per year to 6963 per year in males and 1609 per year to 6952 per year in females between 1981 and 2018. Early diagnosis and treatment, as with any other disease will have a positive outcome in terms of survival and costs of management. Advances in technology have allowed the development of tools that provide rapid and sensitive diagnosis of many diseases. This paper describes the development and use of a thermal based technique which directly measures the thermal properties of skin. The Thermal Product Sensor (TPS), a new biosensor, has been demonstrated in the diagnosis of skin malignancies. The technique is quantitative and is shown to distinguish between normal and malignant skin. The study demonstrates on 12 patients the thermal product technique successfully detected skin cancers in comparison to normal skin.

INTRODUCTION

Skin cancer is currently a global public health problem that is escalating. In the UK, the incidence of malignant melanoma has increased from 837 per year to 6963 per year in males and 1609 per year to 6952 per year in females between 1981 and 2018[1]. Early diagnosis and treatment, as with any other disease will have a positive outcome in terms of survival and costs of management. Advances in technology have allowed the development of tools that provide rapid and sensitive diagnosis of many diseases. This paper describes the development and use of a Thermal Product Sensor (TPS), a new biosensor, in the diagnosis of skin malignancies.

Skin is the largest organ of the human body. It has many functions including protection of deeper biological layers, heat regulation, secretion, sensation, and absorption. The structure of skin comprises two layers, the epidermis and dermis. The outermost layer, the epidermis, is composed of keratinocytes, Merkel cells, and Langerhans's cells[2]. It is in this layer that most skin cancers arise.

According to Zhang et al[3] in 2019 there were 4.0 million Basal Cell Carcinomas (BCC), 2.4 million Squamous Cell Carcinomas (SCC), 0.3 million Malignant skin Melanomas (MSM). As a result, there were approximately 62.8 thousand deaths and 1.7 million disability -adjusted life years (DALYs) due to MM, 56.1 thousand deaths and 1.2 million DALYs secondary to SCC, respectively. This highlights the economic and healthcare burden caused by skin cancer.

The diagnosis of skin cancers, in the first instance relies upon clinical review and visual inspection. This is usually followed by dermoscopic examination and then biopsy with histological analysis. Other technologies have also been developed to improve the diagnoses of skin[4] cancers. After clinical diagnoses of a malignant skin lesion dermatologists perform either a biopsy or an excision of the lesion prior to the radical resection of the tumour, to evaluate histological stage (tumour thickness). Potential drawback with this method of diagnostics is the lag between biopsy and histological analysis.

The purpose of new technologies is to provide rapid, non-invasive, highly sensitive and possible remote diagnosis of skin cancers. However, new technologies are limited by high expenses, low specificity, and the requirement of specially trained, qualified operators.

Biosensors are technological devices with the ability to sense the difference between various biomolecules[5]. They are integrated receptor-transducer devices that convert biological responses to electrical signals[6]. The use of biosensors in healthcare with a diversity of applications has been widely reported[6].

This pilot study focuses on the application of thermal product, in the diagnosis of skin cancers. Thermal product dictates the amount of heat absorbed by the material it comes into contact with. The measurement is dependent on density, specific heat capacity and thermal conductivity of the material. This energy transfer is quantified by directly measuring temperature which can be recorded. The feasibility of distinguishing between normal skin, benign skin lesions and malignant lesions using the TPS was tested on freshly excised skin lesions from 12 patients in a dermatology clinic. The key advantages of this technique are it has high sensitivity, real time

diagnostics, simple user interface and a portable hand-held device. The thermal product technique requires skin/sensor interface temperature for approximately 5ms to characterise the thermal product of the skin or other biological tissue. The TPs is able to identify melanoma and other skin cancer type by measuring differences in the thermal product between lesions and the surrounding healthy skin.

PATIENTS AND METHODS

Study oversight

The study protocol was approved by the institutional review board at Brighton and Sussex University Hospital in 2018 (Research and Innovation Clinical Research Facility). The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent before enrolment.

Study Design

Patients of varying demographics (Table 1) were identified and recruited from dermatology day surgery over a two week period in June 2017. Twelve patients underwent direct closure excision under local anaesthetic (Xylocaine 1% with adrenaline 1,200,000).

Table 1: Patient Demographics

Case	Sex	Age	Location	Diagnosis	Breslow thickness (mm)	Tumour size (mm)	Tumour thickness (mm)
1	Female	60	Right upper arm	Lentigo Maligna	-	4x2	-
2	Female	90	Left Leg	Nodular BCC	-	15x10	8
3	Male	65	Scalp	Lentigo maligna melanoma	1	50x50	-
4	Male	66	Right forearm	scarring only – (post SCC excision)			
5	Female	90	Left hand	scarring only – (previous melanoma)			
6	Male	35	Mid back	scarring only – (previous melanoma)			
7	Male	70	Left cheek	Lentigo maligna Melanoma	0.9	17x14	
8	Female	63	Scalp	Lentigo maligna - MIS		13x8	
9	Female	32	Left Popliteal fossa	scarring only – (previous melanoma)			
10	Male	31	Back	scarring only – (previous melanoma)			
11	Male	63	Right cheek	Bowenoid actinic keratosis		5x5	
12	Female	58	Left arm	Malignant Melanoma	0.4	9x7	

Once excised, the samples were tested with TPS on both lesional skin, and the adjacent Burow's triangle of normal skin before submitting the sample in formalin for histological analysis. One patient was histologically diagnosed with Melanoma, and two patients diagnosied with Lentigo Maligna Melanoma, three patients were diagnosed with Lentigo Maligna, one with a Basal cell carcinoma and one with Bownoid Actinic Keratosis. The remaining five had scar tissue from previous excision

Experimental Set Up

Figure 1a: Platinum and gold based Thermal Product sensor

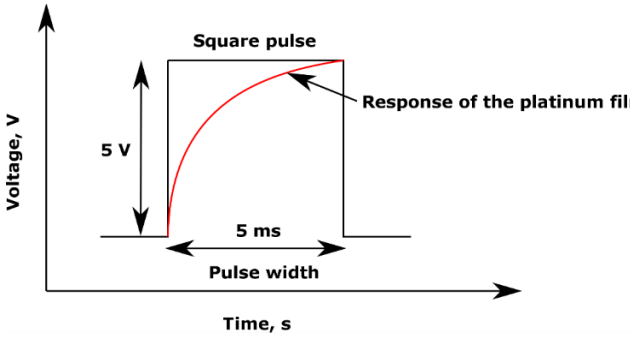

Figure 1b: Electrical pulse and response of the sensor

The sensor had two thin film gauges made of platinum by painting them on a MACOR® substrate (Figure 1a). The sensor was connected to an electronic device to send the electrical pulse and measure the response, the sensor system was manufactured by Proxisense®. The device consists of a 24-bit Analog to Digital Converter sampling at 4.8 kHz and can be configured to have varying pulse amplitude, width, and frequency. For the tests, the pulse amplitude was fixed at 5 V, the duration was 5ms and the frequency of pulsing was 2 s (Figure 1b). The data from the device was acquired and then analysed using MATLAB®.

Principle of Thermal Product Measurement

The sensor's working principle is based on measuring the thermal product of a material in contact with the sensor. The sensor contains thin film platinum gauges painted on an insulating disc such as a vitreous or ceramic substrate and when an electrical square wave pulse of certain amplitude and duration is passed through the sensor, the sensor's temperature increases due to its high resistance. The heat generated will be dissipated in the sensor substrate bottom and some is dissipated in the material surrounding the sensor. This will dictate the temperature recorded by the sensor. As the surrounding material composition changes, the dissipated heat split between the sensor substrate and surrounding material changes which can be correlated to the change in thermal product of the material in contact and near the sensor[7]. In the case of detecting biological tissues, it is known that the thermal properties of tissues are quite different for different layers in the body and hence the heat absorbed will be different. For example, González et al.[8] showed the thermal signatures of the melanoma and normal skin tissue to be significantly different. The relation between heat transfer and thermal product is derived as follows:

The theory can be derived from the 1-dimensional transient heat conduction equation with a step change in heat input

$$\frac{\partial^2 T(x,t)}{\partial x^2} = \frac{1}{\propto(x)} \frac{\partial T(x,t)}{\partial t}$$

where T is temperature, **x** is distance within the substrate, **t** is time

where $\propto = \frac{k}{\rho c}$

k is thermal conductivity, ρ is density and c is specific heat capacity.

The analytical solution for a step function in temperature of this equation is

$$\dot{q}_{wall} = (T_{wall}(t) - T_0)\frac{\sqrt{\pi}}{2}\frac{\sqrt{\rho c k}}{\sqrt{t}}$$

where $\dot{q}_{wall}$ is heat transfer rate, T_{wall} is wall temperature, T_0 initial conditions

Hence, $\dot{q}_{wall} \propto \sqrt{\rho c k}$

The sensor has a wide range of applications and is being actively used in non-healthcare fields for detecting contamination in oil, fuel, or any liquid. It has also been used for detecting and classifying counterfeit pharmaceutical drugs as well as natural and reconstituted rock samples and on polycrystalline diamond for evaluating the heat dissipating properties.

Recently it was used to classify types of biological tissue in porcine samples, and it was found that the sensor was able to differentiate tissues from different organs[6]. It was hypothesized that a diseased tissue may have a different value than normal tissue due to differences in the metabolic rate and volume. The same would apply for liquids and gases where effectively, contamination has taken place by disease and its associated biomarkers. This is analogous to the use of the TP technology in the detection of oil contamination in engines.

RESULTS

Twelve excised lesions were analyzed with the TPS (Table 2). Of these, on histological examination, six lesions were proved to be malignant on histology and one lesion was pre-malignant. The remaining five lesions were scar tissue post previous excision. The TPS gave numerical values for the thermal response obtained from the lesion and from the normal skin.

Table 2: The thermal product (TP) values for the 12 samples

Patient	Skin issue from histology	Normal skin thermal product	Abnormal skin thermal product	Difference in Thermal product
1	Lentigo Maligna	560	361	199
2	Nodular BCC	859	826	33
3	Lentigo Maligna Melanoma	762	379	383
4	Scarring post SCC excision	289	443	-154
5	Scarring previous melanoma	677	450	227
6	Scarring previous melanoma	1000	1206	-206
7	Lentigo Maligna Melanoma	687	331	356
8	Lentigo Maligna	718	443	275
9	Scarring previous melanoma	787	693	94
10	scarring previous melanoma	248	286	-38
11	Bowenoid actinic keratosis	531	860	-329
12	Malignant Melanoma	680	650	30

Of the malignant lesions, two lesions were shown to be lentigo maligna (melanoma in situ) on histology see Figure 2. These lesions typically gave an average positive reading difference of 237 between the lesion and normal skin within the sample. Two lesions were lentigo maligna melanoma (melanoma arising within lentigo maligna). These lesions gave an average positive reading difference of 369.5 The positive difference of these lentigo maligna and lentigo maligna melanoma lesions ranged from 199-383. The TP reading for these four lesions ranged between 331 and 443 (average 379). One lesion was proved to be a Basal cell carcinoma and within this lesion there was a positive difference of 33 between the lesion and normal skin. The thermal product reading for the BCC was 826 compared to the normal skin reading of 859. One lesion was a malignant melanoma (TP reading of 650 compared with a normal skin reading of 680 giving a difference of 30).

The premalignant lesion was a Bowenoid actinic keratosis and this gave a negative difference of 329 between the lesion and the normal skin. Of the 4 post excision scar lesions, three gave negative values of 132 on average with one lesion giving a difference of negative 207.

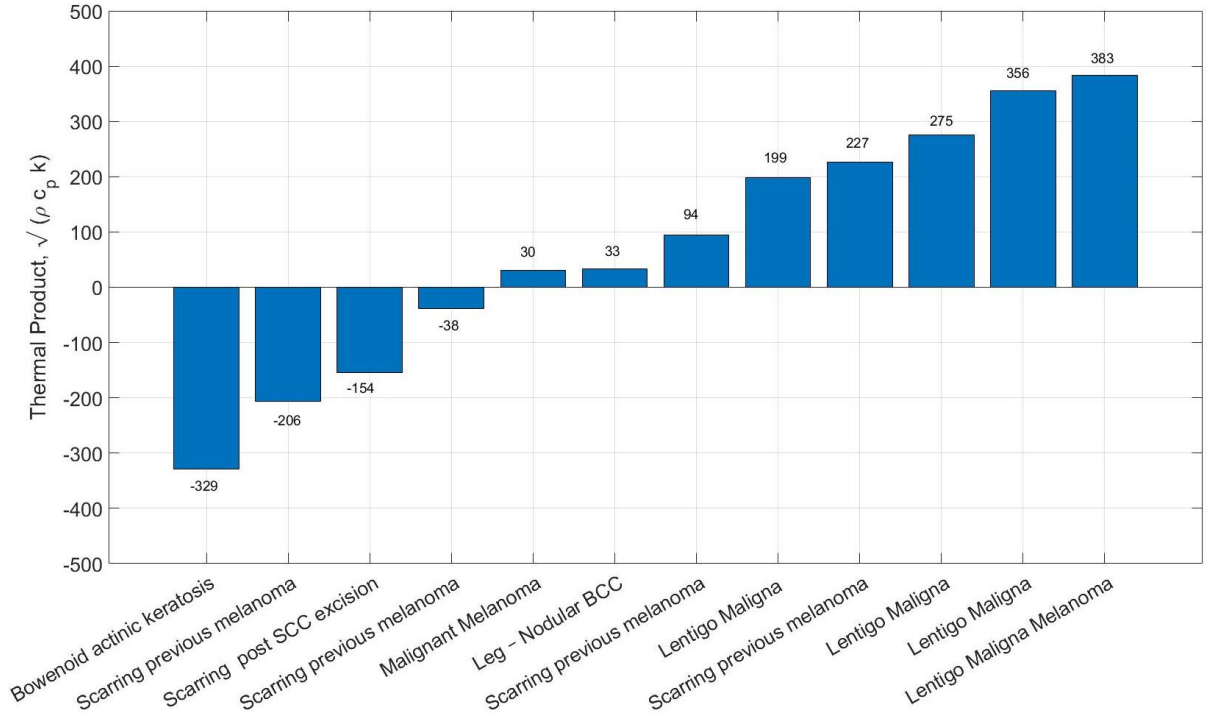

Figure 2. Difference in Thermal product readings

Figures 3 to 14 show the patient lesion photographs and the thermal response to normal and abnormal skin. The thermal response curves are initially converted to temperature by using the temperature coefficient of resistance calibration for the sensor thin film gauge and, subsequently to thermal product using a calibration of samples with known thermal properties. The sensor is initially tested in air as a functional check that it is operating correctly.

Figure 3 (Patient 1) shows the freshly excised specimen of skin (B) of a patient with lentigo maligna on their arm. The lesion and junction of the lesion and normal skin were immediately interrogated using the TPSP. The thermal response shown in the graph (C) demonstrates the curve corresponding to air (functional check, blue curve) and a clear difference in the curve corresponding to normal skin (red curve) compared to the curve corresponding to the center of the lesion (yellow curve) and skin to the side or junctional skin (purple curve).

Figure 4 (Patient2) shows a photograph (A) of a nodular basal cell carcinoma removed from the leg of a patient with the corresponding thermal response graph (B). The ellipse of skin excised encompasses two lesions. The thermal response curve of the normal skin (orange curve) differs to that of the curves relating to the curves (yellow and purple) which are similar.

Figure 5 (Patient 3) shows a photograph of a lentigo maligna melanoma from the scalp (A), a specimen of skin excised from a skin graft from the thigh of the patient taken for the procedure (B) and the corresponding thermal response curves (C). These show that lentigo maligna curve (light green curve) differs significantly to the curves related to the normal skin around the lesion (orange curve)

and the skin graft skin (light blue curve). The normal skin surrounding the tissue and the skin graft skin have remarkably similar curves.

Figure 6 (patient 4) shows the excised skin and specimen (B) of a scar where a previous squamous cell carcinoma had been excised from a patient's arm. The corresponding graph (C) demonstrates that the normal skin curve (red curve) and the curve relating to the abnormal skin (scarring) differ significantly (yellow curve)

Figure 7 (Patient 5) shows an excised scar specimen of skin (A) where a previous malignant melanoma had been excised. The thermal property curves (B) demonstrate that the normal skin curve (red curve) differs markedly from the scarred skin.

Figure 8 (patient 6) shows an excised specimen of skin (A) from where a previous melanoma had been removed. The thermal property (C) differs in the scarred tissue (yellow curve) when compared with the curve (red curve) for normal skin.

Figure 9 (Patient 7) shows the excised specimen containing a lentigo maligna (A). The corresponding curves of thermal property show a clear difference between the curve for the lesion (yellow curve) and normal skin (red curve).

Figure 10 (Patient 8) shows the excised specimen of skin containing a lentigo maligna lesion (A). Again, the curves representing their respective thermal properties (B) show a clear difference between the lesion (red curve) and normal skin (yellow curve).

Figure 11 (Patient 9) shows the excised specimen of skin from a patient with a previous melanoma excised from the same site (A). The thermal property curves (B) of normal skin (red curve) and abnormal skin (yellow curve) demonstrate a clear difference.

Figure 12 (patient 10) shows an ellipse of skin excised form a site of a previously excised malignant melanoma (A). The scarred tissue (yellow curve) and normal skin (red curve) show a difference in their thermal property (B).

Figure 13 (Patient 11) shows an ellipse of skin (A) excised for a Bowenoid actinic keratosis at its center. The corresponding graph (B) demonstrates that the curve for normal skin (red curve) and the lesion (yellow curve) are significantly different in their thermal property.

Figure 14 (Patient 12) shows an excision of a malignant melanoma (A) and the thermal property graph (B). The curve representing the lesion (yellow curve) is different compared to the curve associated with normal skin (red curve).

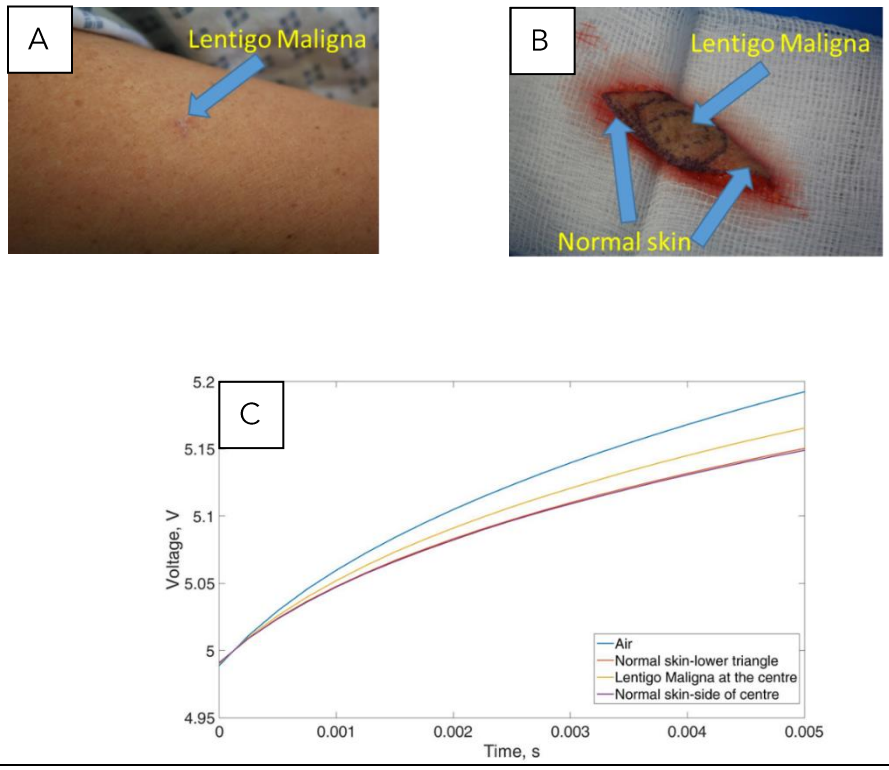

Figure 3. Patient 1 – (A) Arm Lentigo Maligna, (B) Normal skin and Lentigo Maligna markings and (C) Thermal response to normal and abnormal skin

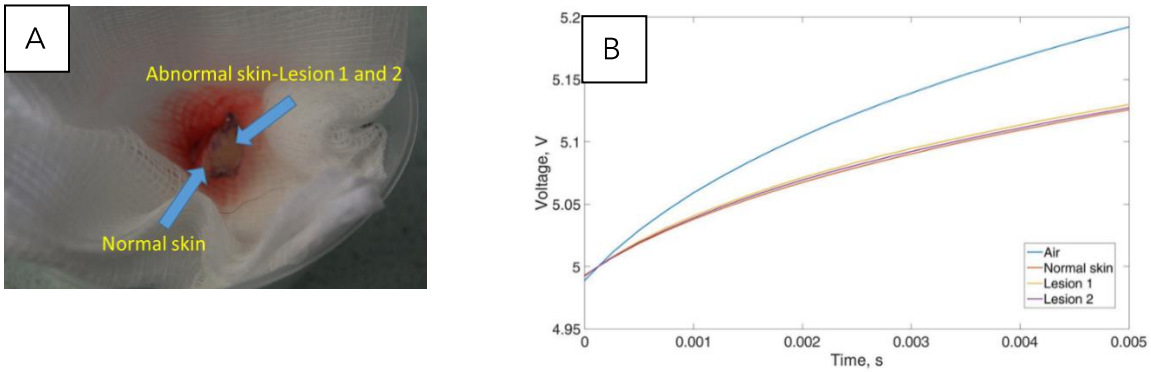

Figure 4. Patient 2- (A) Leg Nodular BCC and (B) Thermal response to normal and abnormal skin

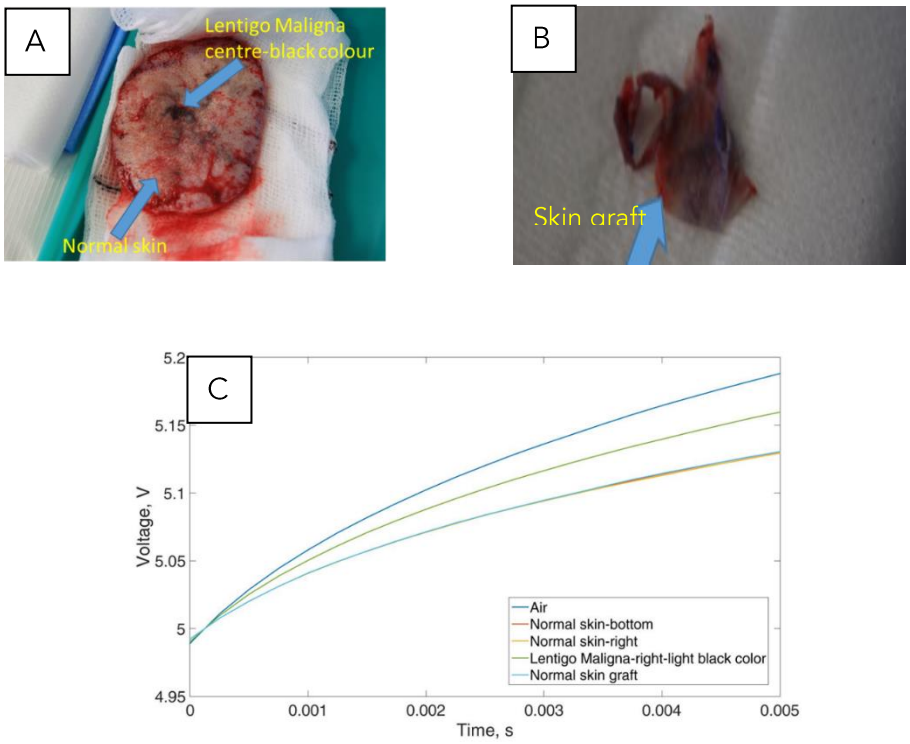

Figure 5. Patient 3- (A) Scalp Lentigo Maligna Melanoma, (B) leg (thigh) normal graft skin and (C) Thermal response to normal skin scalp/leg and abnormal skin

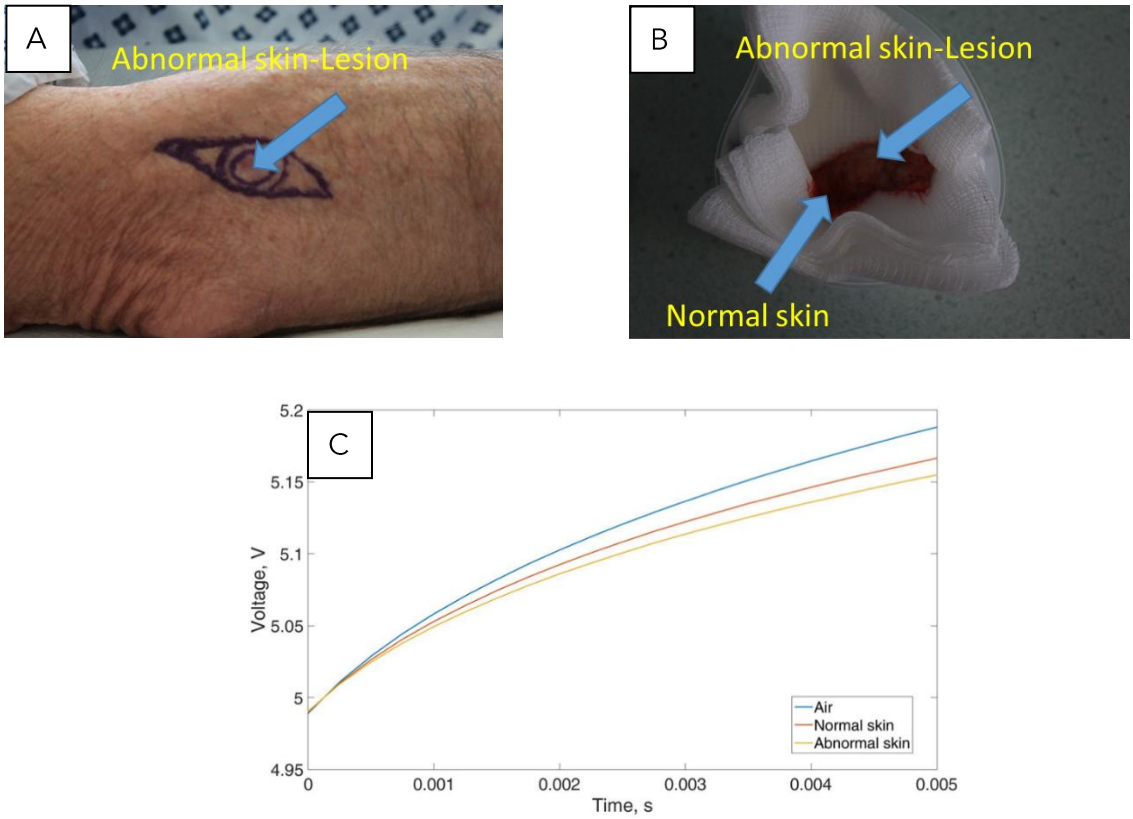

Figure 6. Patient 4- (A) Arm Scarring only, post scc excision, (B) Normal and abnormal skin and (C) Thermal response to normal and abnormal skin

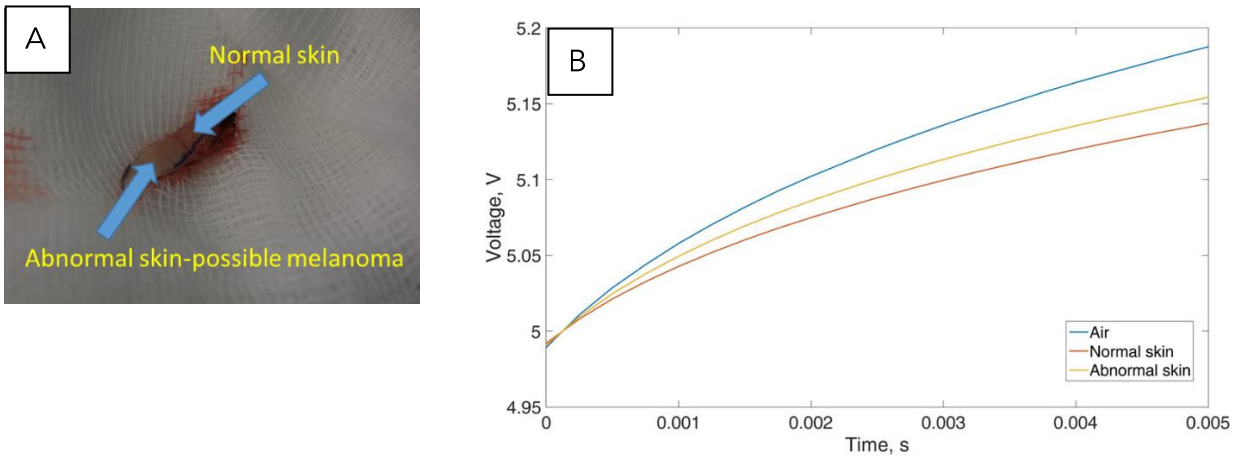

Figure 7. Patient 5- (A) Scarring only, previous melanoma and (B) Thermal response to scarring and normal skin

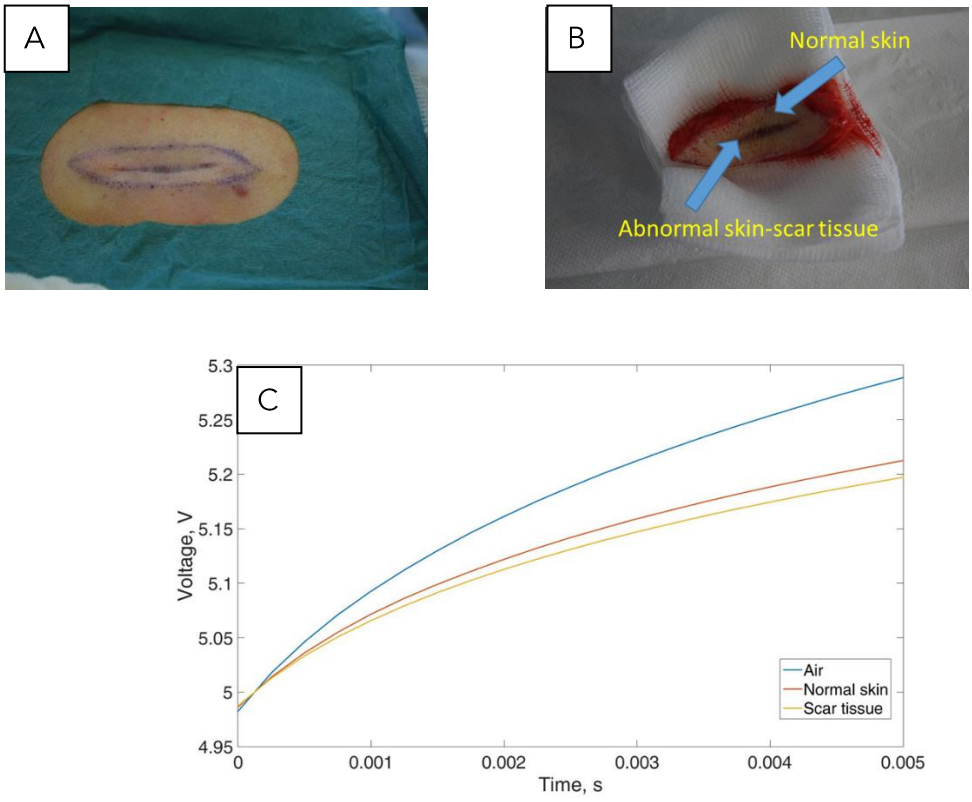

Figure 8. Patient 6- (A) Scar tissue from excised melanoma scarring only, previous melanoma, (B) Normal and abnormal skin and (C) Thermal response to normal and scar tissue

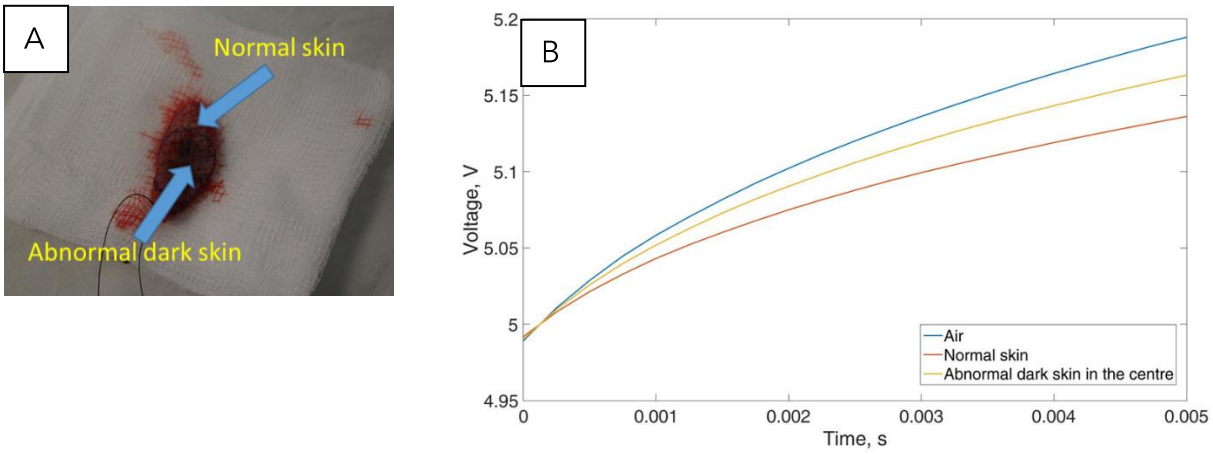

Figure 9. Patient 7- (A) Lentigo maligna melanoma and (B) Thermal response to normal and abnormal skin

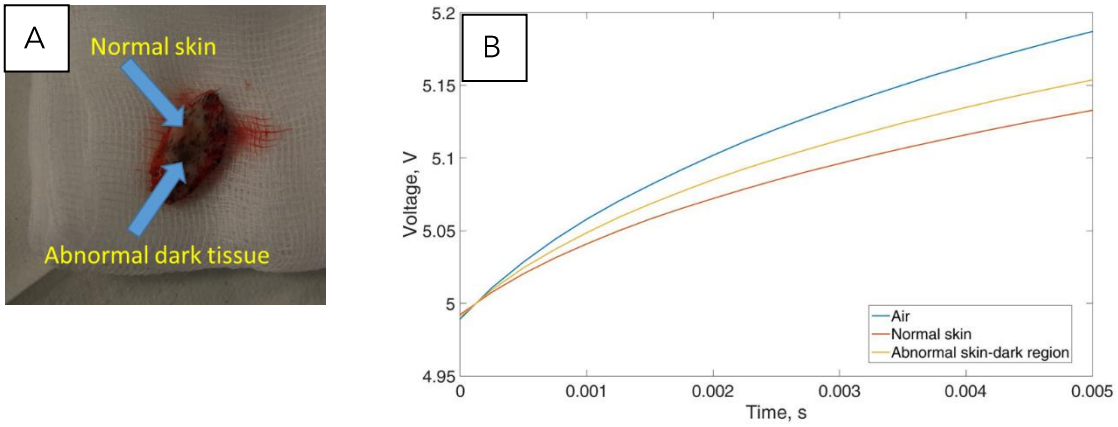

Figure 10. Patient 8- (A) Lentigo maligna and (B) Thermal response to normal and abnormal skin

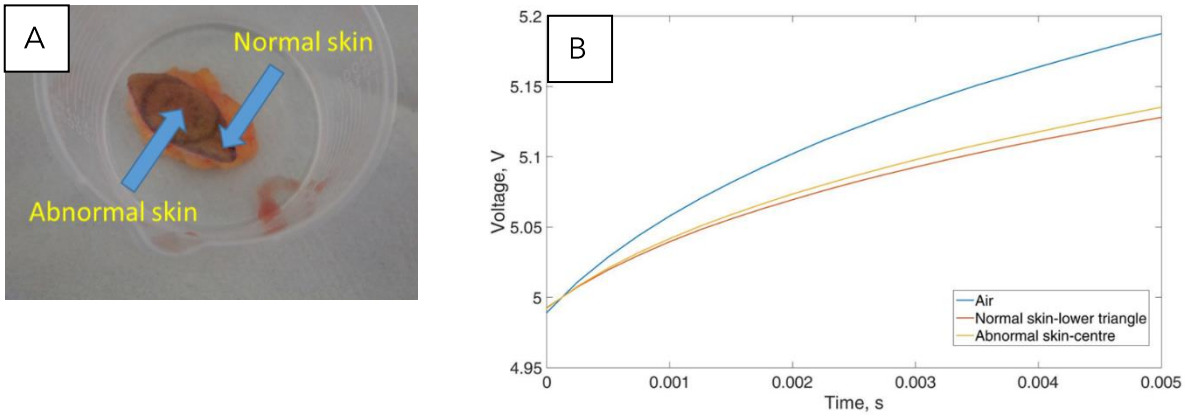

Figure 11. Patient 9- (A) Scarring only, previous melanoma and (B) Thermal response to scarring and normal skin

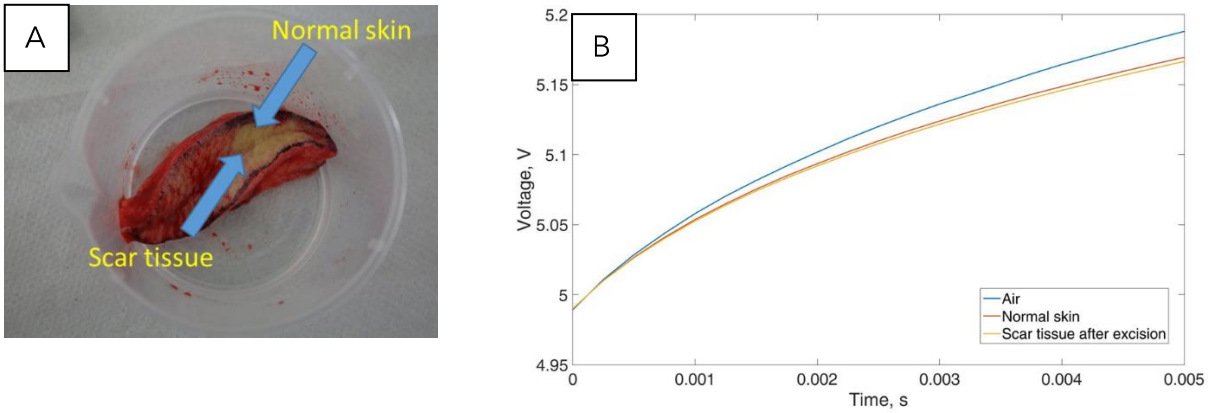

Figure 12. Patient 10- (A) Scarring only, previous melanoma and (B) Thermal response to normal skin and scar tissue

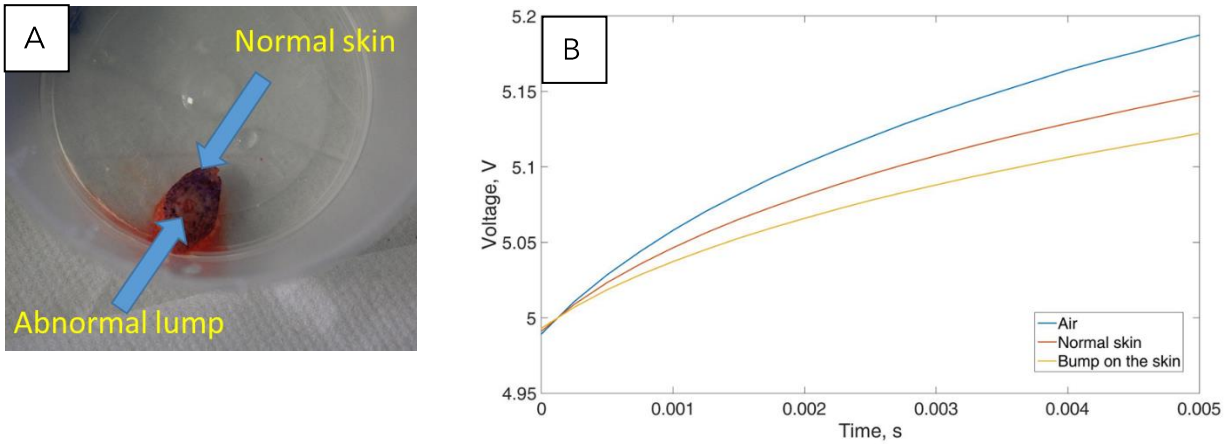

Figure 13. Patient 11- (A) Bowenoid actinic keratosis and (B) Thermal response to normal and abnormal skin

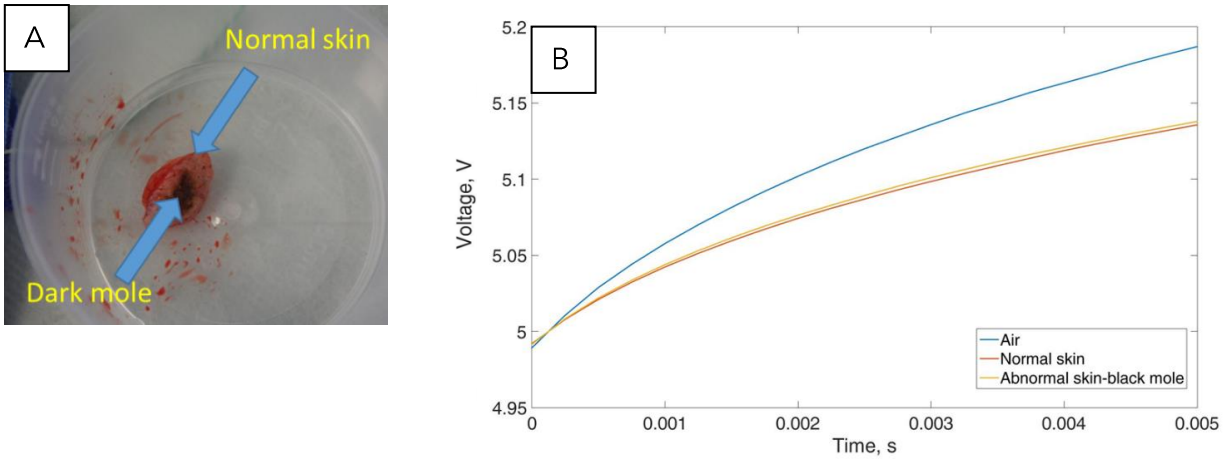

Figure 14. Patient 12- (A) Malignant Melanoma and (B) Thermal response to normal and abnormal skin

DISCUSSION

These results demonstrate a clear difference in Thermal Product (TP) between skin lesions which are benign, pre-malignant or malignant and the normal surrounding skin. It is this difference in the numerical value of TP that may allow the rapid clinical diagnosis of skin lesions.

González et al. performed a review of thirty patients with melanoma and non-melanoma skin cancers and reported a difference between the thermal signature of normal skin and that of melanoma[8]. This is due to the difference not only in vascularity but also the metabolic heat production. Okabe et al[9] more recently have demonstrated the use of a guard heated thermistor probe to measure the absolute value of skin surface temperature and the effective thermal conductivity of skin and thereby distinguishing between melanoma types and between skin lesions and normal skin. The authors of this article have described in an original article[7] the use of Thermal Product Sensor in distinguishing between different types of biological tissue by utilising the differences in thermal properties of different tissues. This concept has now been applied to the potential diagnosis of skin abnormalities using the thermal product sensor system.

The results from this pilot study suggest that the difference in numerical value of TP between pathological skin lesions and skin is markedly different when compared to differences in benign premalignant non melanotic lesions (in this case a Bowenoid acinitic keratosis) and scarred skin from previous lesion excisions. These samples gave highly negative differences in TP value compared with the highly positive differences in TP seen with the excised specimens of lentigo maligna (in situ melanoma) and lentigo maligna melanoma (Figure 2). It is also notable that the highest difference in TP between the lesion and normal skin was in patient 3, where the histological diagnosis was of a Lentigo Malignant Melanoma (invasive melanoma). Malignant skin lesions showed a higher absolute thermal product value in comparison to the surrounding normal skin, the benign lesion showed lower thermal product values in comparison to the surrounding normal skin. This raises the possibility of using the TPS, not only to distinguish between normal skin and skin lesions but also premalignant lesions such as lentigo maligna and invasive melanoma. Notably, in this patient the TP values for normal scalp and leg skin (graft) gave identical values indicating that for a given patient the TP values of skin from different anatomical regions may be consistent.

Although our sample size in this pilot study is small, the results demonstrate that the TPS is able to distinguish between normal skin, scarring and skin lesions. The TPS is portable and does not rely on specific training for the operator and therefore a possible advantage would be rapid, almost instantaneous diagnosis of skin lesions that may be applied by non-trained individuals or clinicians in outpatient settings. A further potential use may be in the use of the TPS in the mapping of skin lesions prior to excision so as to define safe margins and full excision of premalignant and malignant skin lesions. The most obvious advantage would be preventing unnecessary excisions and biopsies, avoiding surgical complications and anxiety for patients and saving precious healthcare resources.

The investigation showed that the thermal product shows promise as a skin cancer diagnostic technique however, the precise pathological processes that result in the correlation between the thermal product value and melanoma are not yet well understood.

The authors stress that this is a pilot study and a larger cohort of patients will be required to demonstrate significance and also to interrogate a wider range of skin pathologies such as squamous cell carcinoma with the TPS as well as further studies looking at distinguishing premalignant lesions from invasive carcinoma.

CONCLUSION

Skin malignancy continues to be a world-wide health care issue and there are many challenges in the diagnosis of skin lesions. The weight of diagnosis falls on clinical examination and the most desirable methods of investigation are none invasive. Many methods have been developed and trialed. This paper presents an innovative thermal based method that shows promise in being able to diagnose skin malignancy.

An investigation in the use of thermal product for the detection of skin malignancy is presented in this paper. The results are based on a comparison of the thermal product of the lesion and the surrounding normal skin for each patient. The findings of the 12-patient study showed that the histological analysis of the excised lesions agreed with the thermal product measured data. Summary of the key results are given below:

1. Successfully trialed a thermal based technique to measure skin thermal product.
2. Accurately measured the difference in thermal product between the lesions and normal skin
3. The sensitivity of the thermal product technique was validated to differentiate between skin malignancy and normal skin, although on a small sample size.
4. The thermal product measurements of the malignant skin tissue had a higher thermal product value in comparison to the normal skin, whereas the benign skin lesion showed a lower thermal product value.

Contribution by each author and confirmation of no competing interest:

DeGiovanni C

Coordinating the trial. Performing the excision of the lesions and the thermal product assessment. Writing and editing the original manuscript.

Patel M

Minal is part of the dermatology team that carried out the excision of the lesions and collated data for the manuscript. She took part in writing the manuscript and formulating the tables.

Drake P

Paul was part of the dermatology/plastic surgery team that saw and treated patients with the skin lesions. He took part in excision and was involved with data collation and analysis as well as writing of the manuscript.

Sains P

Parv came up with the original concept of the use of the Thermal Product Sensor to diagnose malignant skin lesions. He submitted the original ethics approval documents to the Research and Development department and edited the original and

subsequent final manuscript. He integrated the engineering/medical aspects of this project.

Sridhar V

Vikram has been a long-standing part of the Thermofluids team at Oxford University was integrally involved in the development of Thermal Product and the sensor. He wrote the original part of the manuscript alluding to the engineering concepts and technology.

Kam Chana

Kam is the inventor of the Thermal Product measurement technique. He developed the sensor (hardware and software) and managed the transferability of the technology from engineering to medical application. He edited the final manuscript as well as writing the original technical description of the thermal product concept.

Data set availability:

The data sets used or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest:

None

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None

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