

Faculdade de Engenharia da Universidade do Porto



**Skin Neoplasms Characterization Through
Standardized Medical Thermography**

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"Success requires no explanations. Failure permits no alibis."
Napoleon Hill

Abstract

The systematic process of skin cells regeneration can be affected of several factors causing an abnormal grow of new cells. The excess of cells may form a mass of tissue called neoplasm. The neoplasm may be benign or malignant. Benign neoplasms rarely require treatment, just periodic checkups are recommended to control and to ensure that they do not evolve into malignancy. Within the malignant neoplasms, the most relevant are melanoma, basal cell carcinoma and squamous cell carcinoma which have effective treatments. Contrary, malignant melanoma can only be remised with an aggressive treatment in an early phase. According World Health Organization (WHO), the incidence of this type of cancer in the European Union (27 countries) are 12.2 persons per 1M inhabitants, the mortality is approximately 2.2 persons, and the prevalence at 1st, 2nd and 3rd years are 12 %, 34.1 % and 53.9 % respectively. Thus, it is necessary to find new cost-effective tools that can contribute to early diagnosis or treatment assessment. Medical thermography is a non-invasive, non-ionizing, non-contact and reliable medical imaging method, which allows monitoring the temperature distribution on the skin surface. This information is directly related to the physiology, enabling a real-time monitoring, especially in peripheral microvascular and autonomous nervous systems.

This study aims to use the medical thermography for physiological characterization of skin neoplasms. It is a retrospective and explorative study consisting of a control group and a group of malignancy holders. Skin surface temperature was characterized according to the dermatomes location of the autonomous nervous system and main blood vessels location of the microvascular system. The relationship of these characteristics with the type of recurrent skin neoplasms was assessed.

It was possible to characterize the temperature of skin neoplasms, facilitating early diagnosis, targeting adequate treatments and a substantial reduction of associated costs.

Keywords: Medical thermography; Monitoring; Skin cancer; Skin surface temperature; Skin neoplasms.

Resumo

O processo sistemático de regeneração das células da pele pode ser afetado por vários fatores causando um crescimento anormal de novas células. Esse excesso pode formar uma massa de tecido designada por neoplasia (benignas ou malignas). As benignas raramente necessitam de tratamento, apenas são recomendados exames periódicos para controlo, de forma a garantir que não evoluem para malignas. Das neoplasias malignas destacam-se os melanomas, os carcinomas basocelulares e os espinho-celulares. Os carcinomas basocelulares e espinocelular são os mais comuns, tendo um tratamento bastante eficaz. Pelo contrário, o melanoma apenas pode entrar em remissão, com um diagnóstico precoce e tratamento agressivo. A incidência deste tipo de neoplasia na União Europeia - 27 países (UE27) é de 12.2 pessoas por 100000 habitantes, a mortalidade cerca de 2.8 pessoas e a prevalência no 1º, 2º e 3º ano é de 12%, 34.1% e 53.9% respetivamente.

Assim sendo, é necessário encontrar novas ferramentas que contribuam para um diagnóstico precoce ou avaliação de tratamento e que sejam financeiramente atrativas. A termografia médica é um método de imagem clínica não invasivo, não ionizante e preciso, que permite monitorizar a distribuição da temperatura à superfície da pele. Esta informação está diretamente relacionada com a fisiologia, permitindo a sua monitorização em tempo real, nomeadamente dos sistemas microvascular periférico e nervoso autónomo.

Esta investigação teve como finalidade utilizar esta técnica para avaliação fisiológica, caracterizando as lesões neoplásicas da pele. Trata-se de um estudo retrospectivo e explorativo constituído por um grupo de controlo e indivíduos detentores de neoplasias. Usando a termografia de forma padronizada, caracterizou-se a temperatura à superfície da pele de acordo com a localização dos dermatomas do sistema nervoso autónomo, e com a localização dos vasos sanguíneos principais do sistema microvascular de cada indivíduo. Avaliou-se também a possível relação destas características com o tipo de neoplasia recorrente nos indivíduos.

Foi possível caracterizar a temperatura das neoplasias, facilitando o diagnóstico atempado, tratamento direcionado e uma redução substancial dos custos associados a estas patologias.

Palavras-chave: *Cancro de pele , Monitorização, Neoplasias de pele, Termografia médica, Temperatura superficial da pele.*

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Acronyms and Symbols

ANS	<i>Autonomous Nervous System</i>
BMI	<i>Body Mass Index</i>
FEUP	<i>Faculdade de Engenharia da Universidade do Porto</i>
IPO-Porto	<i>Instituto Português de Oncologia do Porto</i>
ITI	<i>Intraoperative Thermal Imaging</i>
MS	<i>Microvascular System</i>
ROIs	<i>Regions of Interest</i>
TS	<i>Thermal symmetry</i>
ΔT	<i>Temperature difference between the left and the right side of skin neoplasms</i>
U	<i>U-Mann Whitney</i>
W	<i>Wilcoxon W</i>
Z	<i>Wilcoxon Z</i>

Chapter 1.

1.1 Introduction

Skin neoplasms are an abnormal mass of tissue that results from an abnormal growth, or cell division. There are two types of skin neoplasms, benign and malignant, also called skin cancers.

A benign neoplasm is localized, manifests itself by growing above the skin surface, does not invade adjacent tissues, does not spread to other parts of the body, and can easily be removed, rarely puts the patient's life at risk. On the other hand, the malignant neoplasm presents an uncontrolled growth of abnormal skin cells. This situation occurs when unrepaired DNA damaged skin cells (most often caused by ultraviolet radiation from sunshine or tanning beds), triggers mutations, or genetic defects, which lead the skin cells to multiply rapidly. The main types of skin malignant neoplasms are: basal cell carcinoma and squamous cell carcinoma (non-melanoma skin cancer) and melanoma [1]. Table 1 shows the countries that have a higher incidence of skin cancer: Australia, New Zealand, Switzerland, Denmark and Norway [2].

Table 1: Melanoma incidence rate in the 5 countries with more pathology prevalence [2].

Country	Skin cancer incidence rate (1 to 100000)
Australia	36.7
New Zealand	36.2
Switzerland	25.8
Denmark	24.1
Norway	25.3
Portugal	8.2
UE27	13

The incidence of both, non-melanoma and melanoma skin cancer, has been increasing over the past decades. Currently, between 2 and 3 million non-melanoma skin cancers and 132 thousands melanoma skin cancers occur globally each year. Basal cell carcinoma is the most common form of skin cancer and the squamous cell carcinoma is the second. Melanoma is generally the most serious form of malignant neoplasms because it tends to spread (metastasize) throughout the body quickly. According to the American Cancer Society, one person dies of melanoma approximately every hour [5].

In Portugal, there are about 700 new cases of melanoma annually [3]. The incidence of this type of cancer in the European Union of 27 countries (EU27) is of 13 persons per 100000 people, the mortality is approximately 2.2 persons, and the prevalence at 1st year is 12%, in the 2nd year is 34.1% and finally, in the 3rd year is 53.9% respectively [3, 4].

This year an estimated of 76100 new cases of invasive melanoma will be diagnosed in the United States and 9710 people will die of melanoma [5].

In United States, the cost of skin cancer treatment varies, depending on the size, type, depth and location of the lesions, and, most important, the stage in which it was detected. One study published in the Archives of Dermatology found average treatment costs for skin cancers to range from 1732 to 56059 United States Dollars (USD) depending on the stage of the disease [6]. The costs associated with melanomas treatment exceed USD 740 million annually [7]. In 2009, the average monthly cost per patient with melanoma was approximately about USD 2194 during the first four months of treatment. For people aged 65 or older, the annual cost was around USD 390 million [8, 9].

Australia is the country in the world with the highest incidence of melanoma patients. Every year, 10430 new cases are identified. The costs associated with cancer in this country are of 3.8 billion Australian Dollars (AUD) per year in direct costs of health care. Worrying is the fact that only 1% (AUD 30 million) are spent on treatments of melanomas [8]. Non-melanoma skin cancers have cost to the Australian health system more than AUD 500 million in 2010 and are expected to cost AUD 700 million by 2015.

Medical Thermography is an imaging technique that allows mapping the thermal radiation emitted by the surface of the human body skin, which under some conditions may reflect abnormal or normal situations of human physiology. Thermography is technique a non-invasive, non-contact, non-ionizing and therefore safe for the patients. This technique is passive, and relies on the registration of the thermal radiation emitted by the surface of the skin from various parts of the body through a set of appropriate sensors that create an image of the surface temperature. The capture protocol recommended for medical thermography defines the environment in which an examination should be performed; the ambient temperature should be between 18 and 24 °C, relative humidity be less than 50%, the air flow should be less than 2 m/s and there should be absence of light incident upon the subject [10-12].

1.2. Aim

This work aims to investigate the use of medical thermography for physiological assessment, characterization and monitoring skin neoplasms in several areas of the body, on IPO patients.

Two different studies will be made. The first has the objective to characterize the temperature of skin surface in asymptomatic individuals, based on dermatomes distribution of the Autonomous Nervous System (ANS) and in the perforated blood vessels of the Microvascular System (MVS), and their relationships with individual's characteristics. In this group a wind stimulus (fan) will be applied during a period of two minutes, in order to evaluate the physiological response of the face. Thus, it was possible to perform a characterization study of the skin surface temperatures of the two systems (ANS and MVS).

The second study, will be focused on the characterization of the skin surface temperature in patients with various skin neoplasms (benign or malign) and individuals who have already undergone in treatment. It will also be evaluate the relationship between individual's characteristics and skin neoplasms type. In addition, a comparison case study will be performed with basal cell carcinoma individuals and a control group with similar BMI and gender.

The results of this research will enable improvements in early diagnosis of skin neoplasms, targeting adequate therapies, and leading to a reduction of these pathologies associated costs.

1.3. Dissertation Outline

This document is organized in six sections. The first introduces the topic and characterization of the problem and its context. The literature review describes additional information found in the literature, which is relevant for the present work. The third section, outline the materials and methods used during this research. The fourth section presents the results for each experiment. In the fifth section, there is a discussion and analyzes of the significance of the obtained results. Finally, the conclusion addresses the final considerations and main achievements, as well as the future work. The structure of the dissertation and the links between different parts of this document can be seen in figure 1.

Dissertation Outline

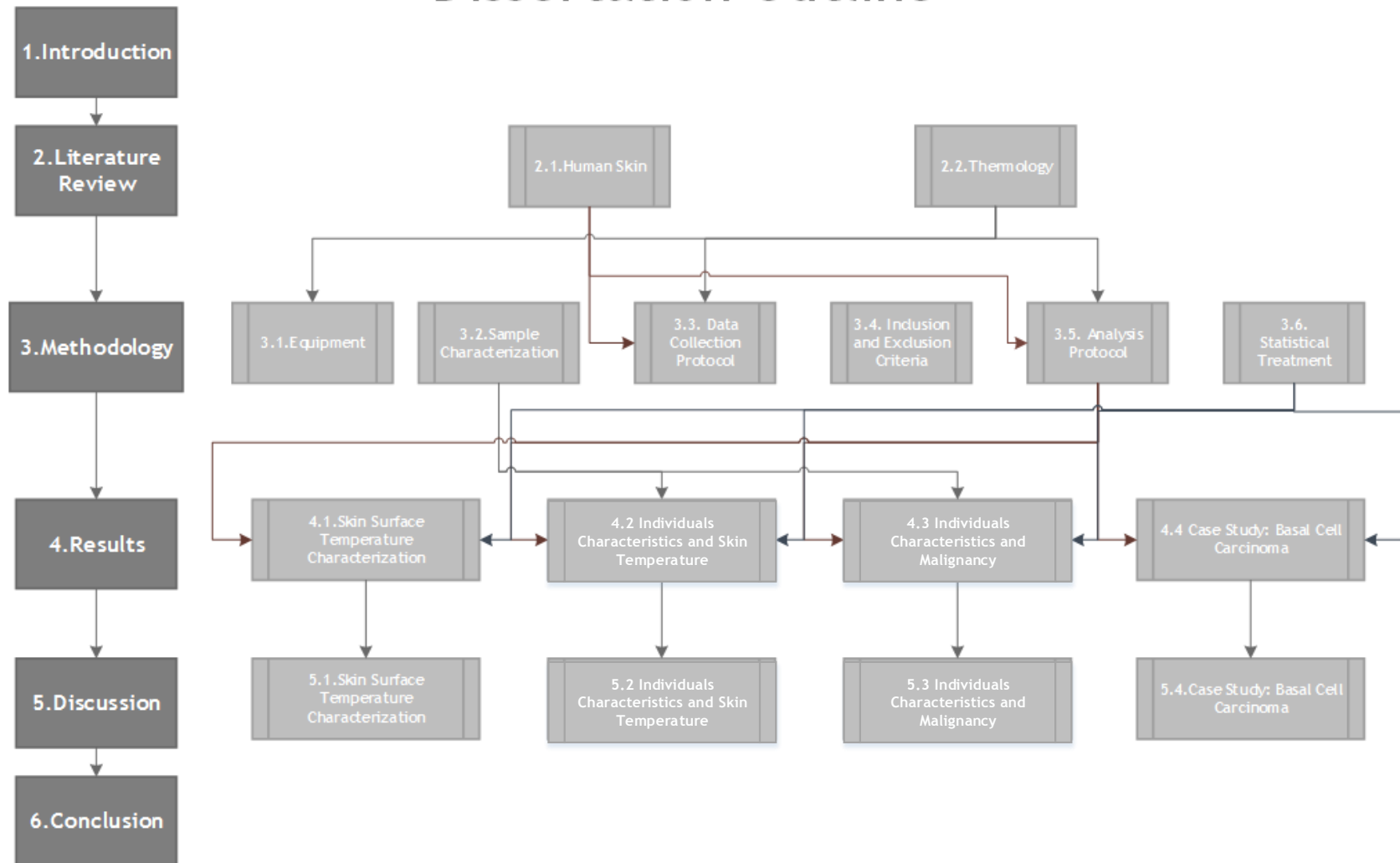


Figure 1: Dissertation Outline.

Chapter 2.

Literature review

As a start, it is important to understand the anatomy of the skin, nerves, arteries and veins, the role of skin in thermoregulation, and the neoplasms associated with this part of the body. It is also necessary to understand their risk factors, treatment and diagnosis. Skin Neoplasm is a lump or growth that is formed from abnormal cells.

Thermology is the science that studies temperature and its exchange process. It covers all thermal energy transfer processes such as: heating or cooling. Thus, this encompasses how heat can be exchanged between objects, as well as the features that this process involves. Within this chapter and together with these concepts, a brief introduction of thermography and its physical principles, history and applications in medicine are addressed. The alternative techniques to thermography are also outlined.

2.1 Human skin

The skin is the outer layer of the human body, and his biggest organ, with over 2 m². This extensive area has external environment interaction like sun exposure, resulting on a excessive water loss and insulation [10]. It is composed of a complex structure system: dermis, epidermis and hypodermis [13-15]. The skin possesses, per cm², about 650 sweat glands, 20 blood vessels, over a thousand hair follicles, half a million melanocytes, more than a thousand nerve endings, and also sebaceous glands [10].

The skin protects the body from heat, injury and infection, as well as damage caused by UV radiation from the sun. It stores water and fat, which participates in homeostasis, and plays an important role in thermoregulation [16-18].

The epidermis is the outer layer of the skin, composed mostly of squamous cells on the top and basal cells and scattered melanocytes on the bottom. Melanocytes are responsible for melanin production, the main pigment responsible for skin colour. When the human body is exposed to UV radiation, melanocytes acquire pigmentation, becoming darker [10, 11, 17, 19].

The dermis is the layer under the epidermis, thicker than the latter. The main components of this layer are collagen and elastin fibers. The dermis contains various types of

cells, such as blood vessels, lymphatic vessels and glands. Some of these glands are responsible for the production of sweat, which allows the human body to cool down.

Others produce sebum, which helps keep the body dry. Both reach the surface of the skin through little orifices named pores [10, 13, 17, 19]. Figure 2 shows the different layers of skin, namely epidermis and dermis.

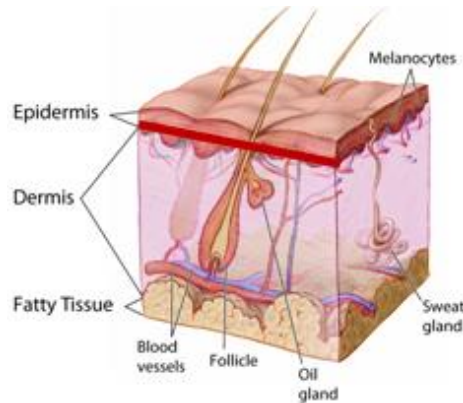


Figure 2: Different layers of the skin, dermis, epidermis and constituents cells [13].

2.1.1 The role of the skin in thermoregulation

Thermoregulation is the ability of an organism to maintain its core body temperature when the temperature of the surrounding environment is different [14]. When the core body temperature increases significantly, it is called hyperthermia, when the opposite occurs it is called hypothermia. The thermoregulation process maintains the core body temperature unchanged, within a constant range, varying only about 0.6°C, even when the organism is exposed to major cold or heat variations [21].

Thermoregulation is performed by a physiological control system, consisting of the central nervous system and peripheral thermoreceptors, an afferent conduction system, a central control for the integration of thermal impulses and an efferent response system which leads to compensatory responses [21].

The hypothalamus lies at the central nervous control system (brain) and regulates the body core temperature by integrating thermal impulses coming from peripheral thermoreceptors. The hypothalamus receives inputs from two sets of thermoreceptors, receptors which monitor the temperature of the blood that goes through the brain, and skin receptors, which monitor exterior temperature. Both supply the necessary information for the body to make appropriate adjustments. When the integrated impulse exceeds or falls below the temperature range, autonomic thermoregulatory responses happen in order to maintain appropriate body temperature.

Due to skin relationship with the circulatory system, skin vessels dilate whenever the temperature rises above the expected, favouring heat exchange with the environment. This process is called vasodilation. Vasoconstriction is the opposite of vasodilation. In case of the

latter, the blood vessels narrow as a result of the contraction of the vessels' muscle wall, in particular, major arteries and small arterioles in response to a cold environment.

Figure 3 shows the vasodilation and vasoconstriction processes, when in a hot or cold environment.

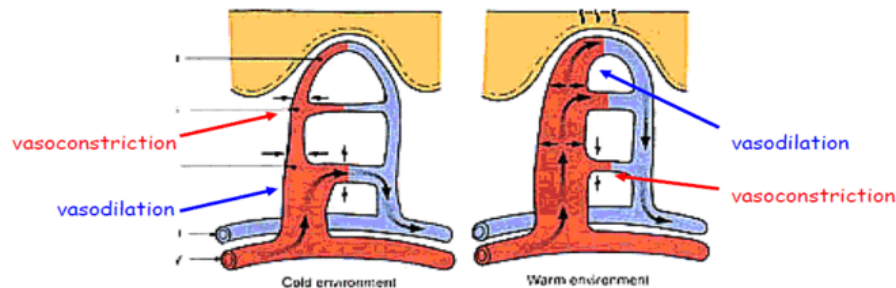


Figure 3: Processes of vasodilatation and vasoconstriction in different environments, on the left cold environment, on the right warm environment [22].

Muscle contractions also act in the regulation of body temperature allowing heat recovering by increasing the internal body temperature. Another characteristic of the human skin is its ability to produce sweat or perspiration, which leads to a rapid temperature decrease [21].

Energy transfer by evaporation occurs by heat action when, a liquid becomes a gas. The human body is formed of approximately 70% of water and a large amount of this is released via the skin (by mucous membranes and breathing) [52].

2.1.2 Anatomy of nerves, arteries and veins of the face

Since the study in control group involves the face, it is necessary to understand its anatomy: nerves, arteries and veins. One of the major nerves of the face is the trigeminal nerve. It is a nerve responsible for sensation in the face and some motor functions such as biting and chewing. It is the largest of the cranial nerves. It has three major branches: the ophthalmic nerve, the maxillary nerve, and the mandibular nerve. The ophthalmic and maxillary nerves are purely sensory, while the mandibular nerve has both cutaneous and motor functions. Parallel pathways in the central nervous system process sensory information from the face and the body.

The dermatomes (area of skin that is mainly supplied by a single spinal nerve) of the three branches of the trigeminal nerve have sharp borders with relatively little overlap. Injury or disease processes, though may affect two or all three branches of the trigeminal nerve, and in these cases the involved branches may be termed as illustrated in figure 4, both the anterior and lateral view [22].

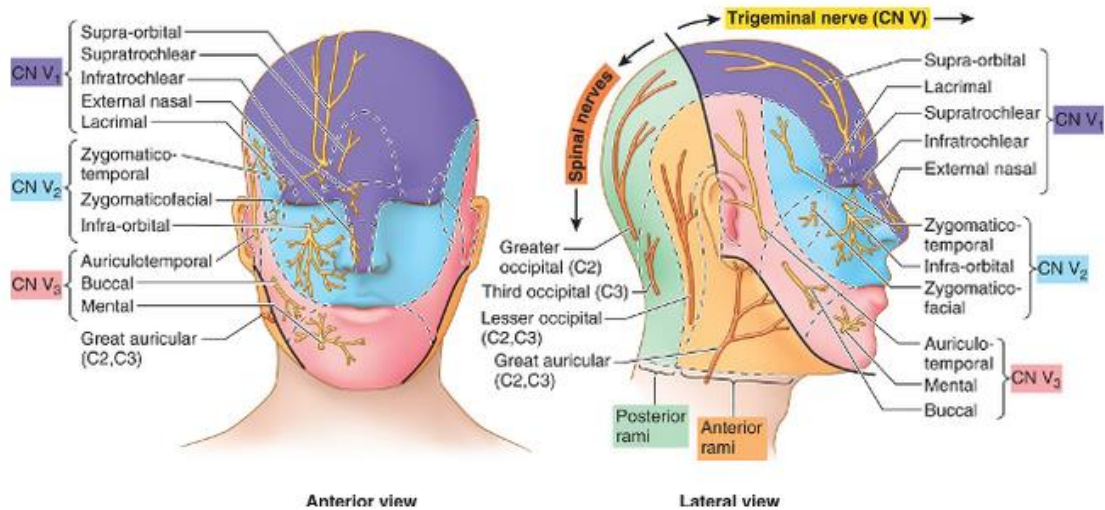


Figure 4: Dermatome distribution of the trigeminal nerve (v1- ophthalmic nerve, v2-maxillary nerve and v3-mandibular nerve) [24].

On the other hand, a series of veins and arteries provides circulation of blood to the various tissues of the face. Most superficial arteries of the face are branches or derivatives of the external carotid artery. It arises from the external carotid artery and winds its way to the inferior border of the mandible. Most external veins are drained by veins that accompany the arteries of the face [23]. The superficial arteries and veins of face and scalp are represented in figure 5.

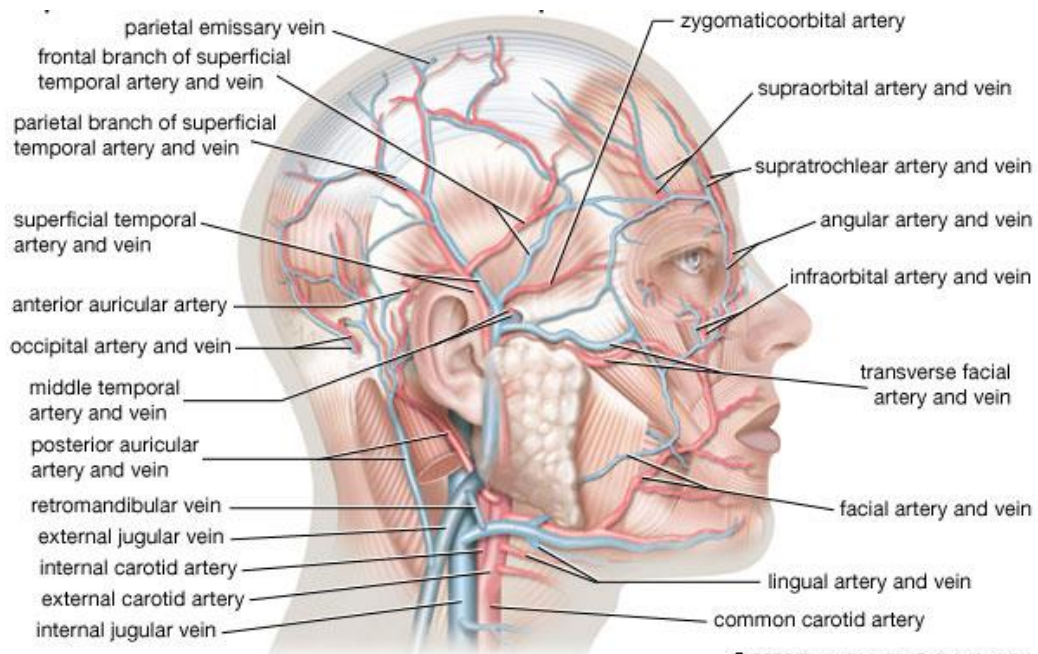


Figure 5: Superficial arteries and veins of face and scalp [26].

2.1.3 Skin Neoplasms

Neoplasm originates in the cells, which are the main components of tissue. Usually, these grow and divide in order to form new cells. During their life cycle, they age, die and are replaced by new cells. However, many times this process does not happen efficiently, leading to the formation of a population of extra cells, which frequently forms a mass tissue called neoplasm. A neoplasm can be benign or malignant, with the latter being called cancer [24].

A benign neoplasm is localized, manifests itself by taking up space, does not invade adjacent tissues, does not metastasize and can be easily removed without growing back. It rarely puts the patient's life at risk [25, 26]. Among these are seborrheic keratosis, actinic keratosis, melanocytic nevus and dysplastic nevus (as can be seen on figure 6). Seborrheic keratosis is a common skin growth that emerges through the epidermis. It may look worrisome, but is benign. Most often keratosis are tan or brown. Actinic keratosis is a rough, dry, scaly patch or growth that forms on the skin. It is considered a premalignant condition. Melanocytic nevi are small patches on the skin which may be flattened or raised. Usually are round and have regular format. The majority of melanocytic nevi appear during the first two decades of a person's life. Dysplastic nevi have different appearance of the melanocytic nevus. Usually are larger than the previous, and their edges can be irregular or undefined.

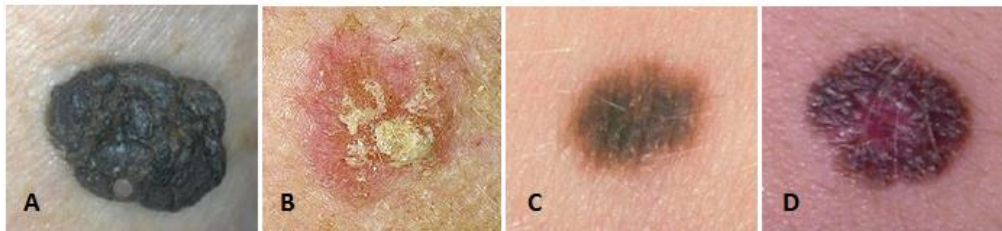


Figure 6: Different types of benign skin neoplasms, A- seborrheic keratosis, B- actinic keratosis, C- melanocytic nevus, D- dysplastic nevus (adapted from [16]).

In contrast, a malignant neoplasm has the ability to invade adjacent tissue, to metastasize, and even after being removed, cells may grow back. Also it has the ability to spread to other parts of the body, which can become fatal for patient [25, 26]. In other words, a malignant neoplasm is characterized by an abnormal cell growth, caused by multiple changes in an individual's gene expression, leading to an uncontrolled balance in cell proliferation, thus causing cellular death [27].

A malignant skin neoplasm is a tumour formed by skin cells which have suffered changes and multiplied abnormally, creating new tissue [17, 26]. According to literature, the most commonly known malignant skin neoplasms are basal cell carcinoma, squamous cell carcinoma and melanoma. On the other hand, the rarest is merkel cell carcinoma.

A basal cell carcinoma begins in the basal cell layer of the skin. It usually appears in parts of the body frequently exposed to the sun. In women, approximately 80% of cases happen in

the head and neck, and can appear quite frequently in the face, torso and lower limbs. It is slow-growing, but, if it spreads deeply, it can cause major damage, especially around the eyes, nose and ears [28].

A squamous cell carcinoma is the most common type of malignant skin neoplasm found in dark-skinned individuals. It is characterized by the uncontrolled growth of abnormal cells, which starts at the squamous cells located in the epidermis. This pathology can occur in all areas of the body, including mucous membranes and genitalia. However, the areas where this type of tumour appear are those more frequently exposed to the sun, such as the earlobes, lower lip, face, scalp, neck, hands and also the legs [29-32].

Melanomas start in the melanocytes that can occur at the surface of the skin. In men, they are frequently found in the head or neck, but they can also be found in other anatomical locations such as the shoulders and hips [17]. In the case of women, they are more commonly found in the skin of the lower legs, between the shoulders or in the hips. Melanoma is rare in darker-skinned people. In this type of population, it appears in areas such as under the finger and toenails, in the palms of the hands or in the soles of the feet [17].

The three most famous types of malignant skin neoplasm can be seen in figure 7.



Figure 7: Different types of malignant skin neoplasms, A-basal cell carcinoma-, B-squamous cell carcinoma, C-Melanoma (adapted from [28], [29]).

Merkel cell carcinoma is a very rare type of skin cancer that affects merkel cells. These cells are found in the top layer of the skin and are very close to the nerve endings that receive the sensation of touch. Merkel cell carcinoma forms when merkel cells growth out of control. Tends to grow quickly and to metastasize (spread) at an early stage.

Besides what has been previously mentioned, the high skin temperature frequently observed in skin neoplasms is caused by an increased blood flow in the affected area. This blood flow can happen due to hyper-vascularization (an increase in the size of blood vessels) associated with neoplasm malignancy, or a higher blood flow through microvascular structuring [26, 33].

2.1.3.1 Skin cancer risk factors

There are multiple risk factors associated with the onset of skin cancer. The risk factors described in literature and which are common to these three types of cancer are exposure to sunlight, deep sunburns, use of tanning beds, personal clinical history, family history, skin that burns easily and some clinical conditions (such as some immunosuppressant drugs,

antibiotics, hormones or antidepressants which make the skin more sensitive, and some clinical conditions that suppress the immune system) [17].

The high risk factor associated to the development of skin cancer is exposure to UV radiation [34]. When the skin is under intense sunlight, its immune system is weakened, which means the genetic material of the cells is damaged and changed, i.e., DNA is directly affected [35]. The damage caused by UV radiation cannot be eliminated by the human body defence mechanisms. As such, this incorrect information is transmitted to future daughter cells, and can later lead to skin cancer [36-38].

Similarly, severe sunburns, present themselves as a result of prolonged sun exposure, increasing the probability of contracting skin cancer, as that reaction indicates that a large quantity of UV radiation has deeply penetrated the skin [39].

Additionally, tanning beds used in tanning salons contain artificial tanning lamps, which offer a quick and effective alternative to natural sunlight. However, there is growing evidence that UV radiation emitted by these lamps can damage the skin and significantly increase the probability of developing skin cancer [36, 37].

The person's clinical history is also important, since a patient who has had one of these types of neoplasm before has an high risk of developing another type of skin neoplasm [38]. Family history must also be considered a risk factor. Melanoma can be hereditary, if anyone has two or more close relatives who have contracted melanomas, there is an higher probability of later developing this disease. About 10% of all people with melanoma has a family history of this condition [5].

Other important risk factors include skin that burns easily, people with freckles, low phototype, light hair, blue or grey eyes, red or blond hair and also clinic conditions such as some antibiotics, hormones, antidepressants (increase skin sensitivity) [5].

In the case of basal cell carcinoma and squamous cell carcinoma, there are more specific risk factors, such as old scars, burns, ulcers and inflamed skin areas, arsenic exposure and radiation therapy [17, 40-42].

For the particular case of squamous cell carcinoma, actinic keratosis and Human papillomavirus (HPV) are considered to be risk factors [43-45]. Finally, when it comes to melanomas, other than what has been previously indicated, one should also consider risk factors such as the dysplastic nevi. These are benign nevi, and not common, which can resemble melanoma, and people with a large number of this type of nevus spread over their bodies are more likely to later develop melanomas [46, 47].

2.1.3.2 Diagnosis and treatment

Much dermatological pathologies can be diagnosed through their clinical appearance, i.e. what they look like to the naked eye. The characteristics of an early clinical diagnosis are similar, regardless of the medical location. It is essential that doctors are able to recognize these characteristics [48].

Unlike benign pigmented lesions, which are usually round, symmetrical and have regular borders, malignant lesions are usually asymmetrical and their borders are irregular. Unlike pigmented lesions, melanomas can present various shades between brown and black and have diameters larger than 6 mm. Thus, this classification can be made for the superficial spreading melanoma, based on the ABCD classification system (A-asymmetry, B-border irregularity, C-colour variation, D-diameter) [49]. The differences between malignant neoplasms and benign neoplasms based on the ABCD classification can be seen in figure 8.

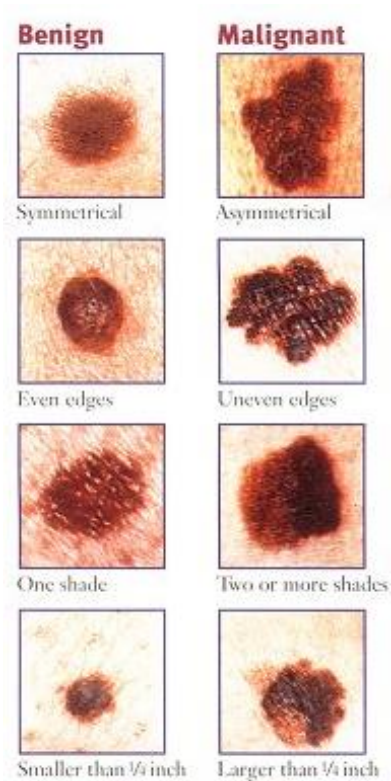


Figure 8: Differences between benign and malignant neoplasms relative to ABCD analysis [50].

In table 2 are described the different diagnosis techniques and treatment options to the four types of skin cancer.

Table 2: Different diagnosis techniques and treatment options to the various types of skin cancer [5, 17].

Types	Diagnosis	Treatment
Melanoma	Medical history and physical exam (ABCD and Woods examination) Biopsy (punch or excisional or incisional) to confirm. To determine the extent: Sentinel lymph node biopsy Imaging tests (CT, MRI and PET)	Surgery Chemotherapy Immunotherapy Radiation therapy Targeted therapies (vemurafenib, trametinib, dabrafenib, and ipilimumab)
Basal cell carcinoma	Medical history and physical exam Biopsy (punch or excisional or incisional) to confirm.	Surgery (excision, Mosh surgery and Cryosurgery) Curettage and electrodesiccation Topical treatments (imiquimod and fluorouracil)
Squamous cell carcinoma	Medical history and physical exam Biopsy (punch or excisional or incisional) to confirm.	Medication - vismodegib (advance stage) Surgery (excision, Mosh surgery and Cryosurgery) Curettage and electrodesiccation Radiation therapy Photodynamic therapy Laser therapy Chemotherapy creams (5-fluorouracil)
Merkel cell carcinoma	Medical history and physical exam Biopsy (punch or excisional or incisional) to confirm. To determine the extent: Sentinel lymph node biopsy Imaging tests (CT, MRI and PET)	Surgery (excision and Mosh surgery) Lymphadenectomy Radiation therapy Chemotherapy

2.2 Thermology

Thermal energy transfer can occur through four different mechanisms individually, or often simultaneously: conduction, convection, radiation and evaporation. The necessary condition for a heat transfer is the existence of a temperature differential or thermal imbalance.

Conduction can be described as a mechanism that transfers thermal energy through a contact between two solid masses [51].

Convection is a process of thermal energy transfer between a solid surface and an adjacent moving substance (liquid or gas). In natural convection, the fluid motion is due to density difference, which is caused by temperature difference. In induced convection, the fluid motion is caused by external forces (for example a ventilator) [51].

Energy transfer by radiation results from the radiant emission (electromagnetic or photonic) by a body with a temperature above $-273.15\text{ }^{\circ}\text{C}$ (0 Kelvin). Radiation is a volumetric phenomenon because it is related to the system volume. All solids, liquids and gases emit, absorb, or transmit radiation in various degrees. In solids, however, the radiation is normally considered as a superficial phenomenon. This happens because the internally emitted radiation never reaches the surface and the incident absorbed radiation reaches only a few microns of thickness surface [51].

Thermography is a technique that allows mapping a body or region skin surface temperature. The use of thermography has various applications such as electrical installations, testing of structures and entire buildings, meteorology and medicine [54].

2.2.1.1 Physical principles

The amount of radiated electromagnetic energy of an object is directly related to its temperature. An object can be characterized by its capacity of absorbing or emitting electromagnetic radiation [55].

Infrared radiation occupies in the spectrum the region between the visible and microwave radiations. All objects in the universe emit radiation in the infrared region as a temperature function. When an object becomes warmer, it emits a more intense infrared radiation and radiates with a shorter wavelength. Figure 9 illustrates the electromagnetic spectrum in terms of frequency and wavelength. The human eye cannot detect infrared rays [55, 57-59].

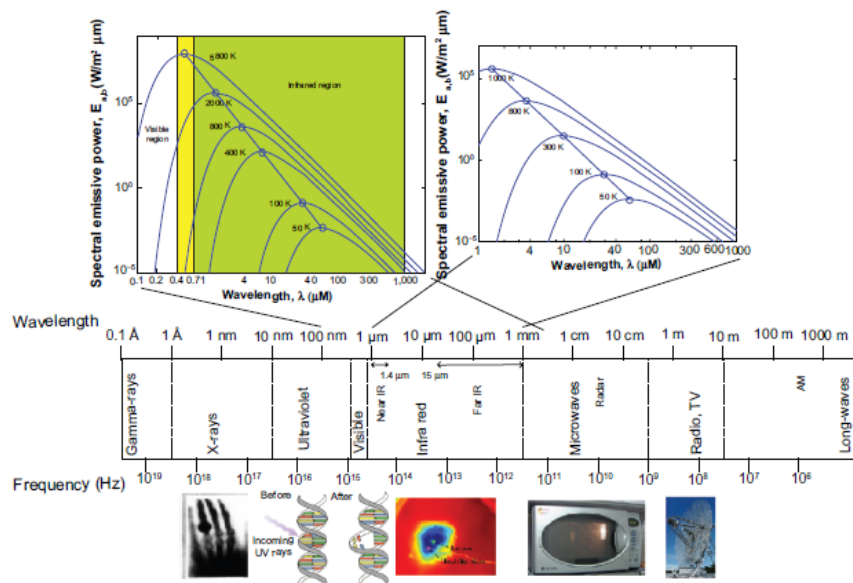


Figure 9: Frequency and wavelength of the electromagnetic spectrum [56].

Stephan-Boltzmann law states that the total energy radiated by a black body, both per unit of surface area and unit of time is directly proportional to the fourth potency of its thermodynamic temperature T . Stephan-Boltzmann law can be expressed as:

$$R_t = \sigma T^4 \quad (1)$$

where R_t represents the total radiance (W/m^2), σ the *Stephan-Boltzmann* constant ($5,6697 \times 10^{-8} W \cdot m^{-2} \cdot K^{-4}$), and T the absolute temperature emitted by the material (K).

2.2.1.2 Infrared Cameras

Although infrared radiation is not perceptible to the human eye, infrared cameras are able to convert it into an image that depicts thermal variations across an object surface.

Thus, infrared cameras are instruments used in thermography to monitor and record the surface temperature of an object [55].

Thermal cameras can have lens with different angles, the normal angle is 24° (for closer distances) and the wide angle lenses 45° (for longer distances) [62].

It is also important to consider other features in respect to these cameras, such as temperature range, thermal sensitivity, thermal resolution, spatial resolution, accuracy and responsivity.

The *temperature range* is the sensor ability to detect heat waves along a certain range of temperatures.

Thermal sensitivity defines the ability to distinguish changes between energy levels. It is expressed in terms of temperature. A low value implies high sensitivity. The most commonly used methods for thermal sensitivity are the noise equivalent temperature difference (NETD) and the minimum detectable temperature (MDT).

The *minimum resolution* of an instrument is defined as the smallest difference that the instrument is capable to distinguishing. The resolution can be quantified in two ways, minimum resolvable temperature difference (MRTD) and slit response function (SRF).

Spatial resolution is the number of the pixels of image, given by columns and lines.

Accuracy is the measure of how close the object temperature is to the true value (typically $\pm 2\%$ of the overall reading) [57].

2.2.2 Medical Thermography

Contact thermometry for many years was the only available method to determine human temperature. Thermometry was slowly developed by Galileo experiments in 1592 [63, 64]. Sanctorio Sanctorius, an Italian physiologist, who invented a clinical mouth thermometer, gave a major step. With this new technology Sanctorius performed quantitative experiments with temperature, respiration, weight, and insensitive perspiration, which laid the foundation for metabolism investigation.

Carl Wunderlich, a German physiology and diagnostic methodologist expert became known for characterizing several conditions [65, 66].

In 1800, William Herschel, an amateur astronomer, discovered the existence of infrared radiation. In 1840, after the death of William, John Herschel, his son drew a simple picture of the evaporation process due to a mixture of carbon and alcohol using focus sunlight, which he called "thermogram" [67].

JD Hardy, an American physiologist, in 1935, demonstrated that the surface of human skin has similar characteristics of a blackbody radiator, being highly efficient at radiating heat exchange [68].

Meanwhile, Professor Samuel Langley provided a major contribution by developing the bolometer, an instrument used in the measurement of incident electromagnetic radiation. This tool forms the basis for a new generation of heat sensors technology.

In UK, Dr. Max Cade built an infrared thermographer, using an indium antimonide electronic detector (InSb). Then, it was created in 1960 the Pyroscan, the first British medical thermographer [67].

The first study published with the thermography application in medicine, was performed by Ray Lawson et al., in 1956, where patients with breast cancer were examined by asymmetric hot spots and vascularity in medical thermography images [69]. The role of this technology in medicine has increased [33, 71-73]. Such advances include a new generation of infrared technology, intelligent image processing algorithms, and better physiological understanding of the captured images. Thus, thermography becomes a new way to monitor the temperature, non-invasive, non-ionizing, unexpensive, convenient and well accepted by the patient.

Medical thermography is a technique based on skin surface temperature analysis (figure 10).

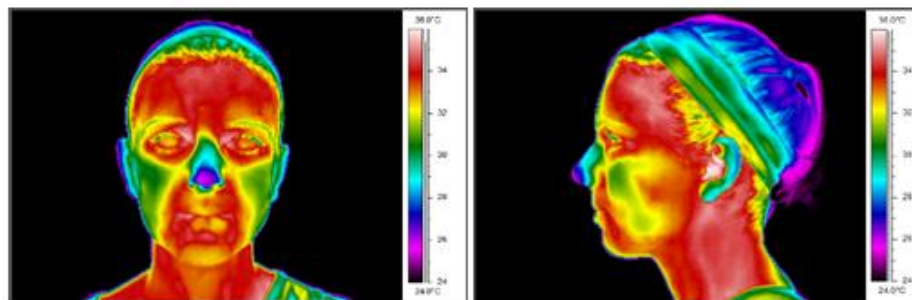


Figure 10: Thermography of woman face in two different positions.

This technique is passive, and relies in the registration of the thermal radiation emitted by the skin surface through an appropriate instrument that creates an image of the surface's temperature. The protocol recommended for medical thermography defines that the environment temperature should be between 18 and 24 °C to facilitate the thermal equilibrium [9, 74, 75].

2.2.2.1 Thermography in Dermatology

The clinical use of thermography in dermatology was first reported by Brasfield et al. [76] in 1964, which indicated the hyper-thermic finding of cutaneous melanoma.

In the following years, many researchers [76-98] had been concerned to investigate the application of medical infrared imaging in the area of dermatology. Thermography research has its focus in four main fields: melanoma diagnosis, follow-up of skin cancer, basal cell carcinoma diagnosis and temperature differences in skin surface.

2.2.2.1.1 Melanoma Diagnosis

In 1977, Tapernoux B. et al. [77], investigated thermography as a tool for the diagnosis of malignant melanoma, and demonstrated a correlation between hyperthermia and malignancy in about two-thirds of the cases examined.

Similarly, Diem et al. [78] evaluated the ability of contact thermography in cutaneous melanomas diagnosis. It was suggested that this technique should be used only as complementary method. It was concluded that positive thermograms should lead to a malignancy diagnosis without being pathognomonic of malignancy.

In contrast, Cristofolini et al. [79] suggested that thermography is useless for diagnosis and follow-up of cutaneous malignant melanomas. They concluded that false-negative and false-positive thermograms of metastatic lymph nodes, subcutaneous nodules and removal site of cutaneous malignant melanomas were too numerous.

Hartmann M. et al. [80] studied telethermography as a diagnosis of malignant melanoma method. In addition, a complete body thermography is complementary to established examination techniques used in evaluation of patients with malignant melanomas. By making visible hypo- or hyper-thermic areas, it helps to detect metastases and confirms or denies suspicious findings obtained by other examination methods.

In 1985, Michel U. et al [81] used infrared thermography in a group of clinically suspected patients of having primary malignant melanoma, suggesting that the larger malignant melanoma was warmer in comparison with the smallest. The highest measurements of infrared radiation were obtained in the nodular and acrolentiginous malignant melanoma, when compared to other melanoma types.

Later, studies of Novak OP. et al. [82] proved that the examination thermographic method was very effective in complex situations, such as patients with complex skin melanomas, early tumour metastasis and recurrence of operative treatment.

Di Carlo et al. [83] described that the usage of different types of thermography, for example, contact thermography or tele-thermography and their clinical applications, with emphasis to melanoma. Tele-thermography is based on the capture at a distance of the infrared energy emitted by the cutaneous surface, and the conversion of this into a video signal. He suggested the application of thermo stimulation assisted tele-thermography to solve the problem of false-negative results reported by other authors [79, 84]. By this procedure it was possible to evaluate the thermogenic capacity of skin lesions against that of the skin in which they are seated, based on the different times of visualization on the screen. In the case of malignant cutaneous tumours, when the skin area concerned is cooled, a very quick hot spot of the tumour follows, given its high esothermic metabolism, whereas the hypothermia of the healthy skin protracts. It was concluded that thermo stimulation assisted tele-thermography can be considered a valid and very useful diagnostic tool, not only in the

diagnosis of skin tumours (particularly melanomas), but also in more extensive applications concerning the microcirculation physiopathology.

Buzug TM. et al. [85] investigated the early diagnosis of malignant skin cancer by functional infrared imaging. It was assumed that malignant melanoma had higher metabolism, increasing blood flow and presented slightly higher temperature when compared to the healthy skin. It was concluded that this method turns out to be promising, especially in the case of basal-cell carcinoma, because it yields a clear diagnostic result.

Cila Herman et al. [86] explored the feasibility of infrared imaging as a cost-effective and non-invasive technique. It was used in optical measurements for tumours detection, particularly on the screening and early detection of melanoma. The data presented were obtained in patients who had a pigmented lesion previously diagnosed by a biopsy. They compared the differences in thermal responses between normal and malignant tissue with the results obtained by the biopsy. They used a protocol for image acquisition that involves various steps. In short, they applied a stream of cold air to the area of the patient's skin containing the lesion as well as a 50 mm diameter-surrounding region, for the duration of one minute. After that, they remove the cooling stress to allow the skin to re-warm at room temperature. During the thermal recovery phase, infrared images of pigmented lesion were captured every 2 seconds. Finally, all IR images were saved and stored using the LabVIEW software. IR images are analyzed using a Matlab code in order to obtain accurate transient temperature distributions on the skin surface. The conclusion was that increased metabolic activity of melanoma lesion could be detected through dynamic infrared imaging.

Later, in 2012, Amber L. Shada et al. [87] tried to obtain preliminary estimation of the sensitivity of infrared images for the melanoma metastasis detection, and also to detect metastases, primary on melanomas and nevi. It was also evaluated the reliability of thermography in terms of time logistic constraints and patients tolerability. The conclusion was that melanomas with more than 15 mm of diameter are able to be distinguished from other lesions with excellent sensitivity and specificity (95% and 100% respectively). On the other hand, thermography proved to be tolerant and highly reliable in clinical scenario. Finally, they also observed a great potential of this technique in the evaluation of tumour response to systemic therapy.

Recently, in 2014 Mathias Bonmarin et al. [88] evaluated lock-in thermal imaging for the early-stage detection of cutaneous melanoma. They used a computational model to derive the transient temperature of skin surface subjected to periodic convective heat transfer. The technique demonstrates a great ability to reject disrupting thermal signals coming from sub-cutaneous circulatory and metabolic variations. It was concluded that lock-in thermal imaging exhibit a high signal-to-noise ratio and due to its ability on suppress lateral heat spreading, allows an accurate detection of lesion margins.

2.2.2.1.2 Follow-up of skin cancer

Bourjat P. et al. [89] investigated various malignant melanoma cases which had not been subject of surgical intervention, and proposed a prognostical classification that enables a malignancy evaluation. They also investigated thermography in follow-up detection of local recurrences and/or lymph-node metastases in an infra-clinical state.

Later, Michel U. et al. [90] performed the same study, but with patients with malignant melanomas. They used the preoperative infrared tele-thermograms that were obtained from the draining lymph node, in order to be compared with the clinical and histologic research data. They concluded that the majority of cases (around 95%) with metastatic spread of malignant melanoma had a considerable degree of hyperthermic radiation in the respective axillary or inguinal area.

In 2009, G. A. Santa Cruz et al. [91] investigated the ability of dynamic thermography in monitoring melanoma patients who are treated with Boron neutron capture therapy (BNCT). It was explored the potential of this technique to evaluate early changes in normal skin, as well as the evolution of the tumour after treatment. These authors concluded that thermography might be a useful and sensitive tool to study skin toxicity and control of melanoma treatments with BNCT. This technique can also help locate abnormal regions with high temperature as nodules of melanoma, which are virtually invisible on CT images because of their small contrast differences when compared to normal tissue.

In the same year, Babak Kateb et al. [92], briefly discussed the current status of intraoperative imaging modalities including Intraoperative Thermal Imaging (ITI). It was also presented a case report that evaluated the usefulness of ITI in brain tumour detection and its margins, more specifically in a patient with a metastatic intracortical melanoma. The results of this study suggested that thermal imaging could be used to provide a rapid, non-invasive and real-time intra-operative technique. They concluded that ITI was a cost-efficient imaging method to assist surgeons in identifying tumour location and potentially detect vasculature and other acute abnormalities during the surgery.

Mikulska et al. [93] performed a comparative study with dermoscopy, thermography and histopathology of cutaneous melanocytic nevi. They concluded that thermography may supplement dermoscopy during examination of atypical melanocytic nevi and other skin lesions suspected of neoplastic metaplasia. Additionally, average temperatures of benign and atypical melanocytic nevi do not differ significantly from the average temperature of the skin without pigmented lesions.

A transient thermal imaging system was developed in 2011 by M. Pirtini Çetingül. [1], that allows a more accurate measurement of temperature differences in skin surface. The aim was to aid the detection and diagnosis of metabolically active or malignant skin lesions. It was observed that the feasibility of this technique to distinguish benign from malignant pigmented lesions, and thus, quantify the malignant potential of lesions. The data obtained

from benign and malignant images was compared, and more specifically, correlated the thermal recovery images and data with biopsy results to define thermal associations with malignant potential. Geometrical data obtained from the digital and dermoscopy images was also used and a biopsy report in its computational model to simulate the thermal response of the analyzed lesion. At the end, the results from the modelling effort were compared with clinical data. The thermal response of benign lesions was found to be similar to that of healthy skin tissue. This difference can be used to identify malignant lesions and quantify their malignant potential. On the other hand, the computed results showed that the lesion parameters and properties can be estimated and the influence of malignant lesion on the transient thermal response can be quantified with their computational model.

2.2.2.1.3 Basal Cell Carcinoma Diagnosis

In 1981, several studies were performed. Ratz JL et al. [94] described Liquid-crystal thermography as it is applied to basal-cell carcinomas. Results indicated that it is useful for moderate to heavy cellular density neoplasms but little help in outlining neoplasms of low cellular density like morpheaform basal-cell carcinomas.

In 2011, J.H.Flores Sahagun et al. [95] performed an evaluation of infrared imaging viability in the basal cell carcinoma diagnosis using a normalized conjugated gradients methodology. It was proposed a methodology that has been tested by temperature measurements using infrared imaging and a healthy control group to establish expected normality ranges of basal cell carcinoma patients. The proposed method allows the comparison of measured dimensionless temperature difference values between two symmetric regions of patient's body, taking into account the skin, the surrounding ambient and the individual core temperatures. It was concluded that the normalized conjugated gradients method was simple and capable to differentiate normal from injured tissue and also the conjugated gradients method was efficient to identify injured tissue. It also concluded that the use of dimensionless temperature compensates the temperature readings with respect to variations in the individual's metabolism and ambient temperature at the particular location of the exam.

2.2.2.1.4 Temperature differences in skin surface

Amalric et al. [96] investigated the ability of dynamic tele-thermography in the direct observation of infrared rays emission from the skin of the human body. A number of dermatological diseases such as malignant melanomas can modify this emission and show a larger variation in skin temperature. They defended that other skin black tumours may also benefit from this method.

M. Pirtini Çetingul jointly with other researchers had published several interesting studies [1, 97, 98] with the aim of helping the detection of early malignant lesions in the skin. In 2008, a study [31] based in the use of transient thermal response of skin layers, allowed the determination of the temperature distribution that reflect the properties of subsurface

structures such as lesions. The evaluation of this study was performed by sensitivity metric of the following variables: the surface temperature distribution, variations of thermo-physical properties, blood perfusion rate and thickness of skin layer. First, the model was used to investigate the importance of the aforementioned parameters for surface temperature distribution. Next, the time evolution of the infrared signal was analyzed after a cold stress that was applied to human skin. By considering both, the steady state and transient results, information about the size and depth of masses within the skin layers was registered during recovery. It was observed that variations in these parameters had minimal effects on surface temperature distribution. By selecting the duration of cooling stress, the internal temperature of the skin changes, and this change can be felt at different depths. One year later, the same investigators [98] developed a thermographic system that allows accurate measurement of small temperature differences on the skin surface. This study's purpose was mainly diagnose malignant and pigmentation skin lesions in an early stage of the disease. The method developed by these authors was based on active thermography and a multimodal image analysis strategy, including correction of involuntary body movements and segmentation of pigmented lesions in order to detect malignancy. The system described in this study was tested in a group of patients who had pigmented lesions and also clinical indication for biopsy. The lesions and surrounding tissue received a source of cool air for a period of time (between 30 and 60 seconds). The thermal recovery was recorded by an infrared camera, generating an image of the lesion after the application of the cold source. It was concluded that the benign lesions had a similar thermal recovery to normal skin, while melanomas presented a higher temperature than healthy skin during the process of thermal recovery.

2.2.2.2 Thermal symmetry

A region of interest (ROI) is a selected subset of samples within a dataset identified for a particular purpose. Thermal symmetry is defined as the degree of similarity between two ROIs, mirrored across the human body's longitudinal main axes which are identical in shape, identical in size, and as near identical in position as possible. Based on the fact that the human body is bilateral and practically fully symmetrical with respect to its extremities, the indication is that the human body can have bilateral temperatures symmetry between two ROIs in co-lateral locations.

Significant differences in bilateral temperatures symmetry can be related to pathological states such as structural abnormalities of blood vessels, abnormalities of vascular control, local effects on blood vessels, changes in thermal conductivity of the tissues and increased heat production in the tissues.

Table 3: Thermal symmetry of some ROIs using Medical Thermography [99, 100].

Region of interest	Mean and SD values
Face	0.30 ± 0.20
Neck	0.40 ± 0.30
Arm, upper	0.50 ± 0.40
Forearm, dorsal	0.50 ± 0.30
Forearm, volar	0.30 ± 0.20
Trunk, upper	0.30 ± 0.20
Trunk, medium	0.40 ± 0.30
Trunk, lower	0.30 ± 0.20
Back, upper	0.20 ± 0.20
Back, medium	0.30 ± 0.20
Back, lower	0.30 ± 0.30
Leg, anterior	0.30 ± 0.30
Leg, posterior	0.20 ± 0.20
Thigh anterior	0.20 ± 0.20
Thigh posterior	0.20 ± 0.10

The values taken in consideration are the mean temperature of the ROI and its standard deviation. Table 3 shows these values from the regions of the body that were studied [99, 100].

2.2.3 Non-invasive competing techniques

In this subsection some alternatives to medical thermography are presented as well as their advantages and disadvantages and subsequent comparison with infrared thermography.

2.2.3.1 Contact Thermography

According Sherman et al. [101], the majority of contact thermography systems consists in series of detectors and flexible pillows, generally about 18 (within 46 cm) on each side, containing crystals vectors that changes colour corresponding to a specific temperature. The crystals that are sensitive to different temperatures are closely spaced to form similar pixels to those that produce colloidal images on a TV screen.

In this technique, the pillow is pressed against the body part to be analyzed, and then a colour image is produced with multiple pixels. Temperature differences are required to produce various colours. The differences between each colour may vary from 0.3 to 1.1 °C. This device is theoretically accurate to 0.2 °C [101].

The main advantages of this technique is cost effectiveness, easy to use and calibrate, is suitable for curved surfaces, have a high spatial resolution and it can be reusable [55].

However, the readings are ordinal, but not continuous, because the data are limited to parametric statistical methods and comparisons between devices are limited to non-parametric methods. Contact thermography cannot be used to long term records because the pressure exerted by the plastic screen in the body, changes the heat surface patterns. Also has difficulty reading temperatures on low lighting conditions, has a limited range of temperature and it is a slow technique, because there is the need for a slow photographic record [55, 101].

2.2.3.2 Laser Doppler Flowmetry

According to Frerichs et al. [102], Laser Doppler Flowmetry technique allows a non-invasive and continuous measuring of the local microcirculation and blood flow. The flow estimate is based on the evaluation of the Doppler shift with low-energy laser light, which is scattered by the moving red blood cells [103].

2.2.3.3 Laser Doppler Perfusion Imaging (LDPI)

According to Serov et al. [104], LDPI is an interferometric technique successfully used on two-dimensional visualization of microvascular flow maps and a large number of clinical investigations, including cardiovascular disease, skin irritations, diabetic condition, organ transplantation and burns. Two-dimensional flow maps are obtained by successive measurements of predetermined points.

Fujii et al. [105] and Briers et al. [106] proposed an alternative method, full-field flow imaging techniques, which use a contrast analysis using stains/splashes to monitor blood flow.

2.3 Summary considerations

The traditional method used to diagnose the skin cancer is biopsy. However, medical thermography has shown great potential in the clinical diagnosis of various situations, including some skin cancers. Medical thermography allows mapping a body or region of skin surface temperature. This technique enables the detection of inflammation, as well as changes in functional activities, even when there are no changes at the physical level. The other complementary diagnostic methods do not reveal these information.

Chapter 3.

Materials and Methods

The methodology used in this study lies in the characterization of the temperature distribution in patients with skin neoplasms, and follow-up of skin neoplasms and asymptomatic individuals. This is a retrospective and observational study, it is based on a quantitative methodology, analyzing the data systematically and establishing relationships between variables, in order to characterize the problem. In this chapter the necessary equipment for image acquisition is described, as well as the sample characterization, the data collection and analysis protocol.

3.1 Equipment

The equipment used for data collection includes the infrared camera FLIR A325, the data logger Testo 175 H, a tripod and a VTR-16P fan (220-240 V, 50 Hz, 60 W). The FLIR A325 infrared camera is designed from the ground-up to deliver accurate thermographic imaging and repeatable temperature measure necessary in this study. In all collections the camera was placed at approximately 80 cm from the individual, with a 90° angle and over a tripod at 120 cm height. The main features of this infrared camera includes a 320x240 pixels of resolution a <50 mk of sensitivity and a accuracy of $\pm 2\%$ of the overall reading.

The Testo 175 H is a professional data logger used for monitoring temperature and relative humidity in enclosed places. Figure 11 illustrates the equipment used in the present study for capturing thermographic images in controlled environment.

Regarding software, it was used *FLIR RESEARCHER PRO 2.10* which provides tools for data display and analysis. For selecting regions of interest and to extract data, *FLIR tools* software was used. To gather, organize and storage the measurement data was used the Microsoft Excel 2013. Finally, for statistical analysis Statistical Package for the Social Sciences 22 (SPSS Statistical 22) was used [62, 107].

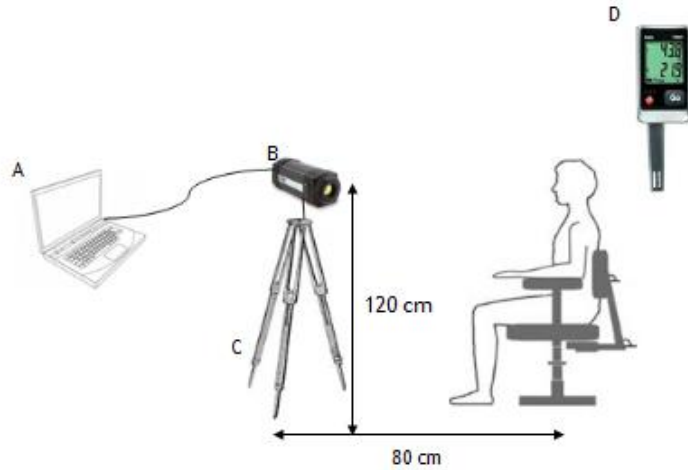


Figure 11: Equipment for capturing thermographic images, A- Computer, B- Thermographic Camera, C-Tripod, D- data logger Testo 175 H.

3.2 Sample Characterization

The present study is characterized as prospective because it examines two groups; one of healthy people (control group) and one with skin neoplasms (oncologic group). The skin neoplasm group is divided into recently diagnosed individuals and follow-up individuals (people who underwent surgery within a period of two weeks to eight years before). The group proportions are presented in the figure 12.

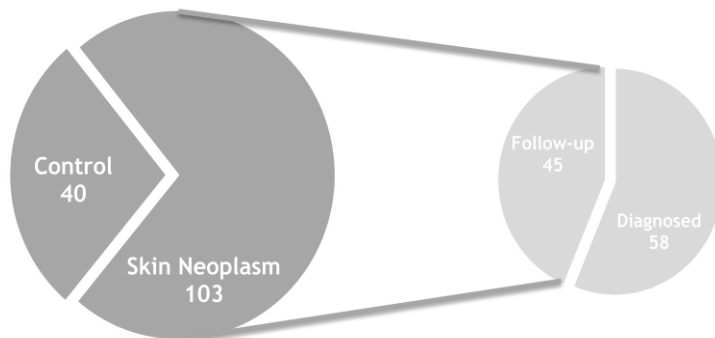


Figure 12: Composition of the population proportions of each group.

Data collections of asymptomatic individuals were performed at the Faculty of Engineering of University of Porto (FEUP) and patients with skin neoplasms in the Portuguese Oncology Institute of Porto (IPO-Porto), more specifically in the Plastic and Reconstructive Surgery Service. The general conditions of room relative humidity and temperature for both groups are show in figure 13 and 14. Box plots were used to locate and analyze the variation of relative humidity and temperature variables. For the control group, relative humidity showed little variations, having a mean value of 44.30% and a variance of 20.46. The temperature also was maintained always within a small acceptable range (<24°C). However,

there were two outliers (stars and circles) outside the upper quartiles, indicating discrepant values.

For the oncologic group, room humidity had more variations, having a mean value of 55.58% and a standard deviation of 0.75. The temperature had small variations, having a median of 24.10 °C and a standard deviation of 0.57. These temperature values are higher than desired. However, there was also an outlier (circle) below the lower quartile.

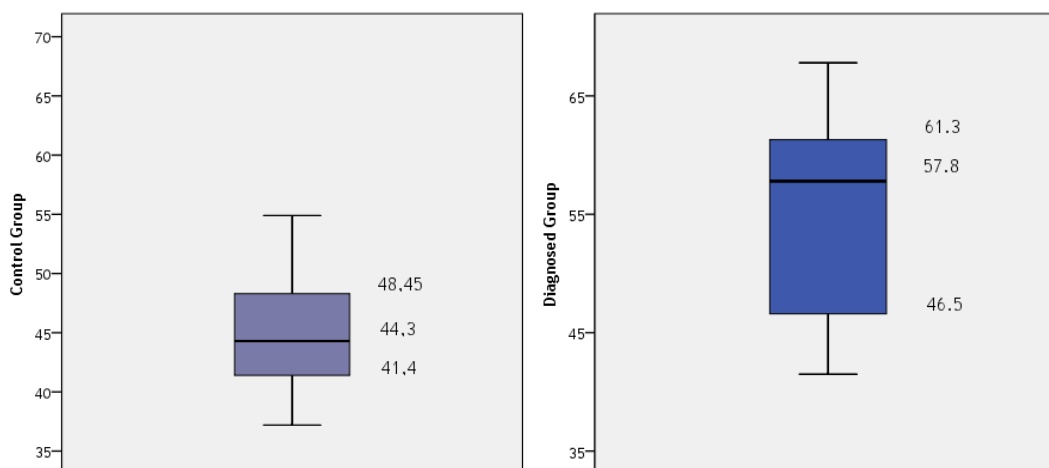


Figure 13: Room humidity distribution in both groups.

At FEUP, 42 volunteers were collected, 23 female and 17 male, where 2 were excluded because they did not meet the inclusion criteria. Data collections at FEUP occurred during the month of May 2014.

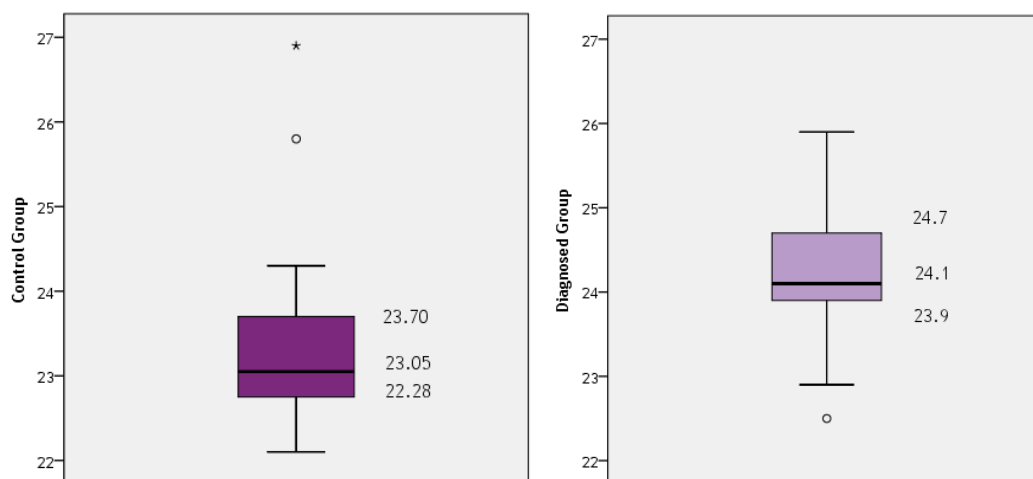


Figure 14: Room temperature distribution in both groups.

At IPO-Porto, 108 lesions in total were collected. Five lesions were excluded because they didn't meet the inclusion criteria. Of the remaining 103, 58 belonged to diagnosed group (26 female and 32 male) and 45 to follow-up group (24 female and 21 male). On the diagnosed group, 75.9% were malign and 12.5% of the follow-up group were benign. Data collections in IPO-Porto occur one day a week since June until August of 2014.

The general specifications of each group, mean and standard deviation are presented in Table 4. Regarding the diagnosed and follow-up groups, the number of different types of neoplasms were analyzed. Particularly, benign neoplasms (melanocytic nevus, atypical nevus, seborrheic keratosis, actinic keratosis) and malignant neoplasms (basal cell carcinoma, squamous cell carcinoma, melanoma and merkel cell carcinoma).

Table 4: General specifications of each group in terms of mean and standard deviation.

	Characteristics	Diagnosed	Follow-up	Control
Subject	Age	70.0 ± 336.99	69.0 ± 323.65	23.0 ± 4.46
	Weight	70.46 ± 13.69	72.60 ± 13.5	65.90 ± 10.34
	Height	1.64 ± 0.12	1.62 ± 0.009	1.70 ± 0.07
	BMI	25.96 ± 3.44	27.12 ± 4.61	22.44± 6.00
	Sun Sensibility	31.0 ± 32.47	32 ± 23.29	29.83 ± 4.59
	N	58	45	40

The type of skin neoplasm more prevalent in the diagnosed group was basal cell carcinoma, with 28 cases followed by 11 cases of melanomas and 8 cases of melanocytic nevus. Within the less prevalent were seborrheic and actinic keratosis with 3 cases (figure 15-b). In follow-up group melanoma stands up with the heights of prevalence, 21 cases, followed by basal cell carcinoma and squamous cell carcinoma with 12 and 8 cases respectively (figure 15-a). Regarding the follow-up group, the merkel cell carcinoma and atypical nevus were only 1 case. As can be seen in figure 15, in both groups there were not reported the same types of skin neoplasms. In the skin neoplasm group atypical nevus and merkel cell carcinoma are inexistent and in the follow-up group weren't found seborrheic and actinic keratosis cases.

Globally, the results were similar, basal cell carcinoma and Melanoma had an incidence of 40 and 32 cases and Merkel cell carcinoma and atypical nevus had only 1 case.

Similarly to skin neoplasm the body localization prevalence of them were analyzed. In the diagnosed group 40 cases were found in individual's face (15 cases on the left side, 12 cases on the right side, 10 cases in the nose and 3 cases in the scalp) and only 1 and 2 cases in the chest and upper limbs (figure 16-b). Contrarily, in the follow-up group the highest incidence were in the individuals back with 10 cases and 8 cases in the upper limbs, as can be seen in figure 16-a.

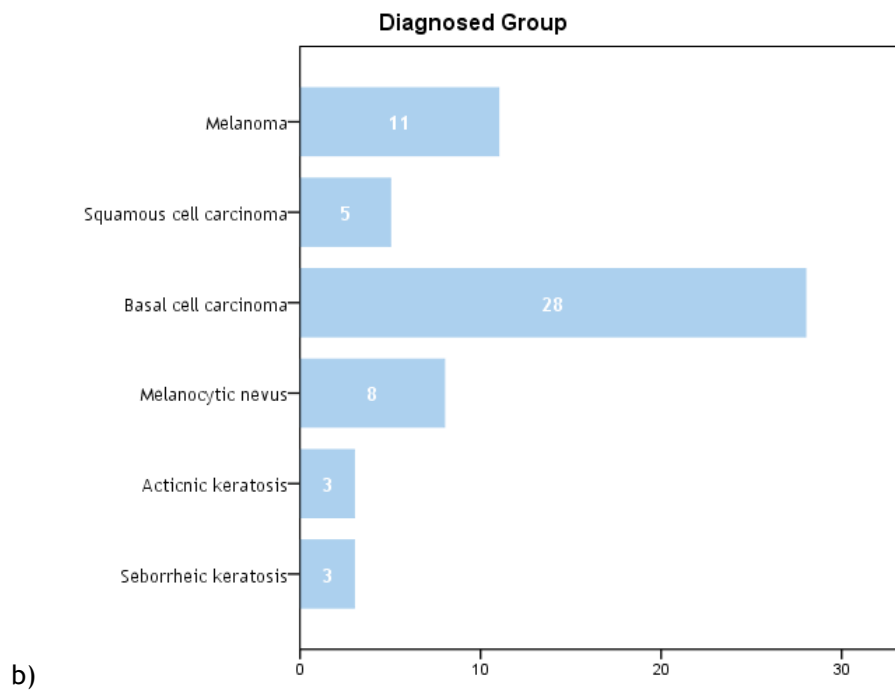
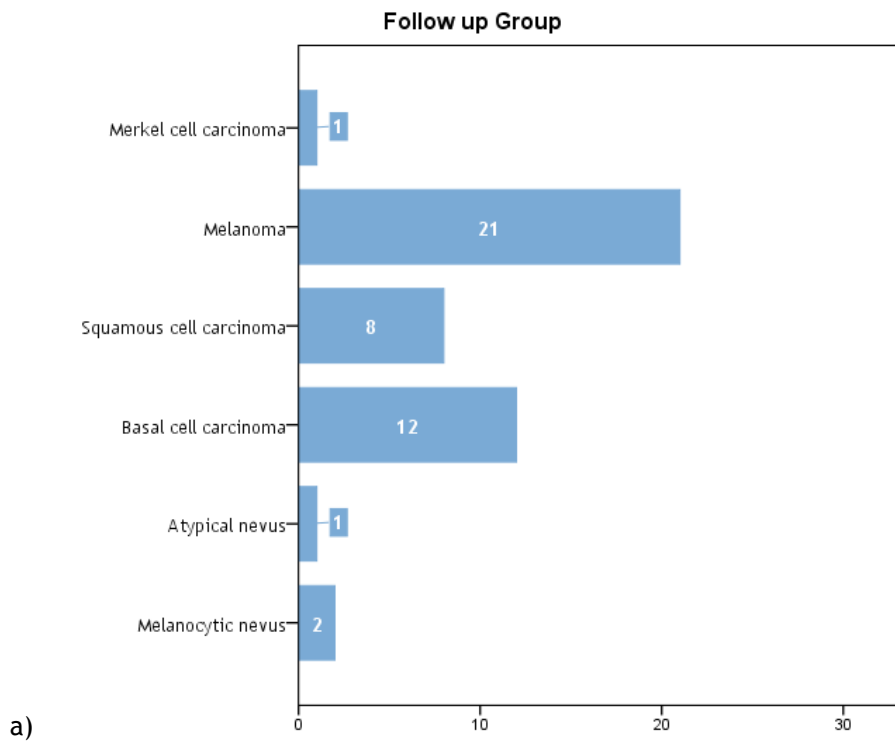


Figure 15: Type of neoplasm prevalence in both groups (a- Follow-up group and b- Diagnosed group).

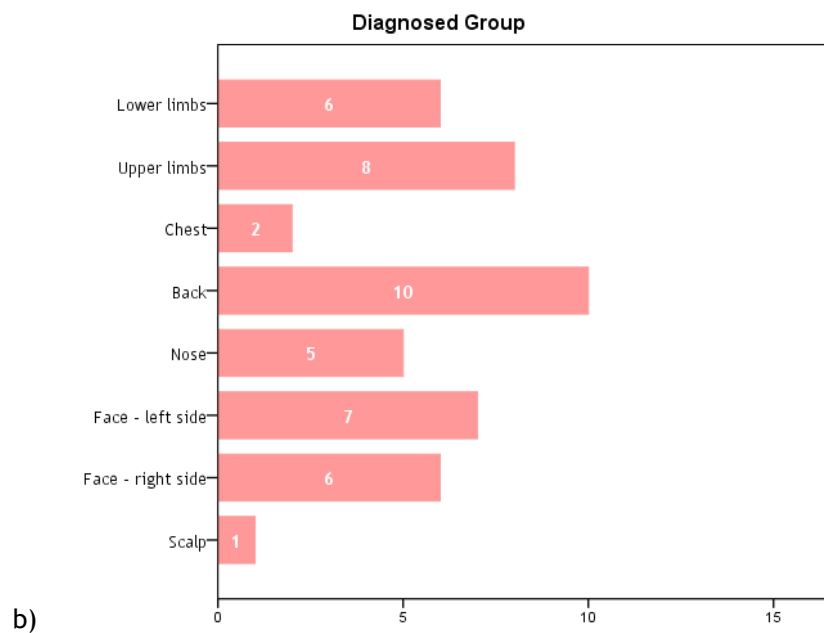
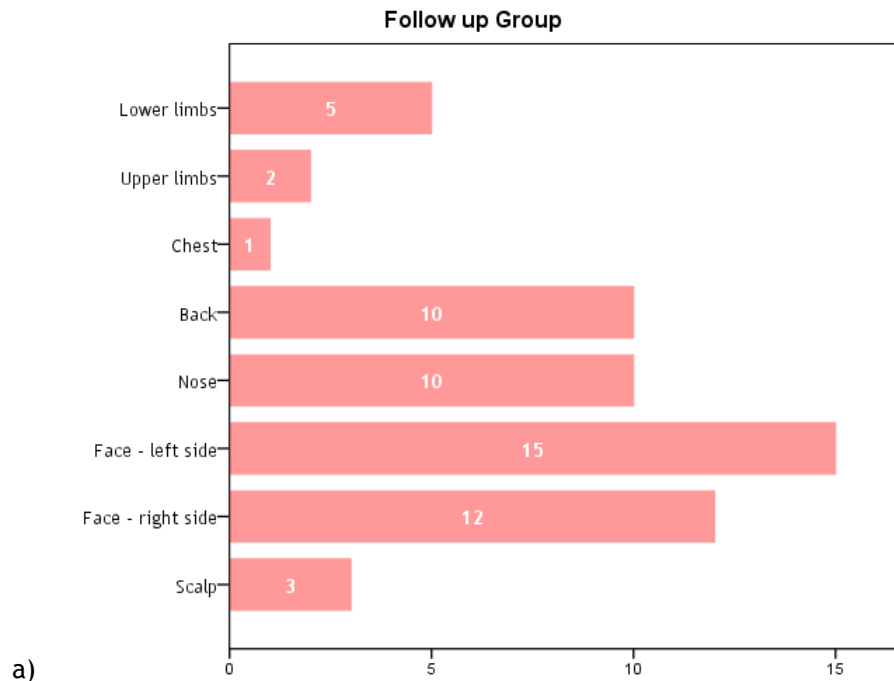


Figure 16: Skin neoplasm location prevalence in both groups (a- Follow-up group and b- Diagnosed group).

3.3 Data collection protocol

The data collection protocol represents an important role in any biomedical investigation. The protocol adopted for this research follows the guidelines of "Glamorgan Protocol". This protocol recommends the standard knowledge for recording and evaluation of human body with thermal images [55].

The protocol is based on the objective target of the anatomical region of interest, face for the control group and the neoplasm location for the oncological group. To achieve this goal, the anatomical landmarks are aligned in each view to the image edge. It allows also to reproduce body positions views to increase the thermal image reproducibility [55].

The protocol incorporates aspects such as communication, preparation and consideration of the patient, exam guidelines, results evaluation and presentation [108, 109].

The capture protocol recommended for medical thermography defines that the environment where the test is performed should have an ambient temperature between 18°C and 24°C, relative humidity below 50%, air flow less than 2m/s and the absence of incident light on the subject.

Before data collection, ethical approval was requested and obtained from the ethics committee of the IPO (appendix I).

The process of data collection involved several common steps to the three groups under test. Before capture, it was necessary that the individual remained in a heated room, exposing the area where the lesion was located. This process took about 10-15 minutes, in order to obtain the desired temperature. Meanwhile, the individual became aware and filled out some questionnaires. Among these were include informed consent, biometric data questionnaire, and pathology questionnaire (appendix II, III and IV). The biometric data questionnaire include questions about mobility, autonomy, usual activities, discomfort, pain, anxiety and depression. The final score obtained in this questionnaire should be zero, for inclusion the individual in the study. Only the control group filled this questionnaire. The pathology questionnaire includes information on parameters such as sun sensibility, and family history. The sun sensibility was scaled between 0 and 40 points (inversely proportional to the sun sensibility). For the control group, the phase of menstrual cycle (follicular and luteal) was also recorded.

It was also essential that the individual knew his weight and height to allow body mass index (BMI) calculation. It is defined as the individual's body mass divided by the square of their height, given in units of kg/m^2 .

Before the data collection period, some precautions should be taken such as:

- Not having a heavy foods prior to data collection;
- No participating in heavy activity or consuming alcohol or hot drinks or smoking 2 hours prior to the pictures being taken;
- Wearing minimal clothing in order to obtain clear thermograms;
- Removing all jewellery prior to the pictures being taken;
- Refraining from applying cosmetics and ointments to the skin prior to the pictures being taken.

Different capture procedures were adopted for the three groups. For the control group, nine different images of face per person were taken, in three different moments and

positions. The positions of the face for each set of three images were frontal, right, and left profiles. Figure 18 shows some thermograms of the control group in three different moments of frontal and right profile.

The first three pictures were taken after the acclimatization period and before applying a provocation test (first moment). The provocation test was a thermal stimulus consisted in a stream of cold air from a fan, facing 90° angle, and applied to the face during 2 minutes. It was applied cold air instead of hot, because in humans the colder sensors react faster than the warm sensors, and thus the examination can be done in less time. Immediately after the application of the thermal stimulus, 3 more images (second moment) were captured. The last 3 images were captured after waiting 5 minutes, in order to re-establish the normal temperature (third moment).

Thus, it is possible to maximize the physiological response of the face. Figure 17 illustrates the data collection protocol in three different moments.

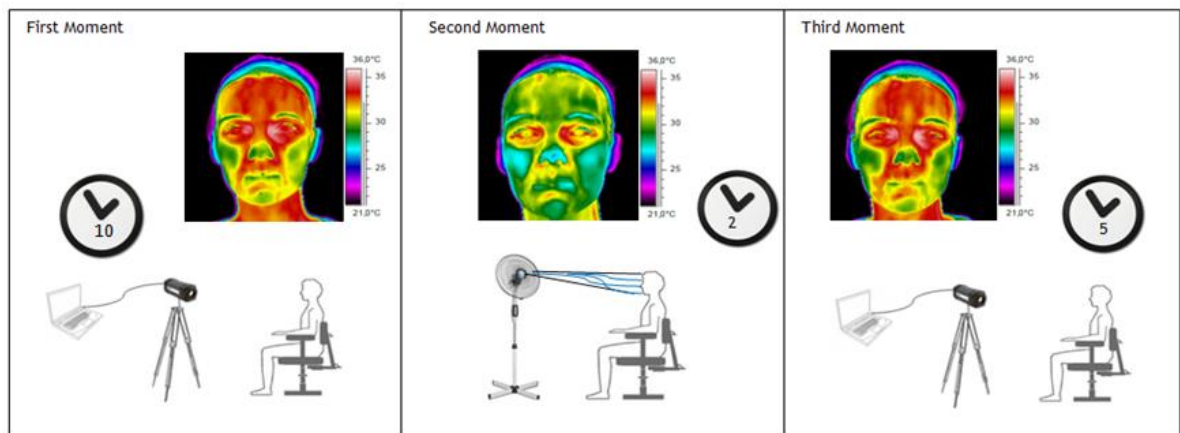


Figure 17: Cold stimulation and recovery collection protocol for three different moments.

For the oncologic group, there was a time constraint to perform the examination, only one image was taken by the individual in the neoplasm location, and the thermal stimulus could not be applied.

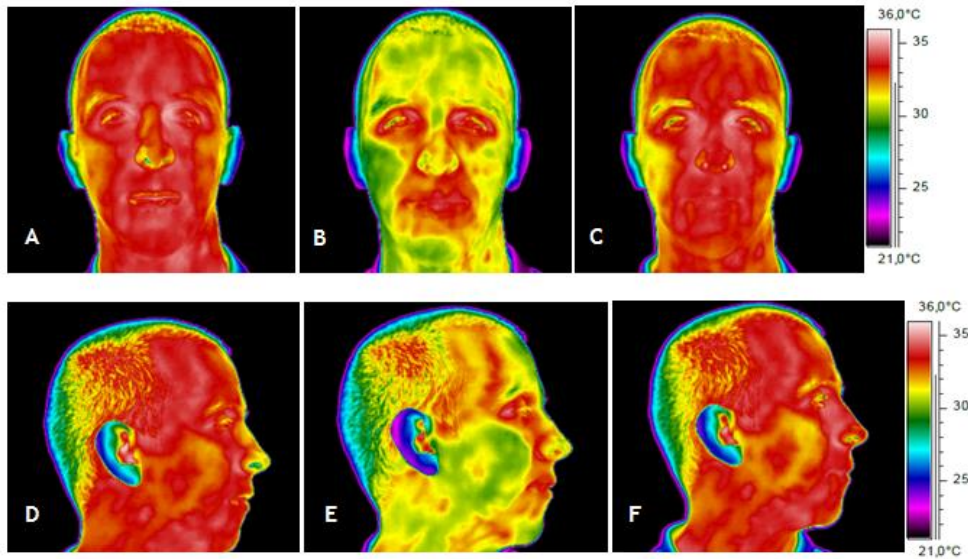


Figure 18: Thermograms of control group in three different moments of frontal and right profile (A- 1st moment, frontal view; B-2nd moment, frontal view; C-3rd moment, frontal view; D- 1st moment, right profile view; E- 2nd moment, right profile view;F-3rd moment, right profile view).

The neoplasm location included parts of body such as scalp, right face profile, left face profile, nose, back, chest, upper limbs (hand, arm, shoulder and axilla) and lower limbs (thigh, leg and foot).

3.4 Inclusion and exclusion criteria

Table 5 presents the inclusion and exclusion criteria of this study.

Table 5: Description of the inclusion and exclusion criteria of this study.

	Inclusion criteria	Exclusion criteria
Control Group	<ul style="list-style-type: none"> - Asymptomatic individuals; - Score null in the biometric survey date; - Individuals belonging to University of Porto. 	<ul style="list-style-type: none"> - Accented facial hair; - Individuals who have consumed caffeine; - Individuals who are smokers; - Individuals who have makeup or facial cream; - Individuals who have practiced intense physical exercises on the previous day; - Individuals minors (under 18 years).
Oncologic Group	<ul style="list-style-type: none"> - Have or had skin neoplasms; - Be a patient on Portuguese Institute of Oncology (IPO). 	<ul style="list-style-type: none"> - Accented facial hair; - Individuals who have consumed caffeine; - Individuals who are smokers; - Individuals who have makeup or facial cream; - Individuals who have practiced intense physical exercises on the previous day; - Individuals without neoplasms; - Individuals with suspicious neoplasm diagnosis.

3.5 Analysis protocol

Data analysis was performed using the *FLIR tools* software which allowed the extraction of maximum, minimum and mean temperature values for each region of interest. However,

regions of interest were selected in different ways for the two groups. After obtaining the results, they were treated in *SPSS Statistical 22* using different statistical methods. All these aspects are described in the following subsection.

3.5.1 Control group analysis

The regions of interest (ROIs) of autonomous nervous system (ANS) were selected according to Netter 3-way division [110] both frontal, right and left profile positions. The frontal images were divided into 16 regions (8 on the right side and 8 on the left side) using squares. The profile images were divided into 8 regions also using squares (see figure 19-A). For the same individual, the squares areas were the same for the right and left sides. Then this were combined in ROI 1, ROI 2 and ROI 3 according to Netter classification (see figure 20-A).

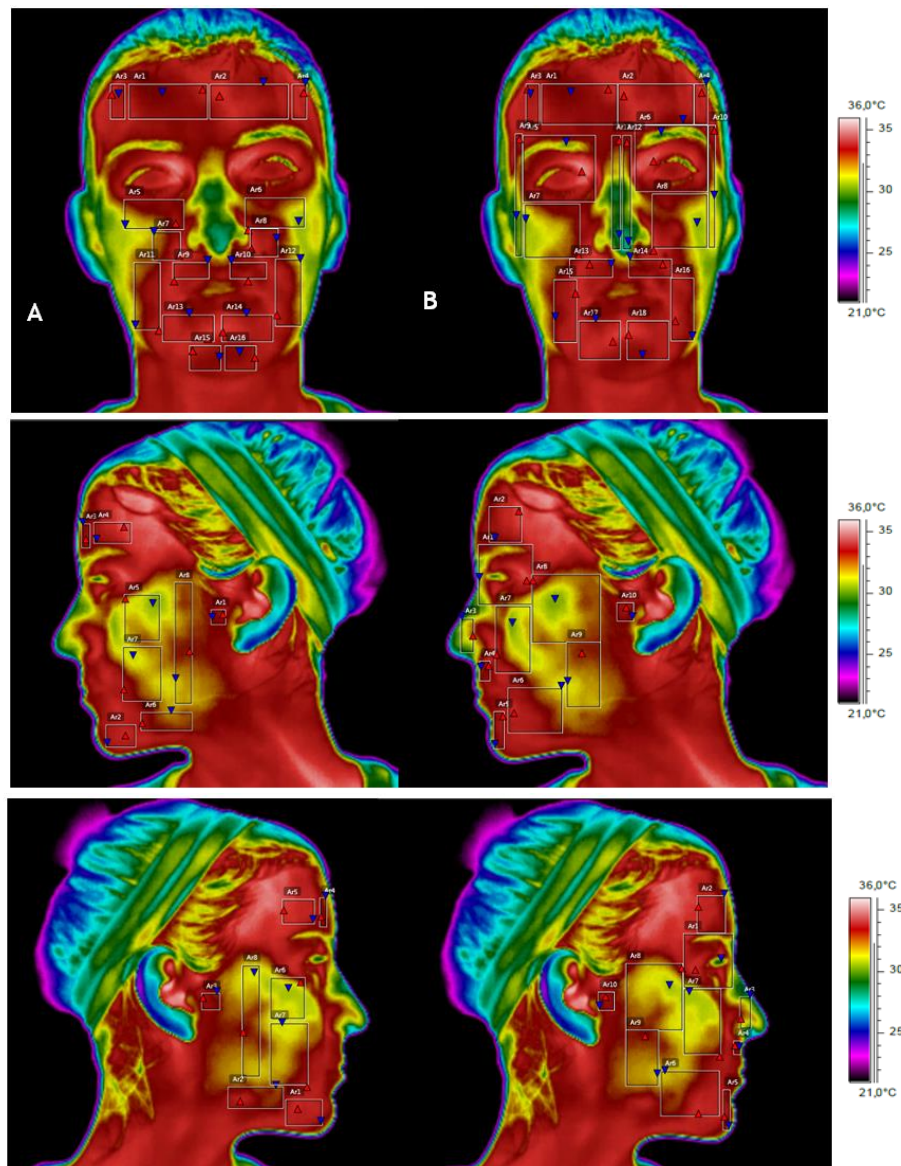


Figure 19: Frontal and profile images with the selected ROIs (A-ANS, B-MS).

From the data obtained, it was used the mean value of temperature, both to the left and right side in different positions. Thus, the thermal symmetry of ROI 1, ROI 2 and ROI 3 was calculated by the equation 3.

$$\text{Thermal Symmetry} = |\text{ROI}_{\text{left}} - \text{ROI}_{\text{right}}| \quad (3)$$

The regions of interest (ROIs) of microvascular system (MS) were selected according to Gratt et al. [111] both front, right and left profile positions. The front images were divided into 18 regions (9 on the right side and 9 on the left side), while the profile images were divided into 10 regions also using squares.

Such as the ANS, the squares areas were the same for the right and left sides (figure 19-B). The regions were then combined in ROI 1, ROI 2, ROI 3, ROI 4, ROI 5, ROI 5, ROI 7, ROI 8 and ROI 9 from front images, and in ROI 1, ROI 2, ROI 3, ROI 4, ROI 5, ROI 6, ROI 7, ROI 8, ROI 9 and ROI 10 from profile images. So, it was obtained a classification according to Gratt et al. (figure 20-B).

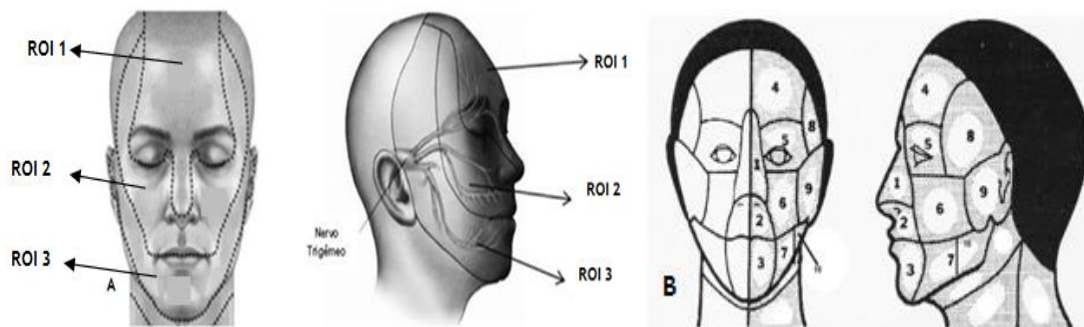


Figure 20: Regions of interest of ANS according to Netter (A) and MS according to Grantt (B) [111].

3.5.2 Diagnosed and Follow-up group analysis

The ROIs of oncologic group analysis were selected according the location of neoplasm. For all cases, it was used two squares in the neoplasm region (one square in the left of neoplasm, other in the right of neoplasm) as can be seen in figure 21 [112].

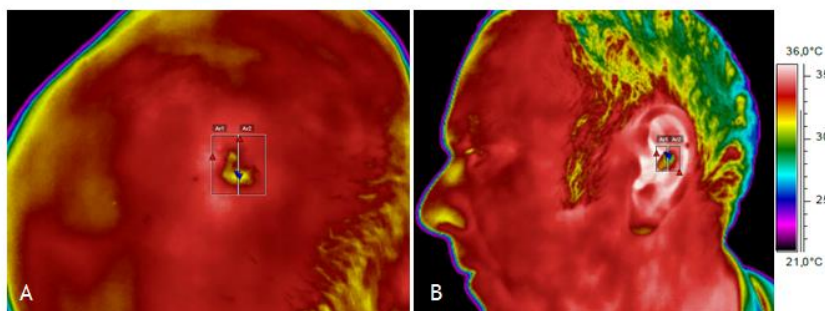


Figure 21: ROI selection on skin neoplasm group, A-Basal Cell carcinoma; B-Squamous Cell carcinoma.

The squares had an area of approximately 8x8 pixels. In these groups it was calculated the absolute difference between the left and right side of skin neoplasms (ΔT).

3.5.3 Case-study

It was also compared some of the individuals who possessed skin neoplasms on the face with a group of controls that had a BMI within the same class and the same gender. In the control group, roughly the same square area was selected around the neoplasm (see figure 22). Thus, it was possible to compare the mean temperature of the individual with skin neoplasm with the appropriate control group.

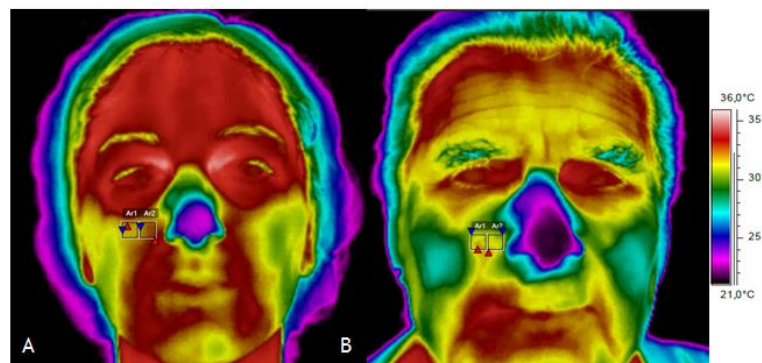


Figure 22: ROI selection in control individual (A) and basal cell carcinoma individual (B).

A total of 4 cases were tested of diagnosed basal cell carcinoma. The minimum number of comparable controls was 14 and the maximum 18.

3.6 Statistical treatment

Unlike the parametric tests, the nonparametric tests do not require strong requirements as normality. They are used when dealing with small samples with a distribution that is not normal. They can also be used if, despite the sample having a size greater than 30, when more conservative conclusions are sought. Non-parametric tests were considered using a significance level of 0.05, table 6.

The U-Mann Whitney test allows the detection of significant differences between the central values of two situations, when considered different subjects. It is the nonparametric alternative to the student t-test for independent samples, when the conditions for the application of a parametric test are not meet.

The Wilcoxon test enables the detection of significant differences between the central values of two situations, when the same subjects are considered. It represent a nonparametric alternative to student's t-test for paired samples.

The Kruskal-Wallis test allows the detection of significant differences between the central values of three or more situations, when different subjects are considered. It represent an nonparametric alternative to ANOVA for independent samples [113].

Table 6: Description of mean distribution equality tests.

	Parametric tests	Non-parametric tests
Two paired samples	T-student Test*	Wilcoxon or Signal Test
Two independent samples	T-student Test* **	U Mann-Whitney Test
More than two independent samples	One Way ANOVA * **	Kruskal-Wallis Test

The chi-square test for independence verifies if there is a statistically significant evidence of association between two characteristics. In other words, it verifies the independence between two variables of any type that are grouped together in contingency tables. This test should not be used if more than 20% of expected frequencies under the assumption of independence are less than 5, or one of them is zero. If this assumption does not occur, the Fisher's test will be used.

Chapter 4.

Results

In this chapter the reader will find the major results of this study. Firstly, the skin surface temperature characterization and the influence of individual characteristics on skin temperature for autonomous nervous system (ANS) and microvascular system (MS) in the control group are described. The skin neoplasm group shows the temperature characterization of skin neoplasms and the impact of the individual characteristics. Later, a comparison of case-study of basal cell carcinoma in four different face locations with control, in order to assess temperature differences was performed.

4.1 Skin surface temperature characterization

4.1.1 Control Group

The first study had the purpose of characterizing the temperature at the skin surface in the ANS and MS. The ROIs mean temperatures of each side were analyzed in each moment, as well as its thermal symmetry.

4.1.1.1 ANS

The ANS was characterized in 3 ROIs in both frontal and profile positions. In the following tables were presented the mean temperature and the corresponding standard deviations to the right and left sides of the ROIs, as well its thermal symmetry.

Table 7: Mean temperature characterization of the right side in each moment, and the corresponding p-values of Wilcoxon test.

	ROIs	1st Moment	2nd Moment	3rd Moment	P _{I-II}	P _{II-III}	P _{I-III}
Frontal	R1	34.35 ± 1.62	32.8 ± 0.52	34.33 ± 0.64	0.000	0.000	0.000
	R2	34.19 ± 0.42	32.69 ± 0.60	33.94 ± 0.78	0.243	0.000	0.000
	R3	33.64 ± 0.82	32.15 ± 1.19	33.15 ± 1.84	0.000	0.000	0.000
Profile	R1	34.15 ± 0.56	32.57 ± 0.65	33.91 ± 0.61	0.000	0.000	0.000
	R2	33.78 ± 0.81	32.38 ± 0.86	33.32 ± 0.92	0.000	0.000	0.000
	R3	33.87 ± 0.80	32.24 ± 0.87	33.36 ± 0.90	0.000	0.000	0.000

It was necessary to assess if the stimulus triggered differences in the mean temperatures of each ROI. Through observation it can be concluded that there was a difference of approximately 2 °C in each moment relatively to each ROI (figure 23).

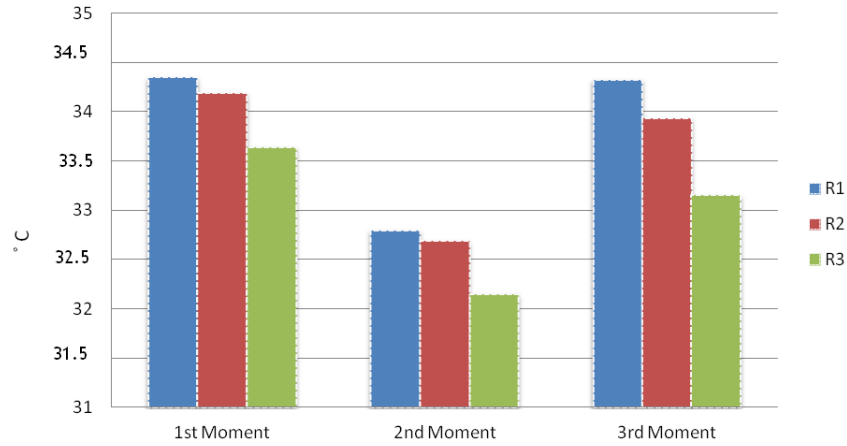


Figure 23: Temperature differences between moments regarding ANS of ROI's.

By this analysis, it looks like the standard deviation besides being higher, are similar between the second and third moment, when compared to the first moment.

Using the Wilcoxon test, it can be stated that there was significant statistical evidence that all mean temperature in each side (right and left) of each ROIs were different between moments, with the exception of frontal ROI R2 between moment I and II (table 7 and table 8).

Table 8: Mean temperature characterization of ROIs left side in each moment. Are also showed the corresponding p-values of Wilcoxon test.

	ROIs	1st Moment	2nd Moment	3rd Moment	P _{I-II}	P _{II-III}	P _{I-III}
Frontal	R1	34.70 ± 0.24	32.75 ± 0.46	34.30 ± 0.61	0.000	0.000	0.000
	R2	34.00 ± 0.47	32.49 ± 0.75	33.91 ± 0.72	0.149	0.000	0.000
	R3	33.55 ± 0.78	32.12 ± 0.64	33.42 ± 0.69	0.100	0.000	0.000
Profile	R1	34.25 ± 0.29	32.6 ± 0.435	33.90 ± 0.39	0.000	0.000	0.000
	R2	33.77 ± 0.84	32.43 ± 0.90	33.32 ± 0.94	0.000	0.000	0.000
	R3	33.89 ± 0.76	32.53 ± 0.69	33.46 ± 0.73	0.000	0.000	0.000

Using the Wilcoxon test it can be stated that there was significant statistical evidence that all thermal symmetry values of each ROI were equal between moments with the exception of frontal ROI R1 between moments I and II and moments I and III (table 9).

Table 9: ROIs thermal symmetry in each moment and the corresponding p-values of Wilcoxon test.

	ROIs	1st Moment	2nd Moment	3rd Moment	P _{I-II}	P _{II-III}	P _{I-III}
Frontal	R1	0.16 ± 0.14	0.25 ± 0.19	1.05 ± 5.38	0.009	0.286	0.011
	R2	0.19 ± 0.05	0.22 ± 0.14	0.21 ± 0.03	0.562	0.878	0.834
	R3	0.25 ± 0.21	0.30 ± 0.25	0.27 ± 0.21	0.400	0.755	0.459
Profile	R1	0.26 ± 0.23	0.32 ± 0.30	0.28 ± 0.24	0.350	0.639	0.512
	R2	0.23 ± 0.16	0.26 ± 0.22	0.20 ± 0.03	0.883	0.431	0.971
	R3	0.18 ± 0.16	0.23 ± 0.20	0.21 ± 0.15	0.174	0.780	0.224

4.1.1.2 MS

The MS was characterized in 9 ROIs in the frontal position and 10 ROIs in the profile position. In the following tables are presented the mean temperatures and the corresponding standard-deviations to the right and left sides of the ROIs, as well its thermal symmetry.

As ANS temperature characterization in MS it was also necessary to assess if the stimulus triggered differences on the mean temperatures in each ROI.

Table 10 : Mean temperature characterization of ROIs right side in each moment and the corresponding p-values of Wilcoxon test.

	ROIs	1st Moment	2nd Moment	3rd Moment	P _{I-II}	P _{II-III}	P _{I-III}
Frontal	R1	32.20 ± 1.41	30.80 ± 1.48	33.00 ± 3.32	0.000	0.000	0.029
	R2	34.20 ± 0.70	32.75 ± 0.77	34.30 ± 0.90	0.000	0.000	0.656
	R3	33.98 ± 0.79	32.35 ± 0.82	33.79 ± 0.88	0.000	0.000	0.031
	R4	34.61 ± 0.49	32.72 ± 0.72	34.50 ± 0.45	0.000	0.000	0.000
	R5	34.25 ± 0.21	32.99 ± 0.51	33.96 ± 0.47	0.000	0.000	0.000
	R6	33.44 ± 0.95	31.51 ± 1.04	32.99 ± 1.17	0.000	0.000	0.005
	R7	33.75 ± 0.90	32.40 ± 1.12	33.42 ± 1.07	0.000	0.000	0.003
	R8	34.80 ± 0.19	33.40 ± 0.48	34.55 ± 0.34	0.000	0.000	0.002
	R9	33.30 ± 0.49	31.85 ± 0.62	32.75 ± 0.83	0.000	0.000	0.000
Profile	R1	31.23 ± 2.09	30.35 ± 2.13	32.55 ± 6.60	0.000	0.000	0.019
	R2	33.60 ± 1.16	32.37 ± 1.03	33.58 ± 1.01	0.000	0.000	0.027
	R3	33.81 ± 0.68	32.13 ± 0.89	33.66 ± 0.81	0.000	0.000	0.049
	R4	34.45 ± 0.37	32.77 ± 0.71	34.20 ± 0.43	0.000	0.000	0.000
	R5	33.95 ± 0.53	32.87 ± 0.58	33.79 ± 0.53	0.000	0.000	0.006
	R6	33.15 ± 1.21	31.70 ± 1.43	32.68 ± 1.24	0.000	0.000	0.000
	R7	34.00 ± 0.81	32.55 ± 1.18	33.50 ± 1.19	0.000	0.000	0.000
	R8	33.70 ± 0.86	32.18 ± 0.91	33.18 ± 0.91	0.000	0.000	0.000
	R9	34.45 ± 0.72	33.00 ± 0.91	33.93 ± 0.73	0.000	0.000	0.000
	R10	33.56 ± 0.98	31.92 ± 1.00	33.02 ± 1.07	0.000	0.000	0.000

Using the Wilcoxon test it can be stated that there is significant statistical evidence that all mean temperatures in right and left sides of each zone were different between moments with the exception of frontal ROI R2 between moment I and III (table 10 and table 11).

Through observation of figure 24, it can be concluded that there was a difference of 1.5°C in each moment relatively to each ROI.

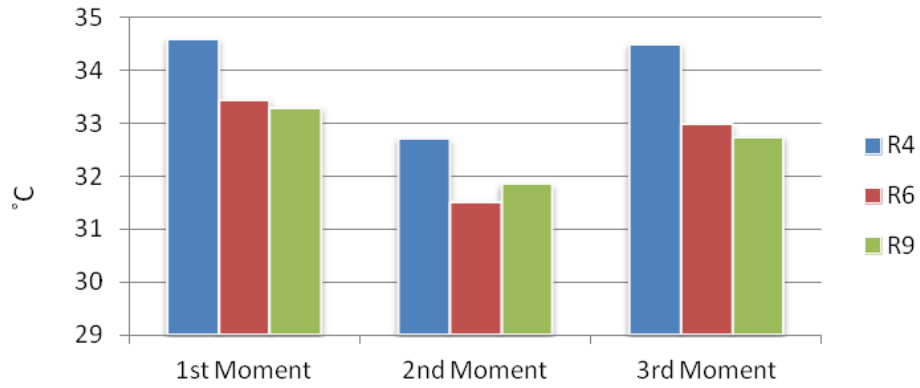


Figure 24: Temperature differences between moments regarding MS of three ROI's.

By this analysis it is also apparent that the standard deviations besides being higher, they are similar between the second and third moment, when compared to the first moment.

Table 11: Mean temperature characterization of the left side in each moment and the corresponding p-values of Wilcoxon test.

	ROIs	1st Moment	2nd Moment	3rd Moment	p _{I-II}	p _{II-III}	p _{I-III}
Frontal	R1	32.31 ± 1.45	31.02 ± 1.53	33.05 ± 3.31	0.000	0.000	0.029
	R2	33.92 ± 0.68	32.59 ± 0.75	33.92 ± 0.75	0.000	0.000	0.656
	R3	33.92 ± 0.76	32.22 ± 0.80	33.64 ± 0.87	0.000	0.000	0.031
	R4	34.61 ± 0.48	32.73 ± 0.67	34.30 ± 0.47	0.000	0.000	0.000
	R5	34.21 ± 0.47	32.97 ± 0.54	33.95 ± 0.47	0.000	0.000	0.000
	R6	33.42 ± 0.97	31.75 ± 1.04	33.40 ± 1.26	0.000	0.000	0.005
	R7	33.87 ± 0.79	32.22 ± 0.80	33.42 ± 0.92	0.000	0.000	0.003
	R8	34.65 ± 0.34	33.20 ± 0.42	34.30 ± 0.32	0.000	0.000	0.002
	R9	33.45 ± 0.58	31.71 ± 0.98	32.72 ± 0.88	0.000	0.000	0.000
Profile	R1	31.24 ± 2.13	30.95 ± 4.85	33.25 ± 7.96	0.000	0.000	0.046
	R2	33.22 ± 0.99	32.34 ± 1.01	33.80 ± 0.94	0.000	0.000	0.008
	R3	33.74 ± 0.68	32.22 ± 0.89	33.54 ± 0.85	0.000	0.000	0.046
	R4	34.50 ± 0.31	32.79 ± 0.63	34.03 ± 0.58	0.000	0.000	0.000
	R5	33.98 ± 0.52	32.84 ± 0.64	33.95 ± 3.23	0.000	0.000	0.005
	R6	33.40 ± 1.14	31.55 ± 1.13	33.10 ± 1.55	0.000	0.000	0.000
	R7	33.87 ± 0.79	32.41 ± 0.85	33.70 ± 0.83	0.000	0.000	0.000
	R8	33.72 ± 0.88	32.28 ± 0.87	33.20 ± 0.97	0.000	0.000	0.000
	R9	34.42 ± 0.67	32.99 ± 0.87	33.91 ± 0.69	0.000	0.000	0.000
	R10	33.48 ± 1.03	31.99 ± 1.09	33.00 ± 1.16	0.000	0.000	0.000

Regarding the thermal symmetry, using the Wilcoxon test, it can be stated that there was significant statistical evidence that all thermal symmetry values of each zone were similar between moments with the exception of the following ROIs: frontals ROI 4 and ROI 8 between moments I and II; frontals ROI 1 and ROI 7 between moments II and III; frontal ROI 4 between moments I and III; profile ROI 4 and ROI 7 between moments I and II; profile ROI 4 between moments II and III and profile ROI 7 between moments I and III (table 12).

Table 12: ROIs thermal symmetry in each moment and the corresponding p-values of Wilcoxon test.

	ROIs	1st Moment	2nd Moment	3rd Moment	P _{I-II}	P _{II-III}	P _{I-III}
Frontal	R1	0.20 ± 0.13	0.30 ± 0.15	0.20 ± 0.03	0.206	0.036	0.453
	R2	0.35 ± 0.10	0.40 ± 0.18	0.30 ± 0.15	0.131	0.462	0.280
	R3	0.20 ± 0.04	0.30 ± 0.04	0.20 ± 0.08	0.252	1,000	0.281
	R4	0.10 ± 0.02	0.20 ± 0.06	0.20 ± 0.02	0.014	0.167	0.019
	R5	0.20 ± 0.01	0.10 ± 0.02	0.10 ± 0.01	0.983	0.079	0.141
	R6	0.25 ± 0.26	0.30 ± 0.04	0.30 ± 0.14	0.565	0.145	0.712
	R7	0.25 ± 0.12	0.40 ± 0.08	0.20 ± 0.18	0.051	0.029	0.660
	R8	0.20 ± 0.12	0.33 ± 0.22	0.20 ± 0.11	0.043	0.331	0.441
	R9	0.30 ± 0.07	0.30 ± 0.16	0.30 ± 0.11	0.676	0.575	0.575
Profile	R1	0.85 ± 0.63	0.60 ± 0.48	0.72 ± 0.57	0.408	0.269	0.174
	R2	0.40 ± 0.19	0.45 ± 0.18	0.41 ± 0.34	0.626	0.059	0.308
	R3	0.20 ± 0.07	0.30 ± 0.13	0.20 ± 0.08	0.071	0.085	0.394
	R4	0.20 ± 0.05	0.30 ± 0.08	0.20 ± 0.06	0.008	0.003	0.626
	R5	0.20 ± 0.03	0.15 ± 0.13	0.20 ± 2.86	0.892	0.707	0.883
	R6	0.30 ± 0.05	0.35 ± 0.12	0.30 ± 0.01	0.086	0.247	0.328
	R7	0.25 ± 0.05	0.30 ± 0.13	0.30 ± 0.11	0.009	0.850	0.002
	R8	0.20 ± 0.05	0.20 ± 0.05	0.15 ± 0.03	0.287	0.594	0.081
	R9	0.30 ± 0.16	0.30 ± 0.08	0.25 ± 0.07	0.595	0.434	0.434
	R10	0.40 ± 0.04	0.20 ± 0.05	0.30 ± 0.06	0.086	0.662	0.138

4.1.2 Oncologic Group

The approach in this group was to determine whether there were differences in temperature surface of skin neoplasms and ΔT in individuals who have been recently diagnosed and others, who have been subjected to surgery. In addition to this analysis, an attempt to distinguish between benign and malignant neoplasms based in temperature values was also performed.

Table 13 shows that the median temperature in benign neoplasms of diagnosed group was approximately 34 °C, and the malignant neoplasms in follow-up group was around 33.7 °C. Although the median temperatures were slightly different through U Mann-Whitney test, it can be settled that the median temperature of benign and malignant skin neoplasms were equal in both groups (table 13).

Table 13: Characterization of median temperature values of skin neoplasms in both groups.

	Diagnosed		Follow-up	
	Right	Left	Right	Left
Benign	33.03 ± 1.10	34.45 ± 1.19	33.07 ± 0.12	33.03 ± 0.10
Malignant	33.83 ± 2.17	33.91 ± 2.05	33.68 ± 1.84	33.77 ± 1.70
U	291.50	279.00	36.00	34.00
W	1281.50	1269.00	42.00	40.00
Z	-0.300	-0.527	-1.230	-1.320
p	0.764	0.598	0.219	0.187

Considering all individuals in both groups, there was assess if the median temperature of benign and malignant skin neoplasm were equal in the follow-up and the skin neoplasm groups. Recurring to U Mann-Whitey test, it can be state that the median temperature of benign and malign skin neoplasm were similar (table 13).

Regarding the ΔT in both groups with malignancy, it was assess if the ΔT values were equal in the follow-up and the skin neoplasm groups (figure 25).

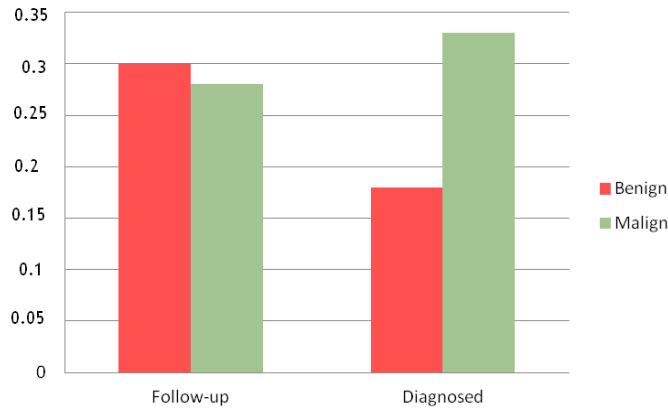


Figure 25: ΔT values of the benign and malign skin neoplasms in both groups of noplasm.

Recurring to U Mann-Whitey test, it can be referred that the ΔT s of benign and malignant skin neoplasm were similar in the diagnosed group and different in the follow-up group (table 14).

Table 14: Description of U Mann-Whitney test results for the ΔT comparison.

	Diagnosed	Follow-up
U	209.500	16.000
W	314.500	22.000
Z	-1.819	-2.264
p	0.069	0.024

The figure 26 illustrates all median ΔT of the different skin neoplasm types regarding its malignancy.

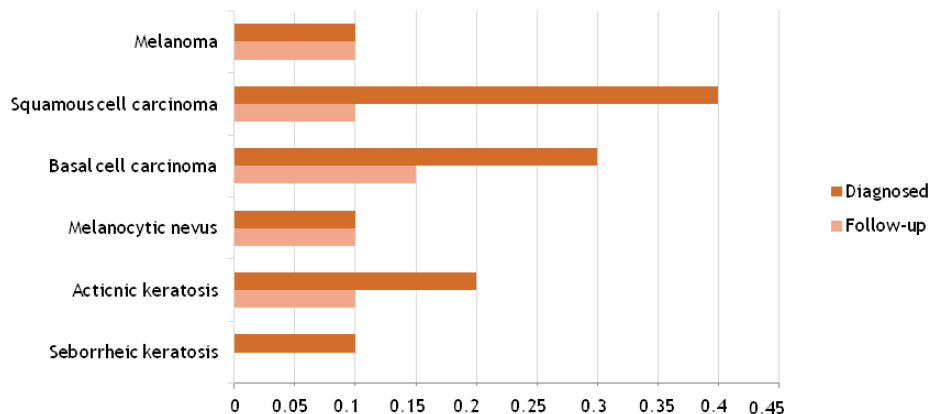


Figure 26: ΔT values of the different type of skin neoplasms in the differences groups.

Through the Kruskal-Wallis test, it can be affirmed that the ΔT s values of different skin neoplasm types were similar ($p_D=0.141$ and $p_F=0.204$).

4.1.2.1 Relation between visible skin neoplasms and oncological thermograms

In the figure 27 are presented some examples of visual images and thermograms of skin neoplasms.

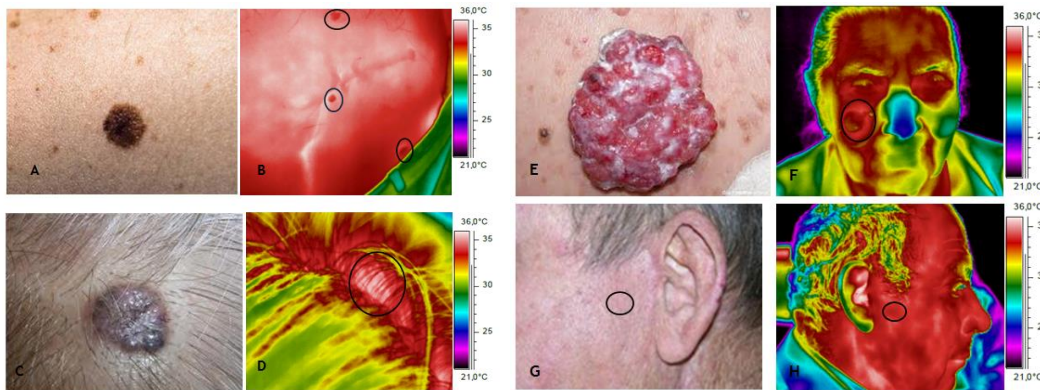


Figure 27: Thermographic and visual images of some skin neoplasms (A-Melanoma in the back, visual image; B-Melanoma in the back, thermogram; C- Melanoma in the scalp, visual image; D- Melanoma in the scalp, thermogram; E- Basal Cell carcinoma in face, visual image; F- Basal cell carcinoma in face, thermogram; G- Follow-up of Squamous cell carcinoma in face, visual image; H-Follow-up of Squamous cell carcinoma in face, thermogram).

It can be observed that melanoma is characterized by higher temperatures. On the other hand, in follow-up images there was a uniform distribution of superficial temperature.

4.2 Individuals characteristics and skin temperature

This study was focused in the influence of the individual's characteristics in the skin surface temperature and thermal symmetry for the control group. Relatively to oncologic group, it was focused in the skin surface temperature and ΔT s.

Characteristics, such as gender, body mass index, sun sensibility and in the case of females the different phases of menstrual cycle. Age, body mass index and sun sensibility were only addressed in oncological group because the control did not have a wide variability within this scope.

4.2.1 Control Group

In this study it was assessed the gender and phase of the menstrual cycle influence between moments for different systems in left and right sides and also in thermal symmetry. The group was composed by 24 females and 16 males, while concerning the menstrual cycle, 14 individuals were in follicular phase and 10 in luteal phase.

4.2.1.1 Autonomous Nervous System

Firstly, it was studied if the gender influences the ANS. It was evaluated if the female and male responses were equal at all moments for the right side in frontal and profile positions (table 15).

Table 15: Mean temperatures to the right side of each gender for three different moments.

	ROIs	Gender	1st Moment	2nd Moment	3rd Moment
Frontal	R1	F	34.55 ± 0.53	34.55 ± 0.53	34.23 ± 0.77
		M	34.55 ± 2.50	34.04 ± 2.50	34.49 ± 0.37
	R2	F	34.55 ± 0.72	33.92 ± 0.72	33.71 ± 0.86
		M	34.55 ± 0.52	34.19 ± 0.52	34.29 ± 0.49
	R3	F	34.55 ± 0.86	33.54 ± 0.86	32.77 ± 2.26
		M	34.55 ± 0.78	33.80 ± 0.78	33.74 ± 0.62
Profile	R1	F	34.55 ± 0.59	32.37 ± 0.71	33.83 ± 0.73
		M	34.55 ± 0.49	32.86 ± 0.43	34.04 ± 0.32
	R2	F	34.55 ± 0.82	31.72 ± 0.87	32.87 ± 0.89
		M	34.55 ± 0.44	32.91 ± 0.42	34.00 ± 0.42
	R3	F	34.55 ± 0.84	31.83 ± 0.82	32.98 ± 0.87
		M	34.55 ± 0.60	32.87 ± 0.48	33.94 ± 0.60

Using U Mann-Whitey test, it can be stated that exists significant statistical evidence to affirm that the mean temperatures of frontals ROI R1, ROI R2 and ROI R3 were similar between moments I and II. On the other hand, between moments II and III frontals ROI R1 and ROI R2 were different. Regarding the profile position, only ROI R1 was equal between moment I and II for both genders. Between moments II and III and moments I and III, all ROIs were different, with exception to ROI R1 between moment I and III. In table 16 it can be observed the p-value, U, W and Z of U Mann-Whitney tests results.

Table 16: Results of p-value, U, W and Z values of U Mann Whitney test between moments for the right side.

		Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	p	U	W	Z	P	U	W	Z	P
Frontal	R1	192	328	0.00	1.000	108	408	-2.34	0.020	166	466	-0.72	0.471
	R2	155	455	-1.02	0.310	110	410	-2.28	0.020	100	400	-2.54	0.011
	R3	158	458	-0.94	0.350	127	427	-1.81	0.070	118	418	-2.06	0.040
Profile	R1	154	454	-1.07	0.280	112	412	-2.21	0.030	171	471	-0.60	0.551
	R2	65	365	-3.52	0.000	34	334	-4.36	0.000	37	337	-4.29	0.000
	R3	117	417	0.00	0.040	52	352	-3.88	0.000	69	369	-3.40	0.001

For left side it was also studied the male and female responses in frontal and profile positions (see table 17).

Table 17: Mean temperatures to the left side of each gender for three different moments.

	ROIs	Gender	1st Moment	2nd Moment	3rd Moment
Frontal	R1	F	34.60 ± 0.55	32.54 ± 0.80	34.23 ± 0.73
		M	34.62 ± 0.40	32.91 ± 0.35	34.41 ± 0.33
	R2	F	33.94 ± 0.77	32.32 ± 0.84	33.74 ± 0.84
		M	34.10 ± 0.54	32.76 ± 0.52	34.15 ± 0.40
	R3	F	33.46 ± 0.76	31.78 ± 0.87	33.16 ± 0.91
		M	33.67 ± 0.81	32.30 ± 0.56	33.61 ± 0.64
Profile	R1	F	34.15 ± 0.53	32.38 ± 0.76	33.75 ± 0.72
		M	34.13 ± 0.58	32.63 ± 0.46	33.90 ± 0.47
	R2	F	33.47 ± 0.87	31.78 ± 0.93	32.87 ± 0.89
		M	34.23 ± 0.55	32.88 ± 0.47	34.00 ± 0.51
	R3	F	33.47 ± 0.74	32.02 ± 0.78	33.03 ± 0.80
		M	34.23 ± 0.68	32.94 ± 0.55	33.96 ± 0.61

Using U Mann-Whitney test it can be referred that there exists significant statistical evidence to affirm that the mean temperatures of all ROIs were similar for all moments in frontal position with an exception of frontal ROI R1 between moments II and III. For profile position all ROIs were different with exception to ROI R1 regarding all moments. In table 18 it can be can observed the results for p-value, U, W and Z.

Table 18: Results of p-value, U, W and Z values of U Mann Whitney test between moments for the left side.

		Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	p	U	W	Z	P	U	W	Z	P
Frontal	R1	190	326	-0.04	0.97	117	417	-2.06	0.04	174	474	-0.50	0.62
	R2	178	478	-0.39	0.7	141	441	-1.39	0.16	131	431	-1.68	0.09
	R3	160	460	-0.87	0.38	134	434	-1.59	0.11	130	430	-1.70	0.09
Profile	R1	192	328	0.00	1.00	146	446	-1.26	0.21	175	475	-0.46	0.65
	R2	96	396	-2.64	0.01	0.21	345	-4.05	0.00	46	346	-4.03	0.00
	R3	110	410	-2.25	0.02	63	363	-3.56	0.00	64	364	-3.53	0.00

Regarding thermal symmetry, it was also performed a comparison of genders response in frontal and profile positions between moments (table 19).

Table 19: Mean temperatures to the thermal symmetry of each gender for three different moments.

	ROIs	Gender	1st Moment	2nd Moment	3rd Moment
Frontal	R1	F	0.18 ± 0.15	0.26 ± 0.18	1.63 ± 6.94
		M	0.14 ± 0.12	0.23 ± 0.22	0.18 ± 0.16
	R2	F	0.25 ± 0.27	0.22 ± 0.15	0.23 ± 0.17
		M	0.22 ± 0.17	0.21 ± 0.12	0.21 ± 0.17
	R3	F	0.25 ± 0.27	0.35 ± 0.28	0.31 ± 0.21
		M	0.22 ± 0.17	0.21 ± 0.17	0.21 ± 0.18
Profile	R1	F	0.28 ± 0.26	0.29 ± 0.22	0.29 ± 0.21
		M	0.24 ± 0.20	0.37 ± 0.40	0.27 ± 0.27
	R2	F	0.26 ± 0.16	0.28 ± 0.23	0.21 ± 0.19
		M	0.20 ± 0.16	0.22 ± 0.21	0.26 ± 0.19
	R3	F	0.22 ± 0.16	0.26 ± 0.22	0.22 ± 0.14
		M	0.11 ± 0.12	0.18 ± 0.17	0.20 ± 0.18

Using U Mann-Whitey test, there is a significant statistical evidence the thermal symmetry is similar for all ROIs between moments for both genders (see table 20), with exception to profile R3 between moment II and III.

Table 20: Results of p-value, U, W and Z values of U Mann Whitney test between moments for thermal symmetry.

		Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	p	U	W	Z	P	U	W	Z	P
Frontal	R1	163	299	-0.84	0.4	168	304	-0.66	0.51	147	283	-1.26	0.21
	R2	191	491	-0.01	0.99	186	486	-0.15	0.88	187	323	-0.12	0.90
	R3	165	301	-0.75	0.46	149	285	-1.19	0.23	135	271	-1.56	0.12
Profile	R1	178	314	-0.38	0.70	182	482	-0.27	0.79	174	310	-0.50	0.62
	R2	150	286	-1.16	0.24	160	296	-0.88	0.38	157	457	-0.97	0.33
	R3	103	239	-2.46	0.01	145	281	-1.29	0.20	162	298	298.5	0.41

Later, it was studied the influence of menstrual cycle phase in ANS. To verify if the menstrual cycle phases had some impact on the mean temperature on skin surface. It was evaluated if the phase's response were identical at all moments to the right side in frontal and profile positions (table 21).

Table 21: Mean temperatures to right side of each phase for three different moments.

	ROIs	Phase	1st Moment	2nd Moment	3rd Moment
Frontal	R1	1	34,58 ± 0,51	32.72 ± 0.87	34.19 ± 0.86
		2	34.52 ± 0.59	32.27 ± 0.72	34.27 ± 0.65
	R2	1	34.00 ± 0.62	32.45 ± 0.74	33.73 ± 0.93
		2	33.80 ± 0.86	31.99 ± 0.92	33.68 ± 0.79
	R3	1	33.67 ± 0.79	31.78 ± 0.89	32.54 ± 2.88
		2	33.37 ± 0.95	31.73 ± 1.74	33.09 ± 0.96
Profile	R1	1	34.11 ± 0.61	32.54 ± 0.76	33.79 ± 0.82
		2	34.00 ± 0.60	32.13 ± 0.59	33.88 ± 0.63
	R2	1	33.5 ± 0.82	31.88 ± 0.78	32.84 ± 0.93
		2	33.33 ± 0.86	31.50 ± 0.98	32.91 ± 0.87
	R3	1	33.71 ± 0.91	31.98 ± 0.7	32.90 ± 0.92
		2	33.55 ± 0.77	31.61 ± 0.96	33.04 ± 0.84

Using U Mann-Whitey test, it can be affirm that in both frontal and profile positions the mean temperatures of right side were similar for all moments in different phases. In appendix V it can be found the results for p, U, W and Z values. After, it was evaluated if the response of the first and second phases were equal at all moments to the left side in frontal and profile positions (see appendix VI). Using U Mann-Whitney test it can be affirm that the mean temperatures are equal for all moments for both phases. The results can be observed in appendix VI.

Table 22: Mean temperatures to thermal symmetry of each phase for three different moments.

	ROIs	Phase	1st Moment	2nd Moment	3rd Moment
Frontal	R1	1	0.17 ± 0.17	0.28 ± 0.14	0.22 ± 0.21
		2	0.18 ± 0.12	0.23 ± 0.23	0.20 ± 0.12
	R2	1	0.25 ± 0.32	0.22 ± 0.14	0.25 ± 0.18
		2	0.26 ± 0.17	0.21 ± 0.17	0.19 ± 0.15
	R3	1	0.29 ± 0.27	0.33 ± 0.27	0.30 ± 0.23
		2	0.26 ± 0.19	0.37 ± 0.31	0.33 ± 0.20
Profile	R1	1	0.34 ± 0.31	0.26 ± 0.20	0.24 ± 0.23
		2	0,20. ± 0.13	0.32 ± 0.25	0.36 ± 0.18
	R2	1	0.19 ± 0.15	0.27 ± 0.18	0.18 ± 0.17
		2	0.34 ± 0.12	0.30 ± 0.29	0.26 ± 0.21
	R3	1	0.24 ± 0.12	0.20 ± 0.16	0.22 ± 0.13
		2	0.19 ± 0.16	0.35 ± 0.27	0.21 ± 0.15

Finally, it was evaluated the influence of menstrual phases in thermal symmetry. The results can be observed in table 22 for all moments.

Table 23: Results of p-value, U, W and Z values of U Mann Whitney test between moments for thermal symmetry.

		Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	P	U	W	Z	P	U	W	Z	p
Frontal	R1	64	169	-0.36	0.71	50	105	-1.16	0.24	59	114	-0.66	0.50
	R2	55	160	-0.85	0.39	65	120	-0.26	0.79	56	111	-0.82	0.41
	R3	69	124	-0.05	0.95	67	172	-0.14	0.88	65	170	-0.26	0.79
Profile	R1	48	103	-1.28	0.19	60	165	-0.56	0.57	44	149	-1.51	0.13
	R2	29	134	-2.38	0.01	68	123	-0.11	0.90	57	162	-0.73	0.46
	R3	59	114	-0.64	0.51	49	154	-1.20	0.22	62	117	-0.44	0.65

Using U Mann-Whitey test, it can be stated that there exists significant statistical evidence to affirm that thermal symmetries were equal for all ROIs in all moments with exception to profile ROI R2 between moment I and II (see table 23).

4.2.1.2 Microvascular System

In this system it was also studied the influence of gender and phase of menstrual cycle. Firstly, it was evaluated if the response of the female and male genders were equal at all moments for the right side in frontal and profile positions (see appendix VII). By U Mann-Whitey test it can be stated that there exist significant statistical evidence to affirm that between moment I and II, all temperatures of all ROIs were similar, with exception to frontal ROI R9 and profile ROIs R6, R7, R8 and R10. Between moments II and III, all temperatures of all ROIs were equal, with exception to frontal R1, R4, R6, R7 and R9 ROIs and profile R1, R3, R6, R7, R8, R9 and R10 ROIs (see appendix VII). Finally, between moments I and III, all temperatures were similar, with exception of frontal R1, R6 and R9 ROIs and profile R1, R2, R6, R7, R8, R9 and R10 ROIs.

Regarding the left side, it was performed the same study (appendix VIII). Using U Mann-Whitey test it can be stated that there exist significant statistical evidence to affirm that all temperatures were similar between moments I and II, with exception to ROIs frontal R5 and R9, and profile R6, R7, R8 and R10. Between moments II and III, all temperatures were identical with exception to frontal R1, R6, R7 and R9 and profile R1, R6, R7, R8, R9 and R10. In sum, between moments I and III all temperatures were equal with exception of profile R1, R3, R6, R7, R8, R9 and R10 and frontal R6, R7 and R8 (appendix VIII).

Relatively to thermal symmetry, the same study was performed, also in frontal and profile positions (appendix IX). Using the U Mann-Whitey test it can be referred that there is significant statistical evidence to affirm that the thermal symmetries were similar for all ROIs in all moments, with exception to profile ROI R3 between moments I and II, frontal R3 and R7 and profile R1, R7 and R8 ROIs between moments II and III. Between moments I and III, only frontal R3 and profile R1 and 7 ROIs were different (see appendix IX).

Secondly, it was studied the influence of menstrual cycle phases in MS in profile and frontal positions (appendix X). Using U Mann-Whitey test it can be stated that there is significant statistical evidence to affirm that the temperatures of right side were equal for all

ROIs in all moments, both profile and frontal positions with exception of frontal ROI R8 between moments II and III. The results can be observed in appendix X. Using U Mann-Whitey test, it can be referred that there is significant statistical evidence to affirm that the temperatures of left side were identical for all ROIs in all moments in both profile and frontal positions (appendix XI).

The thermal symmetry response of different phases in each moment for frontal and profile positions was assess using U Mann-Whitney test (appendix XII). Through this test it can be stated that there is significant statistical evidence to affirm that thermal symmetry are similar for all ROIs in all moments, with exception to profile ROI R3 between moments I and II and frontal ROI R9 between moments II and III and between moments I and III. The results can be observed in appendix XII.

4.2.2 Oncologic Group

For oncologic group, it was studied the influence of individuals characteristics such as gender, age, BMI, sun sensibility and malignancy in ΔT and mean temperature. In relation to diagnosed group, all mentioned characteristics were studied. Concerning the gender, it were recorded 26 females and 32 males. For malignancy, it were recorded 14 benign skin neoplasms and 44 malignant neoplasms of the diagnosed group. The distribution of individuals in each BMI class for diagnosed group was 1 individual bellow age of 18.5, 20 individuals in class]18.5-25], 28 individuals in class]25-30] and 9 individuals in class]30-35]. The distribution in each subject age was 3 individuals in class [18-30], 2 individuals in class]30-40], 2 individuals in class]40-50], 4 individuals in class]50-60], 18 individuals in class]60-70] and 29 individuals with age higher than 70. For sun sensibility, were recorded 6 individuals in class]10-20], 22 individuals in class]20-30] and 30 individuals in class]30-40]. The obtained results for each characteristic were in table 24.

Regarding to follow-up group, it were recorded 24 females and 21 males. For malignancy, it were recorded 3 benign skin neoplasms and 42 malignant neoplasms of the diagnosed group. The distribution of individuals in each BMI class for the diagnosed group was 16 individuals in class]18.5-25], 19 individuals in class]25-30], 8 individuals in class]30-35] and 2 individuals with BMI higher than 35. The distribution in each subject age was 3 individuals in class [18-30], 1 individuals in class]30-40], 3 individuals in class]40-50], 7 individuals in class]50-60], 10 individuals in class]60-70] and 21 individuals with age higher than 70.

Table 24: Obtained results for each characteristic to median temperatures of aright and lefts sides and ΔT s for diagnosed group.

	Classes	Right	Left	ΔT
Subject Age	[18,30]	33.00 \pm 1.48	33.00 \pm 1.34	0.00
]30,40]	33.00 \pm 0.00	32.90 \pm 0.00	0.10 \pm 0.00
]40,50]	33.70 \pm 2.47	33.60 \pm 2.28	0.10 \pm 0.01
]50,60]	34.40 \pm 5.00	34.30 \pm 4.79	0.10 \pm 0.02
]60,70]	34.15 \pm 4.48	34.25 \pm 2.10	0.10 \pm 0.79
	>70	33.80 \pm 2.64	34.00 \pm 2.73	0.20 \pm 0.05
Subject Gender	Female	33.55 \pm 4.41	33.90 \pm 3.69	0.20 \pm 0.33
	Male	34.10 \pm 1.28	34.10 \pm 1.35	0.10 \pm 0.04
BMI]18,5;25]	34.45 \pm 3.74	34.25 \pm 2.24	0.10 \pm 0.48
]25,30]	33.80 \pm 1.62	34.00 \pm 1.54	0.10 \pm 0.07
]30,35]	32.90 \pm 4.56	32.75 \pm 4.59	0.15 \pm 0.01
	<35	34.05 \pm 0.61	34.05 \pm 0.13	0.30
Sun Sensibility]10,20]	33.00 \pm 0.00	32.90 \pm 0.00	0.10 \pm 0.00
]20,30]	34.40 \pm 5.72	34.20 \pm 4.76	0.10 \pm 0.43
]30,40]	33.75 \pm 1.50	33.95 \pm 1.43	0.10 \pm 0.05
Malignancy	Benign	33.00 \pm 0.01	33.00 \pm 0.02	0.00
	Malign	34.15 \pm 3.39	34.05 \pm 2.90	0.10 \pm 0.21

For sun sensibility, it were recorded 1 individual in class]10-20], 18 individuals in class]20-30] and 26 individuals in class]30-40]. The obtained results for each characteristic are presented in table 25.

Table 25: Results follow-up group characteristic to right and lefts sides and ΔT .

Characteristics	Classes	Right	Left	ΔT s
Subject Age	[18,30]	33.00 \pm 1.48	33.00 \pm 1.34	0.00
]40,50]	33.70 \pm 2.47	33.60 \pm 2.28	0.10 \pm 0.01
]50,60]	34.40 \pm 5.00	34.30 \pm 4.79	0.10 \pm 0.02
]60,70]	34.15 \pm 4.48	34.25 \pm 2.10	0.10 \pm 0.79
	>70	33.80 \pm 2.64	34.00 \pm 2.73	0.20 \pm 0.05
	Subject Gender	Female	33.55 \pm 4.41	33.90 \pm 3.69
Male		34.10 \pm 1.28	34.10 \pm 1.35	0.10 \pm 0.04
BMI]18,5;25]	34.45 \pm 3.74	34.25 \pm 2.24	0.10 \pm 0.48
]25,30]	33.80 \pm 1.62	34.00 \pm 1.54	0.10 \pm 0.07
]30,35]	32.90 \pm 4.56	32.75 \pm 4.59	0.15 \pm 0.01
	>35	34.05 \pm 0.61	34.05 \pm 0.13	0.30
Sun Sensibility]10,20]	33.00 \pm 0.00	32.90 \pm 0.00	0.10 \pm 0.00
]20,30]	34.40 \pm 5.72	34.20 \pm 4.76	0.10 \pm 0.43
]30,40]	33.75 \pm 1.50	33.95 \pm 1.43	0.10 \pm 0.05
Malignancy	Benign	33.00 \pm 0.01	33.00 \pm 0.02	0.00
	Malign	34.15 \pm 3.39	34.05 \pm 2.90	0.10 \pm 0.21

It was studied if ΔT was related to these characteristics for both groups. For diagnosed group, with the aid of U Mann-Whitney test it can be stated that there is statistical significant evidence to affirm that the ΔT s referring to malignancy were different (table 26).

Table 26: U Mann Whitney test results in terms of p-value and ranking values for diagnosed group.

Characteristics	U	W	Z	P
Gender	171.00	402.00	1.94	0.05
Malignancy	16.00	22.00	2.26	0.02

Within diagnosed group, using Kruskal-Wallis test there is statistical significance evidence to affirm that the ΔT s were different for the BMI classes (table 27).

Table 27: Kruskal-wallis test results in terms of p-value for diagnosed group.

Characteristics	p
Age	0.33
BMI	0.00
Sun Sensibility	0.53

For the follow-up group, using U Mann-Whitney test there is statistical significance evidence to affirm that the ΔT s referring to gender and malignancy were identical (table 28).

Table 28: U Mann Whitney test results.

Characteristics	U	W	Z	P
Gender	343	694	1.15	0.25
Malignancy	209	314	1.82	0.07

Using Kruskal-Wallis test there is statistical significance evidence to affirm that the ΔT s were different in BMI classes (table 29).

Table 29: Kruskal-wallis test results in terms of p-value.

Characteristics	P
Age	0.51
BMI	0.04
Sun Sensibility	0.64

4.3 Individuals characteristics and malignancy

The fourth part of this study is focused on establishing relations between individual's characteristics and malignancy. Characteristics such age, gender, body mass index, sun sensibility and family history.

It was verified that 83.3% of individuals are within 18 to 30 years old and were benign neoplasms. The prevalence of malign neoplasms was the age group of 40 to 70 years old is also noteworthy (see table 30). Using Pearson chi-square test can be stated that there is statistical significant evidence that the age and malignancy are associated.

Table 30: Prevalence of malignancy by age classes.

	[18,30]]30,40]]40,50]]50,60]]60,70]		>70		P
	N	%	N	%	N	%	N	%	N	%	N	%	
Benign	5	83.3%	2	66.7%	0	0.0%	1	9.1%	4	14.3%	5	100%	0.00
Malign	1	16.7%	1	33.3%	5	100.0%	10	90.9%	24	85.7%	45	90.0%	

A percentage of 14% of female individuals had benign neoplasms (table 31). With Pearson chi-square test, it can be stated that there is no statistical significant evidence that the gender is related with malignancy.

Table 31: Prevalence of malignancy in gender.

	Female		Male		P
	N	%	N	%	
Benign	7	14.0%	10	18.9%	0.506
Malign	43	86.0%	43	81.1%	

A percentage of 5.9% of individuals who had BMI less than 18.5 kg/m² had benign neoplasms. Whereas 44.2% of individuals with BMI between 25 and 30 kg/m² had malignant neoplasms (table 32). Using Pearson chi-square test there is statistical significant evidence to affirm that the BMI classes and malignancy are not associated.

Table 32: Prevalence of malignancy by BMI classes.

	<18,5]18,5;25]]25,30]]30,35]		>35		P
	N	%	N	%	N	%	N	%	N	%	
Benign	1	5.9%	6	35.3%	9	52.9%	1	5.9%	0	0.0%	0.131
Malign	0	0.0%	30	34.9%	38	44.2%	16	18.6%	2	2.3%	

A percentage of 26.8% of individuals who had a sun sensibility between 30 and 40 points had benign neoplasms. However, 97.5% of individuals, who had a sun sensibility between 20 and 30 points had malignant neoplasms (table 33). Using Pearson chi-square test, it can be stated that there is statistical significant evidence that the sun sensibility is related with malignancy.

Table 33: Prevalence of malignancy by sun sensibility classes.

]10,20]]20,30]]30,40]		P
	N	%	N	%	N	%	
Benign	1	14.3%	1	2.5%	15	26.8%	0.007
Malign	6	85.7%	39	97.5%	41	73.2%	

A percentage of 50% of individuals who had family history with paternal relatives had benign neoplasms. Similarly, 50% of individuals who had family history with paternal relatives had malignant neoplasms. It should also be noted that 20% of individuals who had family history with a sibling had benign neoplasms, while 80% of individuals who had family history with a sibling had malign neoplasms (figure 28). Thus, using Pearson chi-square test, it can be

affirmed that exists statistical significant evidence that the family history is not related with malignancy ($p=0.457$).

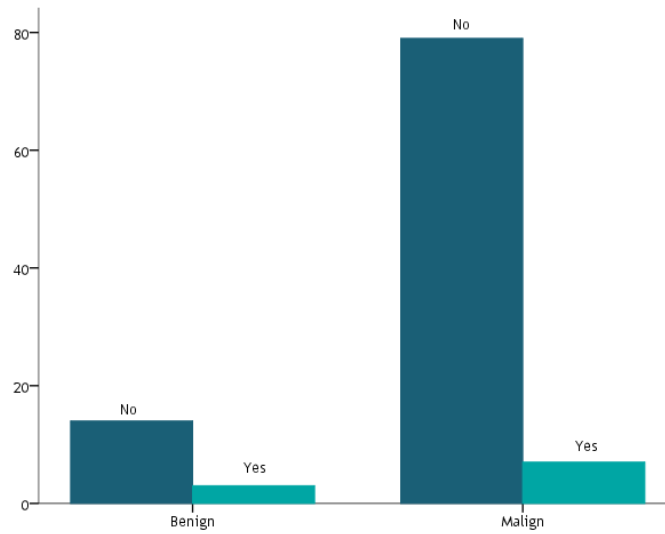


Figure 28: Illustration of the malignancy prevalence with family history.

4.4 Case Study - Basal cell carcinoma

Another study was performed to investigate whether the ΔT value of individuals with basal cell carcinoma in the diagnosed and control group were identical. Four case studies of basal cell carcinoma were studied.

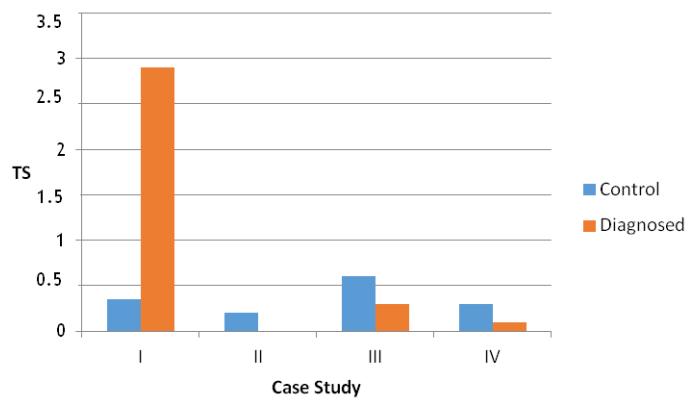


Figure 29: ΔT illustration in the different case studies.

It can be observed in the figure 29 that the ΔT values that stand out correspond to the control groups with the exception of case study I, where the diagnosed individual has a fairly high ΔT .

Table 34: Results of U Mann-Whitney test.

	CS I	CS II	CS III	CS IV
U	0	0.5	0.5	2.5
W	105	1.5	1.5	3.5
Z	-1.639	-1.571	-1.553	-1.184
p	0.101	0.116	0.12	0.236

Using U-Mann Whitney test, it can be affirmed that exists significant statistical evidence that the ΔT values of basal cell carcinoma asymptomatic individuals is similar in all case studies (table 34).

4.5. Summary considerations

The global obtained results showed that the median temperatures between moments of ANS and MS in the control group were different in the majority of ROIs. On the other hand, the thermal symmetry was always similar for the ANS, noting some differences in the MS.

Relatively to oncological skin surface characterization, it was not found differences in the mean temperatures of the right and left sides, neither between the ΔT s of different types of skin neoplasms. However, there are significant differences in the ΔT s of the follow-up group.

When it was studied the influence of the individual's characteristics in skin surface, there was always differences in gender of ANS for the right side, while for the left side there was the opposite. For the MS there were no differences for both sides. With respect to menstrual phase, there was no statistical evidence for both systems.

Finally, it was concluded that BMI characteristic influenced the ΔT of oncologic group, while the malignancy also influenced the ΔT of diagnosed group.

Chapter 5.

Discussion

In this chapter the reader will find a discussions on the facial skin surface temperature characterization, the influence of individual characteristics in facial skin surface temperature, the relationship between individual characteristics with the neoplasm malignancy.

5.1 Skin surface temperature characterization

The first study consisted in an exploratory data analysis of a control group in order to characterize the temperature at the skin surface of the face (most affected region with skin neoplasms) in the autonomous nervous system (ANS) and microvascular system (MS). This study considered the intervention of a thermal stimulus in order to evaluate the physiological response of the face skin surface. It was found that the mean temperature of zones between moments was significantly different. There were always differences between the first and the second moments, as it would be expected with the application of a cold stimulus, similar effect was found at third moment. There was a decline in temperature of approximately 2°C in the ANS and 1.5°C in the MS due to the thermal stimulus. It means that the exposure time period of two minutes used to cool the face surface with the fan was adequate. After applying the stimulus, the autonomic nervous system reacts, trying to prevent a drop in body temperature and readjusting the temperature to its normal levels (homeostasis) correcting the caused disequilibrium. From the second to the third moments there was a clear increase, due to the response of the thermoregulatory system in order to restore the temperature levels. It would be expected that mean temperatures between the first and the third moments to be similar. Despite this fact, there is a small difference of approximately 0.5 °C between the temperature values of the two moments. Which means that the third moment should be longer than 5 minutes to allow for null recovery.

Performing a deeper analysis, in the ANS it was worth noticing that frontal ROI R2 did not register any difference in the mean temperatures between moment I and II for left and right sides. Similarly in the MS the frontal ROI R2 between moment I and III had no differences in

mean temperatures. These results may be due to the fact that in this area of the face being located a large amount of adipose tissue.

Within this group it was also studied the influence of thermal symmetry in both systems. In ANS, all thermal symmetries were identical, with exception to frontal ROI R1 between moment I and II and between moments I and III. To MS, the majority of thermal symmetries were similar, excluding ROI R4 and ROI R7 in frontal and profile positions. These results may be due to poor performance of the fan for ROI R4, or individuals with non-acknowledged teeth condition for ROI R7. Finally, it was calculated the mean thermal symmetries for each system. The ANS presented a mean thermal symmetry of approximately 0.23°C while MS unveiled a mean thermal symmetry of approximately 0.35°C. These values are only suggestive and exploratory. However, they were in agreement with the literature values [99, 100].

Relatively to the oncologic group, it would be expected that, the benign neoplasms exhibit lower temperature than malignant neoplasms, since the greater the degree of inflammation, the higher temperature would be expected in that zone. These results may have been due to an absence of inflammatory processes in the malignant neoplasms at the time of imaging.

It was also expected that newly diagnosed neoplasms, demonstrating higher temperature values when compared to patients who were surgically intervened. Although in some cases this was verified, at a global analysis there are no relevant differences. After this, the mean temperatures of the various types of skin neoplasms were investigated for the oncologic group and the conclusions were confirmed. All types of studied skin neoplasms had equal mean temperatures for the different sides. These values may have been different if the thermographic examination was complemented with the application of a provocative test, similar to the thermal stimulus that was applied to the control group. Some authors [83], [86] argue that thermal stimulation solves the problems of false negatives provided by medical thermography. In the case of malignant neoplasms, when the area of the skin is cooled, an hypertermic manifestation is expected in the middle of the neoplasm, followed by a fast thermal recovery of the neoplasm tissue when compared with the surroundings. The thermal challenge was not applied in this research study with the oncological group due to operational constraints, such as the reconstructive plastic surgery consults had to last between 3 and 10 minutes and there was no extra examination room where the experiments could take part. Another approach that could have been used in an attempt to overcome the presented difficulties, was in the images analysis, to draw two diagonals over the skin neoplasm, named D and D' (figure 30) with a fixed number of points and to calculate a vector V through these following formula: $V_i^N = D_i^N \cdot D_i'^N$.

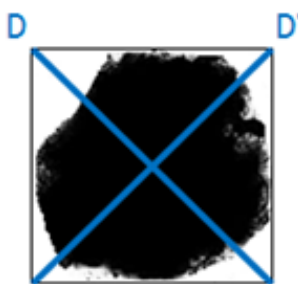


Figure 30: Example of diagonals on skin neoplasm.

Thus, it would be possible to plot a temperature profile along the skin neoplasm, and through the shape of V would be obtained more important and conclusive information, that could characterize it. Although it was not possible to the short time available.

In the oncological group, the influence of ΔT values was also investigated. The ΔT values of benign and malign skin neoplasms were equal in the diagnosed group and different in the follow-up group. These differences may be due to reading error of the thermographic camera, approximately 0.3 °C (2% of the overall reading).

5.2 Individual characteristics and skin temperature

Different results were obtained when it was tested the influence of the individual characteristics in skin surface temperature. In the control group, the influence of individual age, sun sensibility and BMI was not tested, because this group had a narrow interval of these characteristics. With regard to the gender, it was found that the mean temperatures were similar for both genders in most of the ROIs. For the ANS, profile ROIs R2 and R3 had significant differences for right and left sides. In the MS, the same can be stated for frontal ROIs R6, R7 and R9 and profile ROIs R6, R7, R8, R9 and R10 for both sides. Relatively to thermal symmetry the emphasis was to the ANS profile ROI R3 between moment II and III. For MS there was greater variability of significant ROIs. Worth mention that profile ROIs R1, R6, R7 R8 and R9 for their repetitiveness. It was concluded that in these specific areas the different genders do not react the same way for both systems, as it would be expected since there are facial gender differences. Similar results were obtained when testing the influence of the menstrual cycle phase. For both systems, the mean temperatures were similar in the different phases and for each moment. One exception was found for frontal ROI R8 for right side of MS between moments II and III. Few exceptions were found when the thermal symmetry was evaluated. For the ANS there were differences in profile ROI R2 between moments I and II and for MS. It can be underlined that the frontal ROI R9 between moments II and III, and between moments I and III, TS's were different. In the luteal phase there is a higher basal body temperature since there is a substantial increase in the production of

progesterone. These results may have been due to the difficulty to know the menstrual cycle phase of few individuals.

It was also studied if the individual characteristics have an impact on ΔT of the follow-up and skin neoplasms groups. For diagnosed group, it was found that the skin neoplasms type and BMI had impact on ΔT . For the follow-up group, only BMI had impact. Further characteristics such as gender, sun sensibility and age were not significant. The sun sensibility is only an indicative feature for high or low risk of skin neoplasms, not being related with the ΔT .

5.3 Individuals characteristics and malignancy

Various characteristics were tested to establish a relation with the neoplasm type. With respect to age, this is related to the neoplasm type, since older people (> 40 years) are more likely to develop malignant neoplasms, whereas younger people (<30 years) are more likely to develop benign neoplasms. This result was entirely related to prolonged sunlight exposure for many years. This means that people tend to develop malignancies in adulthood.

On the other hand, it can be concluded that the gender is not related to the neoplasm type. These results suffer from selection bias because it was not considered the same number of individuals for different genders. The physician collaborating with this study referred that these diseases are more prevalent in the male gender because they usually have professions with much more prolonged sun exposure.

Furthermore, it was also found that BMI is not related to the neoplasm type, it can be accepted since there are people with different weights and heights, developing neoplasms. However, in the literature [114] there is a relationship between obese (BMI > 30) and the development of nonmelanoma skin cancer. In the current study sample there was a high incidence of malignancies in pre-obese, $24.9 < \text{BMI} < 30$). There was a small incidence of people being obese, but mostly in pre-obesity.

The sun sensibility is found to be related to the neoplasm type. A very sun sensibility person (light skin, light hair, light eyes and has freckles) develops burns much faster, more severe and deeper than a less sun sensibility person, increasing the risk of developing malignancies later.

Family history is unrelated to the skin neoplasms type. Although the literature [5] says that melanoma may be hereditary. It cannot be concluded from this study, since the number of screened melanomas was too small and the vast majority of participants have no melanoma family history. Later, it was found that many of them were not aware, this may be due to the high number of family members, disease illiterate or even memory problems.

5.4 Case studies

The results obtained for the case studies allowed to conclude that ΔT of the skin neoplasm individual and associated control group were similar for diagnosed group. However, this result is contrary to the literature [95]. Many studies shows that in the case of basal cell carcinoma had higher metabolism, increasing blood flow and presented slightly higher temperature when compared to surrounding healthy skin. Therefore, it should have been obtained higher temperatures in the basal cell carcinoma participants than in the control group. However, to the results being more accurate and precise, a larger dimension sample of basal cell carcinoma participants is needed.

Chapter 6.

Conclusion

The aim of this research study was the characterization of the temperature at the skin surface in healthy control and skin oncologic groups, which was fully accomplished. It was also assessed the effect of age, BMI, gender, sun sensibility, malignancy, menstrual cycle phase in females, thermal symmetry and ΔT s in the studied population.

Reference data was provided for facial temperature distribution in autonomous nervous system and microvascular system.

The characteristic factors that had a significant relationship were the BMI for the diagnosed and follow-up groups, and the malignancy factor in the diagnosed group.

It can be concluded that medical thermal imaging proved its importance in the support for the identification and assessment of the skin carcinoma treatments. However, it requires significant research improvements and more tests with large samples in order to be actually used as a complementary method of diagnosis in the field of dermatology. Nevertheless, there were many limitations in this study that could affect the global results:

- It was not impossible to perform the thermo-stimulus in the oncologic group, due to the reduced appointment time for each individual (less than 10 minutes) and the inexistence of a free examination room;
- The impossibility of measure the height and weight of the individuals involved in this study, and thus not accurate.

6.1 Proposed future work

In order to take this work into a further step, the following future work is proposed:

- Build a larger dataset to yield more diverse in order to have more statistical evidence results;
- Develop an efficient cold stimulus for better understanding of the thermophysiology of the skin surface and associated characteristics;

- Development of a dedicated software for standardizing the image analysis in order to improve the reproducibility and accuracy of the method.

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APPENDIXES

Appendix I: Approved ethics Committee document

Parecer CES IPO: 109/014

Assunto: Estudo de Investigação “Análise de Melanomas Através de Termografia Médica Normalizada e Automatizada”.

Investigadora: Liliana Vasconcelos Esteves

Data: 05 de Junho de 2014

PARECER

É parecer desta CES não existir impedimento de natureza ética à realização do referido Estudo de Investigação, desde que anonimizado em termos de formulário e imagens.



Dr. Artur Lima Bastos
Presidente da CES – IPO Porto EPE

Appendix II: Volunteers information

INFORMAÇÃO AOS VOLUNTÁRIOS

Projeto de investigação: **Caracterização de Neoplasias de pele através de Termografia Médica normalizada.**

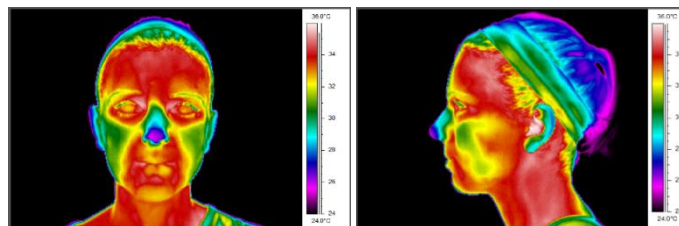
Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E.
Faculdade de Engenharia da Universidade do Porto

1. O porquê deste projeto de investigação?

Este projeto pretende investigar a utilização da termografia médica na avaliação fisiológica tanto na identificação, como na monitorização dos tratamentos dos melanomas (tipo de cancro da pele) na zona onde estiver presente a lesão. Os resultados deste projeto permitirão efetuar estudos de maior dimensão na área dos melanomas e em outras regiões de interesse do corpo humano, possibilitando conhecer melhor a sua fisiologia, encaminhamento para tratamentos mais eficazes, e conseqüentemente, levar à redução substancial dos custos associados a esta patologia.

2. O que é um termograma?

Um termograma é uma imagem da temperatura da pele. Tal pode ser observado nas figuras exibidas em baixo, que representam termogramas da face frontal e lateral, respetivamente.



Estas imagens são obtidas através de captura por parte de câmaras termográficas, das perdas de calor naturais que acontecem à superfície da pele. É um procedimento não-invasivo, inofensivo e indolor, sendo que as fotografias são adquiridas do mesmo modo que o método convencional. As imagens recolhidas vão ser usadas para fins médicos e académicos, sendo que os dados de cada paciente irão ser preservados e mantidos confidenciais, assim como toda a informação irá ser gravada de modo seguro. É impossível identificar um indivíduo através de um termograma, sem que a identificação esteja associada ao mesmo.

3. O que é um melanoma?

Os melanomas são um tipo de cancro que atinge o tecido epitelial, tendo origem nos melanócitos, células localizadas na epiderme, que são responsáveis pela produção de melanina, pigmento que dá à pele a sua cor natural. Têm grande capacidade de metastizar de forma rápida, num estadio da doença relativamente precoce. O melanoma surge quando os melanócitos (células pigmentares), adquirem o estado maligno. Os melanomas são o terceiro tipo de cancro da pele mais comum, que afeta pessoas de todas as faixas etárias. Embora o melanoma seja a maior causa de morte de cancro da pele, se este for detetado num estadio precoce pode ser curável.

4. O que necessito que faça para participar neste projeto?

Venho por este meio, pedir a sua colaboração num projeto de investigação simples e rápido, onde apenas serão retiradas algumas fotografias (uma ou duas) da zona onde poderá estar presente a lesão. Este processo envolve várias etapas.

Necessito que antes da captura das fotografias, o indivíduo permaneça numa sala climatizada, expondo a área onde poderá estar a lesão, com o intuito de a mesma obter a temperatura pretendida. Este processo demora cerca de 10 minutos. Enquanto isso, o indivíduo deverá preencher e tomar conhecimento de alguns formulários. Entre estes incluem-se, o consentimento informado, questionário de dados biométricos, e questionário associado à patologia. O questionário de dados biométricos permite conclusões acerca de problemas relacionados com mobilidade, autonomia, atividades normais, desconforto/dor e também ansiedade/depressão. A pontuação final obtida neste questionário deverá ser igual a zero, para inclusão do indivíduo no projeto. Também é indispensável que este tenha o seu índice de massa corporal (IMC) calculado. Este é um cálculo relativamente simples, bastando para tal dividir a massa por duas vezes a altura. Esta informação é utilizada para agregar os indivíduos com IMC semelhante.

No dia das recolhas algumas precauções deverão ser tomadas antes do período de recolha, tais como:

- Não ingerir uma refeição pesada;
- Não participar em atividades cansativas e desgastantes;
- Não ingerir bebidas alcoólicas e fumar, num período até duas horas antes de as imagens serem recolhidas;
- Deverá ser usado o mínimo vestuário possível para se obterem termogramas claros;
- Remover todo o tipo de bijuteria e relógios durante o período de captura;
- Não aplicar à pele qualquer tipo de creme corporal;
- Por fim, permanecer estático nas posições solicitadas pelo investigador para o procedimento de captura.

5. Quanto tempo vai durar?

A participação de cada indivíduo neste projeto irá demorar aproximadamente 15 minutos (incluindo o tempo de descanso). As recolhas deverão ser feitas quando for da sua conveniência.

6. Vou ser pago pela minha participação?

Infelizmente, o financiamento é limitado, pelo que não irá receber qualquer pagamento pela sua participação neste estudo. Contudo, irá contribuir significativamente para desenvolvimentos únicos e importantes na área da utilização da termografia médica na dermatologia. Após a participação, chocolates e rebuçados serão oferecidos como sinal de gratidão. As imagens recolhidas poderão também ser enviadas via email caso sejam solicitadas pelo voluntário.

7. Contacto

Nome: Liliana Vasconcelos Esteves

Instituição: Faculdade de Engenharia da Universidade do Porto

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telemóvel: 918611971

Appendix III : Consent Form

Consentimento Informado

Considerando a "Declaração de Helsínquia", da Associação Médica Mundial (Helsínquia 1964; Tóquio 1975, Hong Kong 1989; Somerset West 1996; Edimburgo 2000; Washington 2002, Tóquio 2004 e Seoul, 2008)

Designação do projeto de investigação

Análise de melanomas através de Termografia Médica normalizada e automatizada

Eu, abaixo-assinado (nome completo do doente adulto ou do voluntário são)

Recebi o texto de *Informação ao Participante* relativo ao procedimento que concordei efetuar. Compreendi a explicação que me foi fornecida pelo investigador que assina este documento. Foi-me ainda dada oportunidade de fazer as perguntas que julguei necessárias, e de todas obtive resposta satisfatória.

Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objetivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de anular a todo o tempo a minha participação no estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada.

Por isso, consinto que me seja aplicado o método, o tratamento ou o inquérito proposto pelo investigador.

Assinatura do doente ou voluntário são: _____ Data: __/__/201__

Nome do Investigador responsável: _____ Data: __/__/201__

Assinatura do Investigador responsável: _____ Data: __/__/201__

Anulação do Consentimento Informado

Declaro que recebi a *Informação ao Participante* relativo ao projeto de investigação em questão, que me foi proposto pelo investigador que assina este documento e **pretendo anular** o consentimento dado na data __/__/201__.

Assinatura do doente ou voluntário são: _____ Data: __/__/201__

Assinatura do Investigador responsável: _____ Data: __/__/201__

Nota: Fornecimento obrigatório de cópia ao participante.

Appendix IV : Questionnaire

Questionário de dados biométricos

Preencha o questionário abaixo indicado, de forma a avaliar o estado de saúde dos voluntários participantes neste estudo.

Nome: _____

Género: Feminino Masculino Outro

Peso: _____

Idade: _____

Altura: _____

Índice de massa corporal: _____

Lesões ou cirurgias realizadas nos últimos meses: Sim Não

Se respondeu sim, há quanto tempo? _____

Pontuação: _____

De acordo com os tópicos abaixo descritos, por favor assinale aquele com qual se identifica.

Mobilidade	
Não tenho problemas em caminhar	
Tenho alguns problemas ao caminhar	
Estou de cama	
Autonomia	
Não costumo ter problemas no dia à dia	
Tenho alguns problemas em tarefas como lavar-me e vestir-me	
Sou incapaz de realizar tarefas como lavar-me ou vestir-me	
Actividades normais	
Não tenho problemas na realização das tarefas normais (trabalhar, estudar etc.)	
Tenho alguns problemas na realização das tarefas normais (trabalhar, estudar etc...)	
Sou incapaz de realizar as tarefas normais	
Desconforto/Dor	
Não tenho nenhuma dor ou desconforto	
Tenho dor moderada ou desconforto	
Tenho extrema dor ou desconforto	
Ansiedade/Depressão	
Não sofro de ansiedade ou depressão	
Sofro moderadamente de ansiedade/depressão	
Sofro extremamente de ansiedade/depressão	

*Com base em [115]

Nota importante: Só podem realizar os testes pretendidos quem obtiver pontuação nula neste questionário.

1. De acordo com os tópicos abaixo descritos, selecione para cada pergunta, a opção com qual se identifica.

Questões	Respostas	Pontuação
Qual é a cor da sua pele quando não está bronzada?	Avermelhada	1
	Clara/Pálida	2
	Castanho claro	3
	Castanho escuro	4
Tem sardas?	Sim, muitas	1
	Sim, algumas	2
	Sim, poucos	3
	Não	4
Como é que a sua pele reage à exposição solar?	Muito sensível, susceptível a irritação	1
	Sensível, por vezes com irritação	2
	Geralmente sensível, raramente irritação	3
	Insensível, nenhuma irritação	4
Quanto tempo é que se pode expor ao sol, num céu sem nuvens, ao meio dia, sem ficar com queimaduras?	Menos de 15 minutos	1
	Entre 15 a 20 minutos	2
	Entre 25 e 40 minutos	3
	Mais de 40 minutos	4
Como é que a sua pele reage à longa exposição solar?	Sempre com queimaduras solares	1
	Principalmente com queimaduras solares	2
	Muitas vezes com queimaduras solares	3
	Raramente ou nunca com queimaduras solares	4
Que tipo de queimaduras costuma desenvolver sempre que se expõe ao sol durante muito tempo?	Vermelhão forte, bolhas dolorosas, descamação da pele	1
	Vermelho claro, seguido por descamação	2
	Avermelhamento, seguido por vezes por descamação	3
	Quase nunca vermelhão e descamação	4
Alguma vez experimentou efeito de bronzeamento após banhos de sol durante um período de tempo prolongado?	Nunca	1
	Quase nunca	2
	Frequentemente	3
	Quase sempre	4
Como funciona o seu bronzeado após banhos de sol repetidos?	Nunca ou quase nunca	1
	Bronze mínimo	2
	Progressivo, bronze claro	3
	Rápido, bronze profundo	4
Como descreve a sua cor natural de cabelo?	Vermelho até castanho avermelhado	1
	Castanho claro até loiro	2
	Loiro escuro até castanho	3
	Castanho escuro até preto	4
Como descreve a sua cor de olhos?	Azul claro, cinza, ou verde claro	1
	Azul, cinza ou verde	2
	Castanho claro ou cinza escuro	3
	Castanho escuro	4
Total		

2. Tem parentes com melanomas?

- a. Sim
- b. Não
- c. Não sei

2.1. Se respondeu sim à questão anterior, indique qual o grau de parentesco.

- a. Pai/mãe
- b. Tio/Tia
- c. Irmão/Irmã
- d. Filho/Filha
- e. Outro

*Com base em [116, 117].

Nota importante: A pontuação obtida neste questionário diz respeito à sensibilidade solar da pele. Tendo um mínimo de 10, representando alta sensibilidade solar, enquanto que um máximo de 40, representa baixa sensibilidade solar

APPENDIXE V: ANS results of p-value and ranking values to right side of each phase

		Moment I to II				Moment II to III				Moment I to III				
		U	W	Z	p	U	W	Z	p	U	W	Z	p	
Profile	Frontal	R1	66.0	121.0	-0.2	0.80	44.0	99.0	-1.5	0.10	69.5	124.5	0.0	1.00
		R2	63.5	118.5	-0.4	0.70	47.5	102.5	-1.3	0.20	63.0	118.0	-0.4	0.70
		R3	56.5	111.5	-0.8	0.40	59.5	114.5	-0.6	0.50	65.5	120.5	-0.3	0.80
Profile		R1	64.0	119.0	-0.4	0.70	42.0	97.0	-1.6	0.10	70.0	125.0	0.0	1.00
		R2	62.0	117.0	-0.5	0.60	52.0	107.0	-1.1	0.30	70.0	125.0	0.0	1.00
		R3	61.0	116.0	-0.5	0.60	56.5	111.5	-0.8	0.40	66.5	171.5	-0.2	0.80

APPENDICE VI: ANS mean temperatures to left side of each phase and results of p-value and ranking values

	ROIs	Phase	1st Moment	2nd Moment	3rd Moment
Frontal	R1	1	34.64 ± 0.43	32.76 ± 0.84	34.21 ± 0.73
		2	34.54 ± 0.71	32.24 ± 0.67	34.25 ± 0.77
	R2	1	33.97 ± 0.69	32.46 ± 0.66	33.72 ± 0.82
		2	33.90 ± 0.90	32.11 ± 1.04	33.78 ± 0.91
	R3	1	33.72 ± 0.69	31.95 ± 0.70	33.18 ± 0.99
		2	33.10 ± 0.74	31.56 ± 1.07	33.12 ± 0.84
Profile	R1	1	34.28 ± 0.44	32.54 ± 0.79	33.73 ± 0.75
		2	33.98 ± 0.62	32.15 ± 0.69	33.78 ± 0.72
	R2	1	33.61 ± 0.79	31.90 ± 0.85	32.87 ± 0.84
		2	33.26 ± 0.98	31.61 ± 1.06	32.87 ± 1.02
	R3	1	33.79 ± 0.74	32.12 ± 0.64	32.99 ± 0.86
		2	33.51 ± 0.74	31.87 ± 0.97	33.09 ± 0.74

		Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	p	U	W	Z	p	U	W	Z	p
Frontal	R1	66	121	-0.24	0.81	39	94	-1.79	0.07	67	172	-0.18	0.86
	R2	69	124	-0.06	0.95	56	111	-0.82	0.41	66	171	-0.20	0.84
	R3	36	91	-1.96	0.05	55	110	-0.85	0.4	60	115	-0.56	0.58
Profile	R1	50	105	-1.18	0.24	50	105	-1.14	0.25	70	125	0.00	1.00
	R2	53	108	-1.00	0.32	62	117	-0.47	0.64	65	170	-0.29	0.77
	R3	55	110	-0.88	0.38	60	115	-0.56	0.58	68	173	-0.12	0.91

Appendix VII: MS mean temperatures to right side of each gender and results of p-value and U,W an Z values

	ROIs	Gender	1st Moment	2nd Moment	3rd Moment
Frontal	R1	F	32.06 ± 1.56	30.33 ± 1.44	31.98 ± 1.86
		M	32.41 ± 1.16	31.51 ± 1.28	33.43 ± 1.41
	R2	F	33.88 ± 0.91	32.38 ± 0.93	33.75 ± 1.02
		M	33.98 ± 0.73	32.75 ± 0.76	34.26 ± 0.80
	R3	F	33.99 ± 0.81	32.05 ± 1.00	33.66 ± 0.97
		M	33.96 ± 0.78	32.47 ± 0.71	33.98 ± 0.71
	R4	F	34.56 ± 0.53	32.51 ± 0.81	34.11 ± 0.78
		M	34.68 ± 0.43	33.03 ± 0.41	34.49 ± 0.35
	R5	F	34.28 ± 0.46	32.94 ± 0.59	33.95 ± 0.58
		M	34.09 ± 0.44	33.06 ± 0.39	33.97 ± 0.24
	R6	F	33.18 ± 1.06	31.08 ± 1.07	32.46 ± 1.18
		M	33.81 ± 0.62	32.17 ± 0.53	33.78 ± 0.58
	R7	F	33.59 ± 0.95	31.78 ± 1.13	33.07 ± 1.16
		M	34.01 ± 0.88	32.63 ± 0.69	33.94 ± 0.66
	R8	F	34.60 ± 0.50	33.19 ± 0.79	34.36 ± 0.64
		M	34.78 ± 0.31	33.53 ± 0.45	34.74 ± 0.41
	R9	F	32.93 ± 0.68	31.26 ± 0.72	32.32 ± 0.73
		M	33.67 ± 0.45	32.31 ± 0.30	33.39 ± 0.49
Profile	R1	F	30.90 ± 2.25	29.72 ± 2.07	31.04 ± 2.59
		M	31.73 ± 1.77	31.29 ± 1.90	32.96 ± 2.13
	R2	F	33.47 ± 1.15	32.32 ± 0.99	33.59 ± 0.97
		M	33.13 ± 0.96	32.44 ± 1.11	33.58 ± 1.10
	R3	F	33.71 ± 0.79	31.85 ± 0.94	33.45 ± 0.90
		M	33.96 ± 0.47	32.50 ± 0.64	33.96 ± 0.57
	R4	F	34.26 ± 0.66	32.60 ± 0.81	33.86 ± 0.77
		M	34.38 ± 0.53	33.03 ± 0.45	34.23 ± 0.34
	R5	F	33.98 ± 0.50	32.75 ± 0.65	33.71 ± 0.64
		M	33.91 ± 0.57	33.05 ± 0.40	33.91 ± 0.29
	R6	F	32.60 ± 1.12	30.77 ± 1.14	32.05 ± 1.19
		M	33.76 ± 0.61	32.30 ± 0.46	33.62 ± 0.52
	R7	F	33.39 ± 0.89	31.6 ± 0.99	32.84 ± 1.07
		M	34.28 ± 0.62	32.99 ± 0.58	34.07 ± 0.60
	R8	F	33.37 ± 0.88	31.70 ± 0.84	32.73 ± 0.84
		M	34.19 ± 0.55	32.91 ± 0.41	33.86 ± 0.50
	R9	F	34.45 ± 0.82	32.7 ± 0.94	33.68 ± 0.77
		M	34.45 ± 0.57	33.44 ± 0.66	34.31 ± 0.48

	F	33.16 ± 0.99	31.40 ± 0.92	32.46 ± 0.94
R10	M	34.16 ± 0.59	32.70 ± 0.50	33.85 ± 0.63

ROI's	Moment I to II				Moment II to III				Moment I to III				
	U	W	Z	p	U	W	Z	p	U	W	Z	p	
Frontal	R1	166	466	-0.70	0.48	100	400	-2.54	0.01	94	394	-2.69	0.01
	R2	187	487	-0.14	0.89	158	458	-0.94	0.35	132	432	-1.65	0.10
	R3	186	322	-0.17	0.87	151	451	-1.12	0.26	153	453	-1.08	0.28
	R4	173	473	-0.51	0.61	107	407	-2.35	0.02	143	443	-1.36	0.18
	R5	147	283	-1.23	0.22	172	472	-0.55	0.58	176	312	-0.43	0.67
	R6	130	430	-1.70	0.09	70	370	-3.37	0.00	55	355	-3.79	0.00
	R7	140	440	-1.44	0.15	115	415	-2.12	0.03	98	98	-2.60	0.01
	R8	155	455	-1.03	0.30	137	437	-1.51	0.13	126	426	-1.83	0.07
	R9	72	372	-3.32	0.00	39	339	-4.23	0.00	35	335	-4.34	0.00
Profile	R1	150	450	-1.15	0.25	105	405	-2.39	0.02	101	401	-2.51	0.01
	R2	143	279	-1.34	0.18	178	478	-0.37	0.71	190	326	-0.06	0.96
	R3	162	462	-0.82	0.41	109	409	-2.29	0.02	135	435	-1.58	0.12
	R4	180	480	-0.32	0.75	139	439	-1.47	0.14	152	452	-1.11	0.27
	R5	186	322	-0.15	0.88	150	450	-1.16	0.25	173	473	-0.51	0.61
	R6	78	378	-3.14	0.00	31	331	-4.44	0.00	39	339	-4.21	0.00
	R7	82	382	-3.04	0.00	33	333	-4.4	0.00	61	361	-3.62	0.00
	R8	86	386	-2.92	0.00	37	337	-4.29	0.00	48	348	-3.98	0.00
	R9	180	316	-0.33	0.74	100	400	-2.53	0.01	92	392	-2.75	0.01
	R10	79	379	-3.11	0.00	34	334	-4.37	0.00	35	335	-4.33	0.00

Appendix VIII: MS mean temperatures to left side of each gender and results of p-value and U,W an Z values

	ROIs	Gender	1st Moment	2nd Moment	3rd Moment
Frontal	R1	F	32.15 ± 1.57	30.59 ± 1.51	32.16 ± 1.90
		M	32.54 ± 1.25	31.66 ± 1.35	33.36 ± 1.48
	R2	F	33.98 ± 0.64	32.54 ± 0.74	33.87 ± 0.82
		M	33.84 ± 0.75	32.66 ± 0.79	34.01 ± 0.64
	R3	F	33.95 ± 0.71	32.08 ± 0.84	33.50 ± 0.96
		M	33.87 ± 0.86	32.44 ± 0.70	33.86 ± 0.69
	R4	F	34.60 ± 0.54	32.60 ± 0.81	34.10 ± 0.83
		M	34.61 ± 0.41	32.93 ± 0.34	34.39 ± 0.31
	R5	F	34.30 ± 0.51	32.95 ± 0.63	33.95 ± 0.59
		M	34.06 ± 0.38	33.00 ± 0.37	33.93 ± 0.23
	R6	F	33.18 ± 1.08	31.18 ± 1.05	32.74 ± 1.18
		M	33.79 ± 0.67	32.17 ± 0.63	33.75 ± 0.70
	R7	F	33.64 ± 0.86	31.95 ± 0.83	33.17 ± 1.00
		M	33.88 ± 0.78	32.61 ± 0.57	33.78 ± 0.65
	R8	F	34.47 ± 0.66	33.08 ± 0.76	34.13 ± 0.61
		M	34.65 ± 0.46	33.36 ± 0.40	34.54 ± 0.38
	R9	F	32.93 ± 0.81	31.30 ± 0.91	32.29 ± 0.86
		M	33.56 ± 0.47	32.31 ± 0.77	33.35 ± 0.42
Profile	R1	F	30.93 ± 2.32	29.80 ± 2.17	31.03 ± 2.96
		M	31.69 ± 1.78	31.29 ± 1.99	32.94 ± 2.22
	R2	F	33.42 ± 0.91	32.32 ± 0.91	33.57 ± 1.04
		M	32.92 ± 1.06	32.36 ± 1.18	33.59 ± 0.89
	R3	F	33.61 ± 0.70	31.99 ± 0.90	33.32 ± 0.93
		M	33.92 ± 0.62	32.58 ± 0.77	33.88 ± 0.60
	R4	F	34.39 ± 0.55	32.71 ± 0.72	33.95 ± 0.65
		M	34.36 ± 0.59	32.91 ± 0.45	34.15 ± 0.45
	R5	F	34.00 ± 0.57	32.76 ± 0.74	33.68 ± 0.85
		M	33.93 ± 0.45	32.94 ± 0.45	33.21 ± 2.69
	R6	F	32.75 ± 1.10	31.07 ± 1.13	32.22 ± 1.22
		M	33.76 ± 0.68	32.27 ± 0.65	33.62 ± 0.70
	R7	F	33.60 ± 0.78	32.00 ± 0.79	33.14 ± 0.93
		M	34.27 ± 0.62	33.03 ± 0.48	34.09 ± 0.52
	R8	F	33.38 ± 0.89	31.85 ± 0.81	32.72 ± 0.90
		M	34.24 ± 0.58	32.92 ± 0.47	33.93 ± 0.50
	R9	F	34.28 ± 0.77	32.73 ± 0.85	33.62 ± 0.61
		M	34.64 ± 0.44	33.38 ± 0.78	34.35 ± 0.57
R10	F	33.02 ± 0.99	31.42 ± 0.96	32.35 ± 0.92	
	M	34.18 ± 0.65	32.84 ± 0.61	33.96 ± 0.74	

ROI's	Moment I to II				Moment II to III				Moment I to III				
	U	W	Z	p	U	W	Z	p	U	W	Z	p	
Frontal	R1	159	459	-0.89	0.36	112	412	-2.21	0.02	121	421	-1.96	0.05
	R2	172	308	-0.55	0.58	189	489	-0.06	0.94	178	478	-0.37	0.70
	R3	182	318	-0.26	0.79	148	448	-1.20	0.22	144	444	-1.31	0.19
	R4	190	326	-0.05	0.95	134	434	-1.60	0.10	164	464	-0.77	0.43
	R5	121	257	-1.96	0.04	190	490	-0.05	0.95	189	325	-0.08	0.93
	R6	139	439	-1.45	0.14	89	389	-2.84	0.04	86	386	-2.93	0.03
	R7	166	466	-0.71	0.47	99	399	-2.55	0.01	111	411	-2.22	0.02
	R8	157	457	-0.96	0.33	146	446	-1.25	0.20	117	417	-2.06	0.03
	R9	111	411	-2.24	0.02	75	375	-3.21	0.01	52	352	-3.87	0.00
Profile	R1	147	447	-1.24	0.21	117	417	-2.07	0.03	118	418	-2.04	0.04
	R2	135	271	-1.56	0.11	177	313	-0.41	0.67	183	319	-0.23	0.81
	R3	144	444	-1.31	0.18	121	421	-1.94	0.05	118	418	-2.04	0.04
	R4	186	322	-0.16	0.86	151	451	-1.12	0.26	160	460	-0.88	0.37
	R5	175	311	-0.45	0.64	177	477	-0.40	0.68	179	315	-0.36	0.71
	R6	98	398	-2.59	0.00	68	368	-3.41	0.01	51	351	-3.88	0.00
	R7	102	402	-2.47	0.01	48	348	-3.98	0.00	65	365	-3.50	0.00
	R8	83	383	-2.99	0.00	52	352	-3.87	0.00	47	347	-4.00	0.00
	R9	142	442	-1.38	0.16	108	408	-2.30	0.02	70	370	-3.36	0.01
	R10	64	364	-3.52	0.00	37	337	-4.27	0.00	29	329	-4.50	0.00

Appendix IX: MS thermal symmetry of each gender and results of p-value, U,W and Z values

	ROIs	Gender	1st Moment	2nd Moment	3rd Moment
Frontal	R1	F	0.26 ± 0.02	0.32 ± 0.31	0.22 ± 0.16
		M	0.34 ± 0.52	0.39 ± 0.48	0.22 ± 0.18
	R2	F	0.41 ± 0.37	0.52 ± 0.40	0.45 ± 0.44
		M	0.34 ± 0.25	0.48 ± 0.48	0.40 ± 0.30
	R3	F	0.30 ± 0.20	0.38 ± 0.20	0.39 ± 0.33
		M	0.19 ± 0.15	0.19 ± 0.16	0.21 ± 0.17
	R4	F	0.15 ± 0.14	0.26 ± 0.26	0.20 ± 0.15
		M	0.14 ± 0.14	0.24 ± 0.21	0.19 ± 0.16
	R5	F	0.15 ± 0.08	0.16 ± 0.12	0.14 ± 0.11
		M	0.16 ± 0.15	0.14 ± 0.14	0.09 ± 0.10
	R6	F	0.47 ± 0.63	0.30 ± 0.24	0.44 ± 0.45
		M	0.25 ± 0.18	0.29 ± 0.22	0.28 ± 0.19
	R7	F	0.37 ± 0.41	0.54 ± 0.31	0.43 ± 0.52
		M	0.33 ± 0.21	0.33 ± 0.16	0.22 ± 0.18
	R8	F	0.30 ± 0.41	0.36 ± 0.24	0.35 ± 0.39
		M	0.25 ± 0.23	0.28 ± 0.17	0.27 ± 0.23
R9	F	0.35 ± 0.29	0.41 ± 0.32	0.35 ± 0.23	
	M	0.34 ± 0.26	0.38 ± 0.52	0.40 ± 0.31	
Profile	R1	F	0.83 ± 0.68	1.03 ± 0.76	0.90 ± 0.59
		M	0.87 ± 0.56	0.51 ± 0.44	0.44 ± 0.40
	R2	F	0.55 ± 0.40	0.56 ± 0.44	0.44 ± 0.38
		M	0.39 ± 0.48	0.50 ± 0.39	0.35 ± 0.27
	R3	F	0.40 ± 0.29	0.46 ± 0.41	0.34 ± 0.30
		M	0.22 ± 0.21	0.39 ± 0.30	0.20 ± 0.24
	R4	F	0.22 ± 0.27	0.40 ± 0.26	0.23 ± 0.28
		M	0.26 ± 0.15	0.38 ± 0.34	0.22 ± 0.21
	R5	F	0.20 ± 0.15	0.33 ± 0.43	0.35 ± 0.65
		M	0.32 ± 0.21	0.21 ± 0.20	0.86 ± 2.58
	R6	F	0.31 ± 0.23	0.43 ± 0.39	0.34 ± 0.34
		M	0.28 ± 0.21	0.37 ± 0.28	0.35 ± 0.27
	R7	F	0.31 ± 0.26	0.53 ± 0.40	0.50 ± 0.38
		M	0.18 ± 0.14	0.26 ± 0.25	0.24 ± 0.16
	R8	F	0.28 ± 0.24	0.30 ± 0.26	0.22 ± 0.18
		M	0.31 ± 0.21	0.15 ± 0.12	0.20 ± 0.20

R9	F	0.44 ± 0.45	0.41 ± 0.35	0.35 ± 0.25
	M	0.38 ± 0.32	0.31 ± 0.19	0.28 ± 0.29
R10	F	0.39 ± 0.23	0.27 ± 0.23	0.31 ± 0.24
	M	0.34 ± 0.17	0.33 ± 0.23	0.31 ± 0.28

ROI's	Moment I to II				Moment II to III				Moment I to III				
	U	W	Z	p	U	W	Z	p	U	W	Z	p	
Frontal	R1	175	311	-0.48	0.63	181	481	-0.29	0.76	186	322	-0.15	0.87
	R2	181	317	-0.30	0.75	174	310	-0.50	0.61	185	485	-0.19	0.84
	R3	128	264	-1.79	0.07	93	229	-2.76	0.00	113	249	-2.20	0.02
	R4	189	325	-0.07	0.94	190	326	-0.05	0.95	176	312	-0.43	0.66
	R5	175	311	-0.47	0.63	168	304	-0.66	0.50	132	268	-1.74	0.08
	R6	141	277	-1.42	0.13	190	326	-0.04	0.96	156	292	-1.00	0.31
	R7	178	478	-0.37	0.76	104	240	-2.45	0.01	158	294	-0.95	0.33
	R8	192	328	0.00	1	158	294	-0.93	0.34	189	325	-0.07	0.94
	R9	190	490	-0.04	0.96	146	282	-1.26	0.20	164	464	-0.76	0.44
Profile	R1	171	471	-0.58	0.56	110	246	-2.25	0.02	105	241	-2.40	0.01
	R2	141	277	-1.41	0.15	173	309	-0.51	0.60	171	307	-0.56	0.56
	R3	119	255	-2.04	0.04	178	314	-0.39	0.69	136	272	-1.57	0.11
	R4	132	432	-1.69	0.09	172	308	-0.54	0.58	178	478	-0.38	0.70
	R5	124	424	-1.91	0.05	156	292	-1.01	0.31	191	327	-0.02	0.97
	R6	184	320	-0.22	0.82	182	318	-0.27	0.78	176	476	-0.44	0.65
	R7	138	274	-1.51	0.13	111	247	-2.24	0.02	118	254	-2.04	0.04
	R8	166	466	-0.72	0.47	118	254	-2.09	0.03	168	304	-0.68	0.49
	R9	188	324	-0.09	0.92	167	303	-0.69	0.48	146	282	-1.27	0.20
	R10	183	319	-0.23	0.81	155	455	-1.02	0.30	185	321	-0.18	0.85

Appendix X: MS mean temperatures of right side of each phase and results of p-value, U,W and Z values

	ROIs	Phase	1st Moment	2nd Moment	3rd Moment
Frontal	R1	1	32,19 ± 1,31	30,59 ± 1,26	32,29 ± 1,81
		2	31,88 ± 1,92	29,96 ± 1,65	31,55 ± 1,94
	R2	1	34,16 ± 0,70	32,54 ± 0,78	33,79 ± 1,06
		2	33,75 ± 0,92	32,17 ± 1,12	33,69 ± 1,01
	R3	1	34,16 ± 0,70	32,23 ± 1,01	33,68 ± 1,05
		2	33,75 ± 0,92	31,79 ± 0,98	33,64 ± 0,90
	R4	1	34,59 ± 0,49	32,73 ± 0,86	34,03 ± 0,86
		2	34,52 ± 0,60	32,20 ± 0,64	34,22 ± 0,69
	R5	1	34,31 ± 0,36	33,08 ± 0,57	33,90 ± 0,58
		2	34,22 ± 0,58	32,74 ± 0,58	34,01 ± 0,60
	R6	1	33,36 ± 0,96	31,21 ± 1,00	32,45 ± 1,16
		2	32,94 ± 1,20	30,88 ± 1,18	32,48 ± 1,27
	R7	1	33,69 ± 0,92	32,00 ± 0,88	33,11 ± 1,05
		2	33,44 ± 1,01	31,47 ± 1,41	33,01 ± 1,34
	R8	1	34,62 ± 0,48	33,41 ± 0,71	34,31 ± 0,73
		2	34,56 ± 0,55	32,88 ± 0,84	34,42 ± 0,53
	R9	1	33,01 ± 0,62	31,39 ± 0,67	32,28 ± 0,71
		2	32,81 ± 0,78	31,09 ± 0,80	32,38 ± 0,79
Profile	R1	1	31,00 ± 2,21	29,94 ± 2,03	31,39 ± 2,66
		2	30,76 ± 2,42	29,41 ± 2,20	30,55 ± 2,53
	R2	1	33,52 ± 1,17	32,43 ± 1,01	33,66 ± 1,11
		2	33,39 ± 1,18	32,17 ± 1,00	33,49 ± 0,78
	R3	1	33,89 ± 0,67	32,01 ± 0,95	33,49 ± 0,87
		2	33,47 ± 0,90	31,62 ± 0,91	33,41 ± 0,98
	R4	1	34,31 ± 0,62	32,79 ± 0,76	33,81 ± 0,87
		2	34,18 ± 0,74	32,33 ± 0,83	33,93 ± 0,64
	R5	1	34,01 ± 0,4	32,86 ± 0,57	33,69 ± 0,58
		2	33,92 ± 0,65	32,59 ± 0,75	33,75 ± 0,74
	R6	1	32,74 ± 1,00	30,96 ± 0,95	32,02 ± 1,12
		2	32,40 ± 1,30	30,50 ± 1,37	32,1 ± 1,35
	R7	1	33,51 ± 0,86	31,75 ± 0,81	32,87 ± 1,09
		2	33,23 ± 0,96	31,39 ± 1,21	32,79 ± 1,1
	R8	1	33,47 ± 0,85	31,86 ± 0,74	32,67 ± 0,82
		2	33,23 ± 0,96	31,47 ± 0,95	32,8 ± 0,92
	R9	1	34,53 ± 0,93	32,80 ± 0,91	33,67 ± 0,85

	2	34,33 ± 0,93	32,56 ± 1,01	33,68 ± 0,67
R10	1	33,28 ± 1,03	31,60 ± 0,80	32,39 ± 0,96
	2	32,99 ± 0,95	31,20 ± 1,11	32,56 ± 0,94

ROI's	Moment I to II				Moment II to III				Moment I to III				
	U	W	Z	p	U	W	Z	p	U	W	Z	p	
Frontal	R1	59	114	-0.65	0.52	57	112	-0.79	0.43	55	110	-0.91	0.36
	R2	57	112	-0.79	0.43	59	114	-0.68	0.50	66	121	-0.24	0.82
	R3	49	104	-1.27	0.21	50	105	-1.20	0.23	68	123	-0.15	0.88
	R4	64	119	-0.35	0.72	41	95.5	-1.73	0.08	62	167	-0.47	0.64
	R5	51	106	-1.12	0.26	44	99	-1.53	0.13	65	170	-0.32	0.75
	R6	58	113	-0.70	0.48	57	112	-0.76	0.45	68	173	-0.12	0.91
	R7	59	114	-0.68	0.50	58	113	-0.70	0.48	68	123	-0.12	0.91
	R8	64	119	-0.35	0.72	33	88	-2.18	0.03	67	172	-0.18	0.86
	R9	62	117	-0.50	0.62	53	108	-1.03	0.31	68	173	-0.12	0.91
Profile	R1	65	120	-0.32	0.75	61	116	-0.53	0.60	54	109	-0.97	0.33
	R2	61	116	-0.56	0.58	65	120	-0.32	0.75	55	110	-0.88	0.38
	R3	50	105	-1.18	0.24	54	109	-0.97	0.33	62	117	-0.47	0.64
	R4	63	118	-0.41	0.68	45	100	-1.47	0.14	67	172	-0.21	0.84
	R5	60	115	-0.59	0.56	57	112	-0.76	0.45	67	172	-0.21	0.84
	R6	60	115	-0.62	0.54	56	111	-0.85	0.40	67	172	-0.18	0.86
	R7	58	113	-0.71	0.48	59	114	-0.68	0.50	70	125	-0.03	0.98
	R8	60	115	-0.59	0.56	48	103	-1.29	0.20	64	169	-0.35	0.73
	R9	53	108	-1.03	0.30	58	113	-0.73	0.46	67	122	-0.21	0.84
	R10	61	116	-0.56	0.58	54	109	-0.97	0.33	66	171	-0.26	0.79

Appendix XI: MS mean temperatures of left side of each phase and results of p-value, U,W and Z values

	ROIs	Phase	1st Moment	2nd Moment	3rd Moment
Frontal	R1	1	32.26 ± 1.32	30.83 ± 1.33	32.41 ± 1.9
		2	31.99 ± 1.94	30.26 ± 1.76	31.81 ± 1.93
	R2	1	34.11 ± 0.55	32.72 ± 0.58	33.83 ± 0.87
		2	33.78 ± 0.74	32.29 ± 0.89	33.92 ± 0.79
	R3	1	34.12 ± 0.62	32.24 ± 0.67	33.56 ± 0.90
		2	33.72 ± 0.80	31.86 ± 1.03	33.4 ± 1.08
	R4	1	34.12 ± 0.62	32.75 ± 0.83	34.04 ± 0.81
		2	33.72 ± 0.80	32.40 ± 0.77	34.17 ± 0.90
	R5	1	34.30 ± 0.36	33.07 ± 0.61	33.89 ± 0.58
		2	34.31 ± 0.69	32.78 ± 0.65	34.04 ± 0.63
	R6	1	33.32 ± 0.81	31.30 ± 0.73	32.54 ± 1.10
		2	32.97 ± 1.39	31.02 ± 1.41	33.03 ± 1.30
	R7	1	33.64 ± 0.95	32.06 ± 0.63	33.07 ± 1.00
		2	33.64 ± 0.76	31.80 ± 1.07	33.31 ± 1.03
	R8	1	34.41 ± 0.75	33.24 ± 0.61	34.06 ± 0.58
		2	34.56 ± 0.53	32.87 ± 0.91	34.22 ± 0.67
	R9	1	33.04 ± 0.66	31.39 ± 0.58	32.29 ± 0.72
		2	32.77 ± 1.01	31.19 ± 1.26	32.29 ± 1.07
Profile	R1	1	30.93 ± 2.14	29.94 ± 2.10	31.39 ± 2.66
		2	30.93 ± 2.68	29.60 ± 2.37	30.55 ± 2.53
	R2	1	33.52 ± 0.99	32.51 ± 0.87	33.66 ± 1.11
		2	33.27 ± 0.81	32.05 ± 0.94	33.49 ± 0.78
	R3	1	33.84 ± 0.57	32.19 ± 0.73	33.49 ± 0.87
		2	33.29 ± 0.76	31.70 ± 1.06	33.41 ± 0.98
	R4	1	34.51 ± 0.45	32.74 ± 0.77	33.81 ± 0.87
		2	34.22 ± 0.66	32.67 ± 0.69	33.93 ± 0.64
	R5	1	34.11 ± 0.42	32.89 ± 0.63	33.69 ± 0.58
		2	33.86 ± 0.74	32.59 ± 0.87	33.75 ± 0.74
	R6	1	32.95 ± 0.9	31.14 ± 0.82	32.02 ± 1.12
		2	32.46 ± 1.33	30.97 ± 1.51	32.10 ± 1.35
	R7	1	33.76 ± 0.75	32.05 ± 0.64	32.87 ± 1.09
		2	33.36 ± 0.79	31.93 ± 1.00	32.79 ± 1.10
	R8	1	33.49 ± 0.82	31.96 ± 0.68	32.67 ± 0.82
		2	33.22 ± 1.00	31.69 ± 0.98	32.80 ± 0.92
	R9	1	34.33 ± 0.89	32.89 ± 0.81	33.67 ± 0.85

	2	34.20 ± 0.58	32.49 ± 0.88	33.68 ± 0.67
R10	1	33.20 ± 1.05	31.62 ± 0.90	32.39 ± 0.96
	2	32.77 ± 0.89	31.14 ± 1.02	32.56 ± 0.94

	ROI's	Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	p	U	W	Z	p	U	W	Z	p
Frontal	R1	62	117	-0.47	0.64	57	112	-0.76	0.45	57	112	-0.76	0.45
	R2	48	103	-1.29	0.20	49	104	-1.23	0.22	67	172	-0.18	0.86
	R3	51	106	0.84	0.26	50	105	-1.17	0.24	60	115	-0.62	0.54
	R4	63	118	-0.41	0.68	41	96	-1.73	0.08	63	168	-0.44	0.66
	R5	69	124	-0.06	0.95	51	106	-1.12	0.26	64	169	-0.35	0.73
	R6	63	118	-0.44	0.66	67	122	-0.21	0.84	56	161	-0.85	0.40
	R7	64	119	-0.35	0.73	51	106	-1.11	0.27	66	171	-0.24	0.81
	R8	66	171	-0.24	0.81	49	104	-1.23	0.22	57	162	-0.79	0.43
	R9	63	118	-0.44	0.66	59	114	-0.65	0.52	70	125	0.00	1.00
Profile	R1	70	125	-0.03	0.98	65	120	-0.32	0.75	63	118	-0.44	0.66
	R2	57	112	-0.76	0.45	46	101	-1.41	0.16	56	111	-0.82	0.41
	R3	41	96	-1.70	0.09	51	106	-1.11	0.27	61	116	-0.53	0.60
	R4	52	107	-1.06	0.29	67	122	-0.21	0.84	60	165	-0.62	0.54
	R5	54	109	-0.94	0.35	57	112	-0.79	0.43	50	155	-1.20	0.23
	R6	57	112	-0.76	0.45	67	172	-0.18	0.86	61	166	-0.53	0.60
	R7	48	103	-1.32	0.19	63	118	-0.44	0.66	67	122	-0.18	0.86
	R8	58	113	-0.70	0.48	60	115	-0.59	0.56	63	168	-0.41	0.68
	R9	57	112	-0.79	0.43	53	108	-1.03	0.31	54	159	-0.94	0.35
	R10	52	107	-1.09	0.28	52	107	-1.09	0.28	69	174	-0.06	0.95

Appendix XII: MS thermal symmetry of each phase and results of p-value, U,W and Z values

	ROIs	Phase	1st Moment	2nd Moment	3rd Moment
Frontal	R1	1	0.32 ± 0.22	0.31 ± 0.27	0.19 ± 0.14
		2	0.17 ± 0.14	0.32 ± 0.38	0.26 ± 0.19
	R2	1	0.42 ± 0.36	0.50 ± 0.43	0.42 ± 0.47
		2	0.39 ± 0.40	0.54 ± 0.36	0.49 ± 0.41
	R3	1	0.34 ± 0.22	0.36 ± 0.24	0.31 ± 0.21
		2	0.25 ± 0.17	0.39 ± 0.15	0.50 ± 0.45
	R4	1	0.15 ± 0.17	0.25 ± 0.19	0.19 ± 0.12
		2	0.15 ± 0.12	0.28 ± 0.34	0.23 ± 0.18
	R5	1	0.14 ± 0.09	0.19 ± 0.13	0.15 ± 0.11
		2	0.17 ± 0.07	0.12 ± 0.09	0.13 ± 0.12
	R6	1	0.56 ± 0.81	0.29 ± 0.21	0.29 ± 0.23
		2	0.33 ± 0.19	0.32 ± 0.29	0.65 ± 0.59
	R7	1	0.29 ± 0.30	0.45 ± 0.20	0.31 ± 0.43
		2	0.48 ± 0.52	0.67 ± 0.40	0.58 ± 0.62
	R8	1	0.37 ± 0.46	0.36 ± 0.20	0.29 ± 0.24
		2	0.20 ± 0.33	0.35 ± 0.30	0.44 ± 0.53
	R9	1	0.27 ± 0.23	0.27 ± 0.17	0.21 ± 0.24
		2	0.46 ± 0.33	0.60 ± 0.38	0.55 ± 0.37
Profile	R1	1	0.77 ± 0.69	0.86 ± 0.83	0.73 ± 0.55
		2	0.91 ± 0.69	1.27 ± 0.62	1.14 ± 0.60
	R2	1	0.57 ± 0.42	0.57 ± 0.54	0.44 ± 0.42
		2	0.52 ± 0.39	0.54 ± 0.26	0.45 ± 0.32
	R3	1	0.31 ± 0.28	0.35 ± 0.38	0.25 ± 0.27
		2	0.52 ± 0.28	0.62 ± 0.41	0.47 ± 0.32
	R4	1	0.26 ± 0.33	0.36 ± 0.23	0.28 ± 0.33
		2	0.16 ± 0.14	0.46 ± 0.29	0.16 ± 0.16
	R5	1	0.22 ± 0.19	0.24 ± 0.22	0.39 ± 0.85
		2	0.18 ± 0.08	0.46 ± 0.61	0.29 ± 0.18
	R6	1	0.36 ± 0.26	0.39 ± 0.26	0.29 ± 0.39
		2	0.24 ± 0.19	0.49 ± 0.53	0.41 ± 0.26
	R7	1	0.31 ± 0.27	0.43 ± 0.30	0.49 ± 0.41
		2	0.31 ± 0.25	0.66 ± 0.49	0.51 ± 0.35
	R8	1	0.21 ± 0.20	0.24 ± 0.19	0.19 ± 0.19

	2	0.37 ± 0.26	0.40 ± 0.32	0.26 ± 0.16
R9	1	0.51 ± 0.55	0.41 ± 0.31	0.34 ± 0.27
	2	0.33 ± 0.24	0.41 ± 0.41	0.36 ± 0.23
R10	1	0.35 ± 0.22	0.29 ± 0.19	0.28 ± 0.28
	2	0.44 ± 0.24	0.24 ± 0.29	0.36 ± 0.18

	ROI's	Moment I to II				Moment II to III				Moment I to III			
		U	W	Z	p	U	W	Z	p	U	W	Z	p
Frontal	R1	40	95	-1,85	0,07	63	118	-0,41	0,68	55	160	-0,90	0,37
	R2	65	120	-0,30	0,77	59	164	-0,69	0,49	57	162	-0,80	0,42
	R3	56	111	-0,86	0,39	63	168	-0,42	0,68	52	157	-1,10	0,27
	R4	64	169	-0,37	0,71	65	120	-0,30	0,77	62	167	-0,48	0,63
	R5	61	166	-0,57	0,57	46	101	-1,46	0,15	61	116	-0,59	0,55
	R6	66	121	-0,27	0,79	69	174	-0,06	0,95	39	144	-1,86	0,06
	R7	53	158	-1,00	0,32	49	154	-1,27	0,20	43	148	-1,64	0,10
	R8	40	95	-1,82	0,07	60	115	-0,62	0,53	70	125	0,00	1,00
	R9	49	154	-1,27	0,20	32	137	-2,25	0,03	28	133	-2,52	0,01
Profile	R1	61	166	-0,53	0,60	40	145	-1,79	0,07	44	149	-1,53	0,13
	R2	68	123	-0,15	0,88	57	162	-0,80	0,43	64	169	-0,35	0,72
	R3	36	141	-2,01	0,04	41	146	-1,71	0,09	41	146	-1,75	0,08
	R4	62	117	-0,52	0,61	50	155	-1,20	0,23	58	113	-0,75	0,45
	R5	70	125	0,00	1,00	54	159	-0,98	0,33	49	154	-1,29	0,20
	R6	51	106	-1,13	0,26	70	175	-0,03	0,98	46	151	-1,45	0,15
	R7	69	174	-0,09	0,93	50	155	-1,18	0,24	64	169	-0,35	0,72
	R8	44	149	-1,56	0,12	49	154	-1,27	0,20	48	153	-1,35	0,18
	R9	62	117	-0,47	0,64	68	123	-0,15	0,88	65	170	-0,33	0,75
	R10	55	160	-0,92	0,36	51	106	-1,13	0,26	50	155	-1,18	0,24