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EPIDEMIOLOGICAL STUDY OF PRIMARY CUTANEOUS MELANOMA IN CHP-HSA DIAGNOSED BETWEEN 2006-2012

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“You see things; and you say "Why?"
But I dream things that never were; and I say "Why not?".”
George Bernard Shaw - Back to Methuselah, 1921

Acknowledgments

To my parents, for their character and strength of will.

To Dr. Mónica Caetano, for her guidance.

To my friends, for all the support and energy.

Epidemiological study of primary cutaneous melanoma in CHP-HSA 2006-2012

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Chapter 1

Abstract

A) Abstract

Being the main contact of the body with the environment, skin is the body's major organ. The skin is composed by two layers, the epidermis and the dermis, of which the most external one being mainly constituted by keratinocytes and melanocytes. Melanocytes are neuronal crest derived-cells responsible for the production of melanin that can degenerate and give rise to melanoma skin cancer.

Although melanoma rates are increasing world-wide, there is still no consensus concerning the main reason for this occurrence. However, risk factors and the epidemiological numbers are well known.

The main objective of this work was to study the epidemiological characteristics of the population diagnosed with primary melanoma in the Oporto's Hospital Centre (CHP), as well as their melanoma's particular features and follow-up. Moreover, we intended to determine specific characteristics of the population, treatment and follow-up that may influence the incidence and/or outcome, as well as to point out possible ameliorations.

Thereunto, we analyzed the processes of patients diagnosed with primary melanoma in the CHP between 2006 and 2012.

Results indicated 148 patients, of which the most representative patient is a woman between 60 and 69 years old with a superficial spreading melanoma localized in the lower limbs, which, at the time of diagnosis, is at stage I. This patient will be discharge or will have a good evolution in her follow-up, with a survival chance of 97.2%. Furthermore, we also observed that 5% of patients quit the consultation and that there was no data concerning patient's follow-up in 12% of the cases.

This study showed that the melanoma's patients diagnosed in the CHP follow the general world-wide epidemiology, with CHP standing procedure allowing results among the world's best. However, results also indicate that there is still room for improvement, namely in the organizational aspects of the system, which may lead to even better clinical results in the future.

A) Resumo

A pele e os seus derivados constituem o sistema tegumentário que é o maior órgão do corpo humano, correspondendo a 16% do peso total de um adulto.

A pele é composta por duas camadas, a epiderme e a derme. A epiderme é um épitélio estratificado de células queratinizadas escamosas derivadas da ectoderme e formada principalmente por queratinócitos e melanócitos.

Os melanócitos são responsáveis pela produção de melanina e, através das projecções que possuem entre os queratinócitos, os melanócitos transferem grânulos de melanina para os queratinócitos. Dentro dos queratinócitos, os grânulos de melanina formam uma camada protectora ao redor do núcleo, protegendo-os da luz ultra-violeta (UV). A quantidade de melanina nas células epidérmicas origina a cor da pele, quanto mais melanina é produzida mais escura é a pele. A cor da pele é uma das características do “tipo de pele” / fototipo, o qual foi classificado por Fitzpatrick, em 1988, em seis grupos.

Não sendo o único mecanismo fisiopatologico na etiologia do melanoma, os melanócitos podem degenerar e dar origem ao melanoma. O qual é uma neoplasia que possui taxas de incidência em expansão em todo o mundo. Contudo, ainda não há consenso sobre a principal razão para esta ocorrência. Alguns autores referem que pode ser devido a uma maior consciência dos doentes e dos médicos, os quais estão mais atentos ao melanoma, e estão a usar novas classificações. Outros autores indicam que o aumento na incidência ocorre para todos valores de Breslow e que há um aumento nas taxas de mortalidade, contestando o argumento de que o incremento da incidência é causado pelo aumento da vigilância e detecção. Assim, suportam que a epidemia de melanoma é real, e não apenas um artefacto do sobrediagnóstico.

No entanto, os factores de risco e os dados epidemiológicos são bem conhecidos. O melanoma cutâneo é mais comum em países desenvolvidos, nos homens idosos, brancos e de baixa condição socioeconómica.

A incidência da localização anatómica do melanoma varia com o sexo dos pacientes. Nos homens, os melanomas são mais localizado no tronco (55%), especialmente no dorso (39%). Nas mulheres, as lesões de melanoma são mais localizadas nas extremidades inferiores (42%) e no tronco (25%).

O melanoma ocorre tanto em pacientes geneticamente normais como nos predispostos e envolve interacções entre factores ambientais e alterações genéticas (sequenciação, a activação de oncogenes, inactivação de genes supressores de tumor e comprometimento da reparação do DNA).

De entre os factores ambientais, a radiação solar foi classificada como carcinogênica para humanos, com noventa e cinco por cento dos melanomas a se originam na pele, ou seja, em áreas do corpo que são mais sujeitos a radiação UV intermitente (ex: férias). O papel da luz UV no desenvolvimento de melanoma está bem documentado, com a incidência de melanoma a correlacionar-se positivamente com:

- exposição média anual de radiação UV;
- latitude (perto do equador) e gradientes de altitude;
- número de queimaduras solares, independentemente da idade (queimaduras ao longo da vida foram associadas com um aumento linear no risco de melanoma);
- exposição à radiação ultravioleta artificial.

As características individuais também são fundamentais. Vários genes têm sido associados com maior risco de melanoma. Dos genes de alta penetrancia i) a mutação do oncogene BRAF, o qual codifica uma proteína quinase serina-treonina, tem sido associada a 60% de melanomas cutâneos, ii) mutações d p16, foram associadas com 50% de melanoma familiar e com 10% de melanoma primário, iii) mutações no inibidor 2A dependente de ciclina quinase (CDKN2A), estão relacionados com 40% de melanoma hereditário, e 1% de todos os melanomas.

O tipo de pele e o número total nevos melanocíticos também influência a susceptibilidade para melanoma, com o baixo fótotipo e um número elevado de nevos melanocíticos totais aumentando o risco.

O melanoma tem diferentes tipos histológicos. Clark e seus colegas, em 1973, distinguiram quatro tipos de melanoma:

- O melanoma de extensão superficial é o tipo mais comum de melanoma, e ocorre em locais que estão intermitentemente expostos à luz solar.
- Melanoma nodular é o segundo mais comum e o mais agressivo tipo de melanoma. Ele ocorre mais em homens na quinta e sexta décadas de vida, muitas vezes em locais do corpo que são intermitentemente expostos à luz solar.
- O melanoma em lentigo maligno (LMM) é uma forma rara de melanoma, estando associada com altos níveis de exposição solar acumulada, sendo mais comum no rosto, cabeça e pescoço e em idosos.
- Melanoma acral lentiginoso é mais frequente nas palmas das mãos, solas dos pés ou sob as unhas das pessoas adultas não-brancas.

Apesar dos avanços nos meios auxiliares de diagnóstico, a detecção mantem-se um grande desafio, e são necessários melhores métodos para diagnosticar com precisão o melanoma.

A anamnese do doente deve incluir uma análise de sistemas com foco especial para os sinais ou sintomas neurológicos, respiratórios, hepáticos, gastrointestinais, músculo-esqueléticas, pele e linfáticos.

O exame físico deve abarcar uma análise de pele total e palpação dos gânglios linfáticos regionais e à distância. Alterações na assimetria, irregularidade do contorno, a variação da cor e do diâmetro (ABCDE) são, normalmente, os primeiros sinais, fazendo com que a maior parte dos melanomas sejam detectáveis pelo paciente.

A dermatoscopia (uma técnica não-invasiva um dispositivo de aumento que usa luz polarizada numa inclinação de 30º para permitir a visualização de lesões cutâneas superficiais e as estruturas subsuperficiais da epiderme e da derme papilar) é superior ao exame a olho nu sozinho na detecção de melanoma, Possui uma sensibilidade e especificidade de 90%, melhorando a precisão da detecção precoce do melanoma, reduzindo biopsias desnecessárias e permitindo, inclusive, a correlações para estruturas histopatológicos.

As biopsias permitem o diagnóstico histológico, com uma sensibilidade e especificidade boa, mas não excelente.

A American Joint Committee on Cancer (AJCC) é o principal sistema de estadiamento para melanoma, com a espessura de Breslow sendo o componente princípal para determinar o prognóstico Este sistema de estadiamento é baseado na classificação TNM (tumor, gânglios linfáticos regionais e metástases à distância) e estabelece quatro estadios clínicos e patológicos

O principal tratamento para o melanoma cutâneo é a excisão cirúrgica com margens histologicamente negativas. A largura das margens de excisão é determinada principalmente pela espessura da lesão.

Embora a detecção deva ocorrer o mais cedo possível, e exista o risco de reaparecimento e de surgirem outros tumores de pele, ainda não está provado que no seguimento a monitorização clínica leve a melhores taxas de sobrevivência. Além disso, a maioria das recidivas são detectadas pelos pacientes. Portanto, não há um consenso sobre a frequência ideal das consultas de seguimento, nem sobre a utilidade de imagiologia e testes de sangue.

Também ainda não há consenso sobre a prevenção, com referências diferentes apresentando diferentes recomendações. Enquanto alguns autores indicam evitar o sol, outros referem que é preferível uma exposição moderada ao sol. O papel de protector solar na prevenção de melanoma também é controverso, porque ainda não está claro se os filtros solares oferecem protecção contra o desenvolvimento de melanoma, ou se aumentam o risco de cancro de pele devido ao seu uso de forma errada, para prolongar a exposição ao sol.

O principal objectivo deste trabalho foi estudar as características epidemiológicas da população diagnosticada com melanoma cutâneo primário no Centro Hospitalar do Porto (CHP), bem como as particularidades histológicas do melanoma e do seguimento. Além disso, pretendeu-se determinar as características específicas da população, tratamento e do seguimento que pudessem influenciar a incidência e / ou resultado, bem como apontar possíveis aperfeiçoamentos.

Para tal, realizamos um estudo retrospectivo dos casos de melanoma cutâneo primário diagnosticados no Centro Hospitalar do Porto (CHP), entre 2006 e 2012. O estudo foi realizado com a aprovação da Comissão de Ética para a Saúde e do Conselho de Administração do CHP. Durante estudo o anonimato dos pacientes foi mantido.

No estudo foram utilizados 148 casos referenciados com melanoma primário pelo Serviço de Anatomia Patológica do CHP, entre 2006 e 2012. A análise incidiu sobre os principais parâmetros epidemiológicos: número total de casos, sexo, idade, localização do tumor, tipo histológico, estadio, seguimento, profissão, fenótipo de pele, o número total de nevos melanocíticos, presença de nevos displásicos, o tipo de exposição ao sol, exposição artificial a radiação UV, a frequência de queimaduras solares, e história de cancro de pele. As informações foram obtidas utilizando o software Sistema de Apoio ao Médico (Administração Central do Sistema de Saúde, PT) e consultando os processos físicos no arquivo central do CHP.

Os dados foram analisados utilizando o software Excel 2003 (Microsoft Cop., Redmond, WA), com os resultados sendo expressos como o número total de casos, percentagem de casos ou média ± desvio padrão quando se comparou a média de idade dos pacientes nos diferentes locais anatómicos, tipos histológicos e estadios do melanoma.

A análise estatística foi realizada usando o software SPSS 21,0 (SPSS Inc., Chicago / IL). Antes da análise paramétrica, a homogeneidade da variância foi confirmada pelo teste de Levene. As

diferenças gerais foram estudadas por análise de variância de uma entrada (one-way ANOVA) e as variações entre grupos foram avaliados com teste post-hoc de Tukey. Variáveis paramétricas não categoriais foram analisadas com o teste binomial ou Qui-quadrado. A significância estatística foi aceite quando $p < 0,05$.

A análise da incidência de melanoma primário diagnosticado no CHP entre 2006 e 2012 mostrou um aumento no número de diagnósticos neste período, principalmente depois de 2009, e também em comparação com os estudos anteriores sobre a mesma população. Isto ocorreu em ambos os sexos, mas mais pronunciadamente nos homens. Um dos factores que poderá ser responsável por esta observação é classificação em 2010 do serviço de Dermatologia do CHP como centro de referencia para o melanoma.

O estudo da ocorrência de melanoma por sexo ao longo do tempo também indicou que, em geral, a incidência foi maior em mulheres do que em homens. Esta tendência foi confirmada quando se analisou a incidência por género, tendo sido possível observar um maior número de pacientes do sexo feminino com diagnóstico de melanoma primário do que pacientes do sexo masculino, algo que havia sido observado também entre 1996 e 2006.

Este resultado pode ser devido a um maior número de população feminina em Portugal. No entanto, quando se teve em conta este factor e se realizou a análise percentual, a taxa de incidência é ainda maior em mulheres (0,0015%) que em homens (0,0013%), o que está de acordo com os estudos anteriores para a população europeia e Portuguesa.

Estando de acordo com os dados do Reino Unido, o nosso estudo mostrou um aumento das taxas de melanoma cutâneo primário com a idade e que o número de diagnósticos foi maior entre os pacientes com 60-69 anos de idade. No entanto, também foi possível observar que, apesar do aumento da taxa de incidência com a idade, houve um pico nas taxas aos 50-59 anos de idade para os homens e aos 60-69 anos para as mulheres. Considerando que não há uma explicação epidemiológica, clínica nem patológica aparente para essa ocorrência, outras investigações são precisas para esclarecer as possíveis causas desta observação.

O nosso estudo indicou também que, embora não houvesse uma relação entre a distribuição anatómica e a idade, os homens apresentaram uma maior incidência de melanoma no tronco e as mulheres nos membros inferiores, o que está de acordo com os relatórios internacionais e com os estudos anteriores sobre a mesma população. As diferenças entre os géneros na distribuição anatómica do melanoma pode representar as diferenças á exposição solar, geralmente associadas

com as diferenças sexuais nos padrões de vestuário e de corte de cabelo. Além disso, os melanócitos são assimetricamente distribuídos na pele e podem diferir na sua resposta à exposição ao sol de acordo com a sua localização anatómica.

Nos EUA em 2004 e no CHP em 2006, a proporção de tipos histológicos de melanoma foi SM> NM> LM> ALM> outros tipos. O nossos resultados mostraram que, nos casos diagnosticados no CHP, entre 2006 e 2012, o melanoma de extensão superficial tem a maior incidência, sendo seguido pelo tipo nodular, tanto nos homens quanto nas mulheres. Além disso, as mulheres apresentam taxas mais elevadas em todos os tipos histológicos, com excepção do melanoma nodular. Estes resultados estão de acordo com a literatura internacional e com estudos anteriores sobre a mesma população; no entanto, não se observou uma relação entre a idade dos pacientes e o tipo histológico do melanoma, como descrito anteriormente.

O nosso estudo indicou a mesma proporção entre os estadios de melanoma, como descrito anteriormente (estadio I> II> III> IV). Além disso, também foi possível ver que a proporção dos tipos histológicos referidos acima (SM> NM> LM> ALM) é mantido em todas os estadios, com excepção do estadio II em que o tipo nodular tem a maior incidência. Isto pode ser devido ao fato de que, nas fases iniciais, o NM possuir características que o tornam similar a outras patologias, tornando mais difícil o diagnóstico diferencial e dificultando a sua detecção precoce.

Além disso, as mulheres apresentaram um maior número de melanoma estadio 0 e I do que o homem, com o oposto ocorrendo nos estadios III e IV. Estes resultados podem estar relacionados com o facto de i) no momento do diagnóstico a espessura média do NM ser maior do que a do SSM, e ii) em homens este ser tipo histológico com maior incidência.

A incidência da espessura do tumor está relacionada com a idade do paciente, com a ocorrência de tumores mais espessos sendo maior acima de 65 anos de idade. Embora os nossos resultados indiquem uma tendência aparente para a incidência de estadios mais elevados maiores espessuras em idades mais avançadas, estes resultados não foram significativos.

Apesar da falta de consenso sobre o protocolo para o acompanhamento de pacientes tratados por melanoma primário o CHP segue as directrizes ESMO. Para o propósito deste estudo, de modo a analisar o resultado do tratamento e a progressão do paciente foram utilizadas as informações registadas na última avaliação dos pacientes, aquando do momento deste estudo.

Em 2009, a taxa de sobrevivência do melanoma foi calculada em torno de 97,3% ao ano, com uma idade média de morte de 68 anos de idade. Nós observamos uma taxa de mortalidade de 2,4% e uma média de idade no momento da morte de 72 anos, o que está de acordo com a literatura. Os

resultados também indicaram que o maior número de pacientes, no seu último registo de consulta, tinha tido a alta ou bons parâmetros físicos e dermatoscópicos, o que esta de acordo com uma taxa de sobrevivência de 97,6% e com os relatórios anteriores para a mesma população.

Além disso, vimos um número maior de pacientes do sexo feminino em quase todas as classes de follow-up, algo que poderia estar relacionado com o maior número total de pacientes do sexo feminino. No entanto, na classificação "não apropriado" do seguimento o número de pacientes do sexo masculino foi maior do que de pacientes do sexo feminino, que pode ser devido ao homem apresentar um maior número de melanoma nodular e em estadios mais elevados. Isto é consistente com os relatos que indicam que NM contribui significativamente para as mortes de melanoma, pois não é detectado precocemente e, devido à sua a fase de crescimento ser quatro vezes mais rápida.

Apoiando essa visão, os nossos resultados indicam que em pacientes com parâmetros físicos e / ou dermatoscópicos "não apropriados" ou que já morreram, o subtipo de melanoma com mais casos foi o melanoma nodular; enquanto que a maioria dos pacientes que receberam alta ou que apresentaram uma avaliação “apropriada” tiveram melanoma superficial, que é conhecido por ter um melhor prognóstico.

De acordo com a relação entre maior estadio e pior prognóstico os nossos resultados indicam que a proporção de “apropriado”> “não apropriado”> “faleceu” entre as classes de seguimento ocorreu em todos os estadios de diagnóstico. A excepção ocorreu no estadio IV, onde o maior número de pacientes teve parâmetros físicos e / ou dermatoscópicos "não apropriados".

Estudos demonstraram que melanoma no tronco, cabeça ou pescoço confere um prognóstico pior do que em uma extremidade, e que entre os melanomas de localização axial (tronco, cabeça ou pescoço) os do couro cabeludo e pescoço apresentam pior sobrevida. De acordo com a literatura, observou-se que em pacientes que receberam alta ou que apresentavam parâmetros físicos e dermatoscópicos "apropriados”, os membros inferiores foram a localização anatómica com mais casos diagnosticados.

Foi também observado que 6,5% dos doentes desistiram da consulta. Apesar dos bons resultados obtidos na sobrevida dos doentes, é preocupante que doentes desistam da sua consulta, tratamento ou acompanhamento. Perguntas devem ser levantadas sobre os motivos que levam os doentes a ter essa atitude. Em que estadio estavam esses doentes? Será que eles desistem porque, como eles estavam em estadios baixos, eles achavam que não precisavam de tratamento ou acompanhamento? Será que morreram, por causa de melanoma ou por outras causas? Houve algum aspecto da relação

doente-médico que potencializou essa atitude? Mais estudos são necessários para encontrar essas respostas e melhorar este parâmetro.

Também foi interessante observar que em 10% dos casos não foi possível encontrar dados sobre o seguimento dos doentes. Além disso, também foi observado que a maioria dos processos clínicos tinha uma quase total ausência de informação clínica sobre a anamnese do doente. Isto, associado com i) a escrita criptográfica da maioria dos médicos, ii) desorganização total de processos do paciente e iv) a dificuldade de obter os processos, impossibilita a apresentação de resultados robustos sobre factores de risco de melanoma (por exemplo: fototipo, exposição ao sol e número total nevos), que também faziam parte do nosso estudo. Dos processos obtidos (118) apenas 22 tinham alguma informação relevante para o estudo. Destes, a análise descritiva indicou que a maioria dos pacientes (15) apresentava um melanoma cutâneo primário em um nevo pré-existente. A partir dos processos clínicos com informações sobre história pessoal ou familiar de cancro de pele (9), apenas três doentes apresentavam precedentes familiares.

Existem várias possibilidades que podem levar a essa observação: i) quais são os critérios para definir o que é e o que está incluído no seguimento; ii) qual foi o serviço responsável pelo seguimento destes doentes? iii) onde é que devem ter registadas as notas? iv) qual foi o papel desempenhado pela informatização do sistema neste resultado? v) há falta de tempo para as consultas? vi) há um déficit de cultura organizacional das partes envolvidas? Independentemente dos diversos factores possíveis que podem conduzir a este resultado, isto é algo que não pode ser ignorado. Deste modo, mais pesquisas devem ser realizadas para entender melhor as razões por de trás feste resultado e apontar medidas de ajustamento

Para concluir, o nosso estudo mostra que, no CHP o procedimento para o diagnóstico, tratamento e acompanhamento se encontra entre os melhores do mundo permitindo taxas de sobrevivência de 97,2%, com a maioria dos pacientes tendo alta ou uma boa evolução dos seus parâmetros físicos e dermatoscópicos. No entanto, ainda há espaço para melhorias nomeadamente nos aspectos organizacionais do sistema, o que pode levar a ainda melhores resultados clínicos no futuro.

Chapter 2

Introduction

B) Introduction

1) Integumentary system - normal histology and physiology

1.0) Introduction

The skin and its derivatives constitute the integumentary system (Ross and Pawlina, 2011), which is the largest organ in the body, being 16% of the total body weight of an adult.

The skin composed by the epidermis, dermis and the anexial structures (sudoriferous, sebaceous and mamary glands, hair and nails) (Tortora and Derrickson 2009). The subcutaneous layer is found beneath the dermis and, for some authors is not considered part of the skin (Tortora and Derrickson 2009), while for others is the innermost region of human skin (Freedberg et at., 2003).

Skin is categorized as thick or thin, a reflection of the thickness of the epidermal layer and location (McLafferty et al. 2012). Skin thickness varies from 1.5 to 4 mm thick in accordance to its function and area of the body; on the eyelids the skin is 0.5mm thick, but on the soles of the feet it reaches 4mm thick (Tortora and Derrickson 2009).

1.1) Epidermis

The epidermis is a 0.4 to 1.5 mm stratified keratinised squamous epithelium, derived from ectoderm, and contains four main types of cells (McLafferty et al., 2012):

i. Keratinocytes: 90%
ii. Melanocytes: 8% and are responsible for producing the pigment, melanin.
iii. Langerhans cells: involved in the immune response
iv. Merkel cells: function in the sensation of touch (Tortora and Derrickson 2009).

These cells are organized in 5 layers, which represent their different stages of maturation and movement (Burr and Penzer 2005):

i. Stratum basale: the deepest and were occurs cell division
ii. Stratum spinosum
iii. Stratum granulosum
iv. Stratum lucidum (finger tips, palms and soles).
v. Stratum corneum: the top layer and were cells shed.

1.1.1) Stratum basale

The stratum basale is composed of a single row of keratinocytes, melanocytes and Merkel cells (McLafferty et al. 2012).

1.1.1.1) Keratinocytes

In Stratum Basale keratinocytes undergo mitosis, with one cell remaining in the stratum basale and other migrating up to skin's surface, in a process that takes approximately 28 days in a 0.1mm thickness epidermis (Tortora and Derrickson 2009). Because it is avascular, the epidermis is dependent on blood vessels of the dermis for oxygenation, nutrition and removal of metabolic waste products. Therefore, as cells move to surface, they receive less nutrition, die and become more keratinised.

1.1.1.2) Melanocytes

Melanocyte are dendritic, melanin-synthesizing cells derived from neural crest and 1/6 are in the stratum basale and are responsible for the production of melanin (Turkington and Dover 2007). They have projections that extend between the keratinocytes and transfer melanin granules to them. Inside the keratinocytes, the melanin granules form a protective covering around the nucleus, shielding them from UV light.

Melanocytes exist in different tissues: skin, hair, eye (retina and uveal tract), ear (stria vascularis and vestibular region), leptomeninges and mucous membranes. Their density in the epidermis varies in accordance with body location: ≈ 2000 / mm^2 on the skin of the head and forearm and ≈ 1000 / mm^2 on the rest of the body (Freedberg et at., 2003).

The density of melanocytes in the skin is independen of racial backgrounds. With Skin colour being determined mainly by the amount of melanin produced, the mode in which it is transferred to the keratinocytes, and its distribution in the keratinocytes (Freedberg et at., 2003). The more melanin produced the darker the skin (Montagna and Carlisle, 1991; Lin and Fisher, 2007). Skin colour is one of the characteristics of the ‘‘skin type’’/ phototipe, which was classified by Fitzpatrick (1988) into six groups (Table I).

Table I - Fitzpatrick classification of skin type:

Skin Type	**Skin Color**	**Characteristics**
I	White, red or blond hair, blue eyes, freckles	Always burns, never tans
II	White; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white, fair with any eye or hair colour,	Sometimes mild burn, gradually tans
IV	Brown, typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark Brown, Mid-Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Melanocytes can proliferate and form benign aggregates known as melanocytic nevi, which are originated by an interaction of sun / ultraviolet exposure and personal genetic factors (Freedberg et at., 2003).

Both melanocytes and melanocytic nevi can produce melanin, but melanocytic nevi do not have dendritic processes (with the exception of those within blue nevi) and, whereas epidermal melanocytes are evenly distributed as single units, melanocytic nevi can be junctional, compound or intradermal (Freedberg et at., 2003).

Thus, melanocytic naevi were classified according to i) history, in congenital (present at birth or within the first few months of life) or acquired (sub-divided in common or atypical) and ii) histopathology, in junctional, compound and intradermal (Argenziano et al., 2007).

With age, melanocytes migrate down the skin and begin to lose their capacity to produce melanin. This creates an evolution of the nevi with age at which they appear: junctional nevi in early childhood, compound nevi in childhood to early adulthood, and intradermal nevi by the third or fourth decade (Argenziano et al., 2007).

Compound nevi are at the epidermal-dermal junction and, therefore, they have important amounts of pigment, like junctional nevi, and they are raised papules, like intradermal nevi. Compound nevi that appear in late adulthood are at increased risk for being malignant

(Argenziano et al., 2007)

1.1.1.3) Merkel cells

Merkel cells are spread among the keratinocytes making contact with the Merkel disc, a process of a sensory neuron, and, together, they detect the touch.

1.1.2) Stratum spinosum

The Stratum spinosum is 5 to 12 cells thick, which are jointed together via desmosomes. This arrangement contributes to the tensile strength and flexibility of the skin (Thibodeau and Patton 2007).

1.1.2.1) Keratinocytes

As the daughter cells of the keratinocytes move into the stratum spinosum they lose their ability to divide and become rounder and ‘spikier’.

1.1.2.2) Langerhans cells

Langerhans cells are produced in the bone marrow from dendritic cells, and then migrate to the stratum spinosum (Turkington and Dover 2007), where they have a role has antigen-presenting cells (Pringle and Penzer 2002).

1.1.3) Stratum granulosum

The stratum granulosum is composed of 3 to 5 layers of flattened keratinocytes, which have become longer and horizontally flatten as they moved to the skin's surface. They are no longer able to do any metabolic functions and die by apoptosis (Tortora and Derrickson 2009), becoming keratinised (Pringle and Penzer 2002). Odland's bodies, membrane-coating lamellar granules that produce lipid, which extrudes into the spaces between the cells, helps them stick together.

1.1.4) Stratum lucidum

The Stratum lucidum lies between the stratum granulosum and the stratum corneum and contains 3 to 5 of dead keratinocytes that are flattened and made up of large amounts of keratin and thickened plasma membranes. This stratum is only found in areas where the skin is thick, such as the palms of the hands and soles of the feet, and provides some degree of waterproofing to the skin (Tortora and Derrickson 2009).

1.1.4) Stratum corneum

The Stratum corneum is the uppermost skin layer and consists of 25 to 30 layers of flattened, dead keratinocytes. These are arranged in vertical stacks and are composed of cell membranes that are firmly attached to each other by intracellular lipid from the Odland's bodies, of the stratum granulosum.

As cells move through the stratum corneum they lose their stickiness and are shed on a continous basis (Tortora and Derrickson 2009).

1.2) Dermis

Being derived from mesoderm, the dermis lies below the epidermis and above the subcutaneous layer. It is responsible for providing nutrients and physical support to the epidermis (Burr and Penzer 2005), to which it is anchored by folds that stabilise and allow the exchange of nutrients (Turkington and Dover 2007).

The dermis is composed by two layers (Pringle and Penzer 2002):

i. papillary layer: contains the nerves and capillaries for the epidermis,
ii. reticular layer: made up of strong connective tissue containing collagen and elastic fibres.

The dermis also contains lymph vessels, nerve endings, hair follicles and glands (Pringle and Penzer 2002).

1.2.1) Collagen and elastin

Collagen and elastin in the dermis are arranged in a network of fibres that have significant tensile strength to provide the dermis the ability to stretch and contract (McLafferty et al. 2012).

Collagen contributes to 70% of the dry weight of the dermis, and prevents the tearing of the skin when it is stretched (Pringle and Penzer 2002). With age the collagen fibres are reduced, get stiffen and break up, resulting in their lost of shape and tangling.

Elastin fibres are synthesised by fibroblasts. These fibres are thinner than collagen and are found among the collagen bundles. Elastin also has elastic properties that allow the skin to return to its normal position after stretching. With time, the elastin fibres lose some of their elasticity, thicken into bundles and fray (Tortora and Derrickson 2009).

1.2.2) Sweat Glands

The skin contains near four million sweat glands that produced 600ml of sweat daily, having an important role in thermoregulation through evaporation. Based on their structure, location and type of secretion there are two types of sweat glands: i) eccrine and ii) apocrine (Tortora and Derrickson 2009).

1.2.2.1) Eccrine glands

Eccrine glands are simple, coiled glands that are present in several skin areas, but mainly in the forehead, palms of the hands and soles of the feet. They produce sweat, which is predominantly composed of water, sodium and chlorine ions, urea, uric acid, ammonia, amino acids, glucose and lactic acid (Tortora and Derrickson 2009).

1.2.2.2) Apocrine glands

The apocrine glands are also simple, coiled tubular glands, which are activated by sex hormones during puberty (Pringle and Penzer 2002) and are mainly found in the axillae, groin, areolae of the breasts and bearded regions of the face in adult males (Tortora and Derrickson 2009). The sweat produced by the apocrine glands is slightly viscous with a milky or yellowish appearance. This sweat has no smell when it leaves the gland, but, when it meets bacteria on the skin's surface, they metabolise its components and produce a musky odour (Tortora and Derrickson 2009).

1.2.3) Sebaceous glands

Sebaceous glands are simple, branched acinar glands, which have a sac-like secretory unit and an lumen. The majority of sebaceous glands are connected to hair follicles, being most commonly found on the face, neck and back (Pringle and Penzer 2002).

Sebum covers the surface of the hairs and protects them from drying and becoming brittle. Sebum also inhibits excessive evaporation of water from the skin so that the skin remains soft and supple (Tortora and Derrickson 2009).

1.2.4) Ceruminous glands

Ceruminous glands, which are found in the external ear, are modified sweat glands that produce cerumen, a sticky barrier, which, together with the hairs in the external auditory canal, prevents the entrance of foreign bodies into the ear (Tortora and Derrickson 2009).

1.3) Skin functions

Major functions of the skin include (Ross and Pawlina, 2011):

- acting as a barrier that protects against environmental physical, chemical, and biologic agents (i.e., mechanical barrier, permeability barrier, ultraviolet barrier);
- conversing sensory information about the external environment to the nervous system;
- participating in homeostasis by regulating body temperature and water loss;
- functioning in excretion through the exocrine secretion.
- performing endocrine functions by secreting hormones, cytokines, and growth factors and producing vitamin D;
- providing immunologic information obtained during antigen processing to the appropriate effector cells in the lymphatic tissue;

2) Melanoma

2.1) Definition

Primary melanoma is a malignant neoplasm of melanocytes that carries significant morbidity and mortality (Tuong W. et al., 2012)

2.1) Epidemiology

There are reports indicating that while the incidence of melanoma is increasing, (ex: 2.7%/y in USA - Purdue, et al., 2008), the mortality rates are decreasing (Baade and Coory, 2005). The analysis of these numbers should take into consideration that some of the incidence's increase can be due to higher awareness of patients and physicians, which are looking harder for melanoma and with new classifications (Qin et al., 2005; Welch et al., 2005).

However, studies (Linos, et al., 2009; Hollestein, et al., 2012) also indicated that the increase in incidence occurs among all Breslow thickness, and that there is an increase in mortality rates, contesting the argument that increases in incidence are caused by increased surveillance and detection, and that the melanoma epidemic is real, and not just an artefact of overdiagnosis (Little and Eide, 2012).

2.1.1) Incidence

Melanoma´s incidence increased in the past few decades (Erickson and Driscoll, 2010), being estimated, in 2010, to be the fifth and seventh most common cancer diagnosed in men and women, respectively (Jemal, et al., 2010). There are some trends in melanomas incidence, as exposed at followed.

Cutaneous melanoma is most common in **developed countries**, with high numbers of white residents, and among advantaged individuals, being the majority (70 %) very thin (<1 mm Breslow thickness) and with highly curable stages at diagnosis. (Birch-Johansen et al., 2008)

There are gender differences in melanoma incidence. Although the overall lifetime risk of developing melanoma is 1.9% in both genders (Howlader, et al., 2009), in the United States, melanoma is **more prevalent in men** (2.7%) compared with women (1.8%) (Jemal, et al., 2010). Despite these gender differences, melanoma incidence is increasing in younger women because of increased ultraviolet (UV) radiation exposure and use of tanning beds (Hausauer, et al., 2011).

The incidence of melanoma also differs between races, being significantly **higher in white** than in non-white populations (Howlader, et al., 2009, Rigel, 2010). However, Africo-Americans were

much more likely to be diagnosed with metastatic melanoma (Jemal, et al., 2010). This may be may related with the highest incidence of melanoma in individuals of **lower socioeconomic status**, a population with decreased access to health services and therefore less regular screening (Linos, et al., 2009).

There is also a difference in age group, with melanoma risk **increasing with age** (Rigel, 2010)

The **anatomic distribution** of melanoma lesions differs with sex and age.

Ninety five 95% of melanomas originate in the skin, namely in areas of the body that are more subject to intermittent UV radiation (Mulliken, et al., 2012). However, they also develop in other anatomic locations, as the choroid, the vagina and anus (Ross, et al., 1992).

In men melanomas are more located on the trunk (55%), especially the back (39%) (Garbe and Leiter, 2009); but its distribution is altered with age (Elwood and Gallagher, 1998):

- men less than 50 years old: higher at back and the upper arm .
- men more than of 50 years old: higher in the ear, face, neck, and the back.

In women melanoma lesions are more localized in the lower extremities (42%), the trunk (25%) and the back (17%) (Garbe and Leiter, 2009); but, again, its distribution is altered with age (Elwood and Gallagher, 1998):

- women less than 50 years old: the incidence in the back increases
- women more than 50 years old: the density is higher in the face, upper arm and leg.

In a report of 2011, Watson and colleagues reported that in 2006, in USA, the incidence of the **histological types** varied in non-Hispanic whites,

- 57.2% melanoma not-otherwise-specified.
- 28.8% superficial spreading,
- 6.9% nodular,
- 6% lentigo maligna,
- 1% acral lentiginous,

The incidence of **tumour thickness** also changes, and it was reported to be dependent of patient's age (Jamal, et al., 2011):

- <65 years: increased incidence in thin tumours.
- ≥ 65 years: increase incidence in all tumour thickness

2.1.2) Mortality

Studies (Howlader, et al., 2009) indicated that, despite more vigilant screening and early detection efforts, melanoma age adjusted mortality has increased, being 2.7% per year in 2007, with the median age at death being 68 years

Mortality is higher in men compared with women, with a 0.2% annual increase in men, but a 0.6% decreased in women.

Additionally, 5 years survival was higher in:

- women (95.1%) than in men (91.1%),
- individuals less than the age of 45 years at diagnosis, and in
- localized melanoma.

2.2) Etiology

The transformation of melanocytes to tumor cells occurs in both genetically normal and predisposed patients and involves interactions between environmental factors and genetic alterations (sequentiation, activation of oncogenes, inactivation of tumor suppressor genes, and impairment of DNA repair) (Pho, et al., 2006; Uribe, et al., 2005).

2.2.1) Environmental factors

Solar radiation has been classified as carcinogenic to humans, and its role in the development of melanoma is well documented, with melanoma incidence being positively correlated with:

- average annual amounts of UV radiation (Armstrong, et al., 2001);
- latitudinal (near equator) and altitudinal gradients (Berwick and Halpern, 1997);
- frequency of sunburn, regardless of age (Dennis, et al., 2008) (lifetime sunburns were associated with a linear increase in the risk of melanoma (Mulliken, et al., 2012), with a 2x increase in melanoma risk for more than 5 sunburns. (Pfahlberg, et al., 2001).
- Artificial UV radiation exposure (IARC, 2007).

UV light is classified according to its wavelength in UV-A (320-400nm), UV-B (290-320nm), and UV-C (100-290nm).

UV-C radiation is filtered by the ozone layer, whereas UV-A and UV-B radiation reach the earth's surface and have been strongly implicated in the development of cutaneous melanomas (Ley et al., 1989; Romerdahl, et al., 1989).

UV-A light accounts for 95% of the UV radiation that reaches the earth's surface and acts as a potential mutagen through the formation of free radical species, which causes oxidative DNA damage (Kochevar, et al., 1993).

The others 5% of the UV radiation that reaches the earth's surface are UV-B and are responsible for most of the sunburns (El Ghissassi, et al., 2009). Interestingly, UV-B also causes DNA damage, by penetrating to the basal layer of the epidermis and leading to the formation of pyrimidine (thymine) dimers in DNA (Freeman, et al., 1989; Mitchell et al., 1991).

Still, different patterns of sun exposure seem to have different effects in melanoma development:

i) chronic sun exposure (ex: received during outdoor work on a daily basis) does not increase risk for melanoma and is even associated with its inhibition. However, continuous, intermittent sun exposure over a lifetime, is associated with NRAS mutations [Neuroblastoma RAS viral (v-ras) oncogene homolog] among older individuals (Gandini et al., 2005).

ii) intermittent sun exposure, with large blasts of UV radiation (ex: holidays), is the main way of UV radiation inducing melanoma (Armstrong 1988). Furthermore, excessive sunlight exposure in young individuals with aberrant nevogenesis, increases the risk of melanoma associated with BRAF (V-raf murine sarcoma viral oncogene homolog B1) mutations (Thomas, et al., 2007; Whiteman; et al., 2003)

Additionally, there is the negative effects of tanning beds, with early life (<35 years) exposure being the most damaging (Berwick; 2008; IARCWG, 2006; Veierød et al., 2003). Tanning beds contain a similar ratio of UV-A/UV-B to natural sunlight, but they can have 15 times more UV than the noonday sun (IARC, 2006).

Thus, one factor that may contribute to the increase in melanoma incidence is the replacement of outdoor occupations with indoor ones, and the consequent decrease of chronic exposure, which is protective for melanoma, and an increase in intermittent sun exposure (Gallagher et al., 1989).

2.2.2) Family history

Familial melanoma accounts for 10 % of all cases of melanoma (Green and Fraumeni, 1979). There is an association between family history and melanoma risk, with a first degree relative having a twofold higher risk of developing melanoma (Cho, et al., 2005). This form of the disease presents thinner lesions and has a better survival, but appears at younger ages, with multiple primary lesions, and increases the occurrence of non-melanoma cancers (Kopf et al., 1986).

2.2.3) Individual Characteristics

2.2.3.1) Genetic mechanisms

Several genes have been associated with increased risk for melanoma

- High penetrance genes:
  - **BRAF** oncogene, which codes a serine-threonine protein kinase, is found in the Ras/mitogen activated protein kinase (MAPK) pathway. BRAF mutation has been associated with **60%** of cutaneous melanomas and is the target of new mutation-specific therapies. (Smalley, 2010; (Long et al., 2011; Puzanov, et al., 2011)
  - **p16**, alternate reading frame (ARF) - the p16/ARF locus encodes suppressor proteins essential in the regulation of cell growth and apoptosis (Lin, et al., 2008). Mutations in one or both gene products were associated with **50% of familial melanoma** and with 10% of multiple primary melanoma (Pollock, et al., 2003).
  - Mutations in cyclin-dependent kinase inhibitor 2A (**CDKN2A**), on chromosome 19p21, are related with **40% of hereditary melanoma**, and 1% of all melanomas (Begg, et al., 2005).
  - **p53** suppressor gene is frequently mutated in melanoma and is directly altered by UV light (Ouhtit, et al., 1998).

- Low penetrance genes:
  - Polymorphic variants of the melanocyte-stimulating hormone (melanocortin)-1 receptor (MC1R are established as low-risk melanoma susceptibility genes (Cannon-Albright, et al., 1992; Kamb, et al., 1994, Valverde, et al., 1995).

In addition, individuals younger than 20 years with Xeroderma pigmentosum (an autosomal recessive disorder characterized by hypersensitivity to sunlight and the inability to repair UV-induced DNA damage) have a 1000x increased risk for melanoma as well as other cutaneous neoplasms (Kraemer, DiGiovanna, 2003).

2.2.3.2) Personal History

A personal history of non-melanoma skin cancer (ex: squamous cell carcinoma, basal cell carcinoma, premalignant actinic keratoses) confers a relative risk of 17% of developing melanoma (Green and O'Rourke, 1985; Lindelof, et al., 1991, Ferrone, et al., 2005).

2.2.3.3) Melanocytic nevi

The total number of melanocytic nevi and the presence of dysplastic nevi are the most important independent risk factors for melanoma, with the risk for melanoma development increasing nearly

linearly with the total body number of melanocytic nevi and being 10x higher with the presence of dysplastic nevi (Snels, et at., 1999; Gandini, et al., 2005; Tucker, 2009, Olsen, et al., 2010).

Moreover, studies indicated that **25%** of melanoma cases are correlated to the presence of 1 or more atypical/dysplastic nevi and **27%** are attributable to a high count (≥50) of common nevi (Olsen, et al., 2008; Chang et al., 2008; Gandini et al., 2005).

Although the complete excisional biopsy of any pre-existing nevus that has a changed in appearance, itches, or bleeds is recommended (Levine and Shapiro, 2012), the prophylactic excision of dysplastic nevi is not justified (Levine and Shapiro, 2012), because in most patients melanoma arises from normal skin (Gruber, et al., 1989).

2.2.3.4) Phenotype

Phenotypic characteristics, often called ‘‘skin type’’, which was classified by Fitzpatrick (1988) into six groups (Table 1), contribute as risk factor for the development of melanoma, with the risk decreasing with the degree of pigmentation (Lin and Fisher, 2007).

2.2.4) Individual–environment interaction

Individuals have different levels of susceptibility for melanoma depending on their skin type and on the patterns of sun exposure (Armstrong et al., 1997):

- Skin type I and II: risk increases almost linearly, with increasing sun exposure.
- Skin type III and: risk increases slowly and then declines with increasing exposure.
- Skin type V and VI: risk increases, but only with a small amount, and then declines with increasing exposure.

2.3) Pathology

2.3.1) Pathogenic steps

Melanoma progresses in three distinct pathogenic steps:

- early-stage tumor the melanoma, which may be confined to the epidermis and displays only radial or lateral growth.
- microinvasive melanoma, in which microscopic extensions invade the superficial papillary dermis.
- advanced melanomas, which can progress to the involvement of deep dermis and have gained the potential to metastasize (Bandarchi, et al., 2010).

2.3.2) Histological types of melanocytic tumours

The first classification system was proposed by Clark and colleagues (McGovern et al., 1973). This classification distinguished four types of melanoma based on histopathology, anatomical site, degree of sun damage and intraepidermal growth pattern:

- invasive with adjacent intraepidermal component of superficial spreading - superficial spreading melanoma (SSM)
- invasive with adjacent intraepidermal component of lentiginous growth pattern:
  - lentigo maligna melanoma (LMM)
  - acral lentiginous melanoma (ALM)
- invasive without adjacent intraepidermal component - nodular melanoma (NM)

The adjacent intraepidermal component or radial growth phase (RGP) was defined as the early phase of melanoma growth, in which the tumour has an intraepidermal growth extending at least three rate ridge within the epidermis beyond the edge of the dermal component. The dermal invasive and expansible tumour, was defined as vertical growth phase (VGP).

However, this classification does not have significant prognostic or diagnostic value and, consequentially produces little impact on the clinical management. Namely because (Whitman et al., 2011):

- it is difficult to categorize cases based on histopathological criteria alone due to classification criteria overlaping,
- current staging protocols do not distinguish between different sub-categories of melanomas.
- independently of the sub-category of the primary, the disease follows a the same clinical course once metastases have developed.
- cytotoxic and immunological therapies available do not target specific functional or regulatory pathways in cells,

New molecular data have provided genetic support for the notion of biologically distinct sub-types, therefore, the WHO classification of skin tumours maintained the “old” categories and added others (LeBoit et al. 2006). The histologic features evaluated included the (Duncan, 2009):

- intraepidermal and dermal growth pattern,
- anatomic level of invasion into the dermis,
- vascular invasion,

- mitotic activity,
- pattern and density of lymphocytic host response.
- cytologic appearance of the tumor cells,
- epidermal changes (including atrophy and ulceration),
- the maximal tumour thickness (measured perpendicular from the top of the granular cell layer to the epidermal surface),
- presence of solar elastosis,

2.3.2.1) Superficial spreading melanoma

This is the most common type of melanoma, namely in young Caucasians and occurs in locations that are intermittently exposed to sunlight. It has a favourable prognosis (Whitman et al., 2011). Clinically these tumours show:

- a variety of colours, but rarely blue or white.
- a lesion outline usually sharply marginated with one or more irregular peninsula-like protrusions.
- a palpable papule surface or a nodule that extends several millimetres above the skin surface.

Histopathological, the main characteristic of SSM is the presence of enlarged melanocytes, often arranged in aggregates, disperse within the epidermis, a pattern referred to as 'pagetoid' (resembles Paget's disease). The dermal component may also be characterized by numerous nests of variable sizes and occasionally an expansible nodule of tumour (Duncan, 2009).

2.3.2.2) Lentiginous growth pattern

- Lentigo maligna melanoma (LMM)

It is a rare form of melanoma, which is associated with high levels of accumulated sun exposure, being most common in the face (90%), head and neck region and in elderly people. It has a relatively favourable prognosis (Whitman et al., 2011).

Clinically this is a relatively large flat tumour, mostly tan, brown, or black, with an irregular outline.

Histological analysis shows melanocytes arranged as solitary units along the basilar epidermis (lentiginous growth pattern) which fades into the adjacent non-lesional skin, making it very difficult to determine the boundary between melanoma in situ and normal skin. The tumour cells may be so numerous that the basal keratinocytes appear to be replaced by a continuous line of melanoma cells. In the dermis LMM may display spindled cells and tumour cell pigmentation, and it presents a tendency to involve appendageal structures (such as hair follicles in LMM and sweat glands in

ALM). After radial growth there is a vertical growth phase characterized by the presence of a nodule (Duncan, 2009).

- Acral lentiginous melanoma

This melanoma is more often in elderly and in non-white people. Melanocytes also have a lentiginous growth pattern, but more commonly in pigmented lesions that arise on the palm of the hand, sole of the foot or under the nails (Duncan, 2009).

2.3.2.3) Nodular melanoma

This is the second most common and most aggressive type of melanoma (15-30%). It occurs more in males in the 5^{th} and 6^{th} decades of life, often on body sites that are intermittently exposed to sunlight (Whitman et al., 2011).

Clinically these tumours present themselves as a nodule, elevated plaque with irregular outlines, or as a polypoidal often ulcerated, bleeding exophytic tumour, with a relatively uniform, brown, black, or blue-black colour.

Histopatologically NMM is characterized by having a non-significant radial growth phase and an accelerated transition to the VGP. It is a tumour with a predominance of dermal invasion, composed of small nests and aggregates of tumour cells that form the nodule (Duncan, 2009).

2.3.2.4) Other melanoma sub-types

Additional categories of melanomas that have distinctive clinical and/or histopathological features include:

- Desmoplastic melanoma
- Naevoid melanoma
- Melanoma arising from blue naevus
- Melanoma arising in a giant congenital naevus
- Melanoma of childhood
- Persistent melanoma

2.4) Diagnosis

Despite advances in diagnostic aids, detection has remained a significant challenge, and improved methods for accurately diagnosing melanoma are needed.

2.4.1) Anamnesis and physical examination

Patient history should include a review of systems with a particular focus to neurologic, respiratory, hepatic, gastrointestinal, musculoskeletal, skin, and lymphatic signs or symptoms (Bichakjian, et al., 2011).

The physical exam should include a total body skin analysis and palpation of both regional and distant lymph node basins.

Alterations in asymmetry, border irregularity, colour variation and diameter (ABCDE) are, normally, the first signs (Friedman, et al., 1995; Abasi, et al., 2004), making the majority of melanomas detectable by the patient. (Brady, et al., 1999; Kantor, et al., 2009):

- Asymmetry - most early malignant melanomas grow at an irregular rate, resulting in asymmetry, differing from benign pigmented lesions, which are typically round and symmetric.
- Border irregularity - malignant melanomas usually have an irregular border.
- Colour variation – melanomas often contain variable hues of tan, brown, black, red, and white.
- Diameter - most malignant melanomas have diameters of at least 6 mm at the time of diagnosis.
- Evolution - evolving nevi should be particularly observed, focusing on changes to shape, size, symptoms (itching), surface (bleeding, papular or nodular formation), and pigmentation.

However, not all melanomas present all features. Thus, it is the combination of the different ABCDE parameters that makes a cutaneous lesion suspect (Rigel, et al., 2007).

Additionally, the ABCDE criteria have limitations:

- is not helpful in evaluating melanomas with vertical growth involvement.
- it is difficult to apply to amelanotic melanomas, like desmoplastic melanomas (these lesions are characteristically non-pigmented or have minimal residual pigmentation).

Consequently, an increasingly used method is dermoscopy, a non-invasive technique that aids in the visualization of subsurface structures and recognition of early melanoma (Wang and Hashemi, 2010).

In patients with localized disease, of any thickness, and no symptoms, baseline blood tests and imaging studies are not recommended as routine (Bichakjian, et al., 2011).

2.4.2) Dermatoscopy

Dermatoscopy (also known as dermoscopy, epiluminescence microscopy, incident light microscopy, or skin surface microscopy) is a non-invasive technique that uses a magnifying device to allow the visualization of skin lesions surface and subsurface structures, from the epidermis to the superficial papillary dermis. It also permits to established correlations to histopathologic structures (Rao and Ahn, 2012).

Studies showed dermatoscopy to be superior to naked-eye examination alone in melanoma detection, with a **90% sensitivity and specificity** (Vestergaard, et al., 2008). Additionally, dermatoscopy improves early melanoma detection accuracy and reduces unnecessary biopsies (Carli, et al., 2004a Carli, et al., 2004b; de Troya-Martin, et al., 2008; Argenziano, et al., 2012)

However, dermatoscopy is highly user-dependent and its sensitivity and specificity varies with dermatologist's experience (Piccolo, et al., 2002). Additionally, even for expert dermoscopists, accurately diagnosis, particularly in small diameter lesions, is very difficult (Ferris and Harris, 2012). Therefore, it is preferable to make a temporal analysis of the skin lesions, which increases the dermatoscopy sensitivity for melanoma (Haenssle, et al., 2006).

Consequently, dermatoscopic algorithmic methods were developed (Pehamberger et al., 1987; Pehamberger, et al., 1993; Argenziano, et al., 1998; Dal, et al., 1999; Kittler, et al., 1999; Blum, et al., 2003; Soyer, et al., 2004). From those, the 4 most used are (Argenziano, et al., 2003, Haenssle, et al., 2010):

- *Pattern analysis of pigmented lesions:* the most commonly method to evaluate dermatoscopic images (Pehamberger, et al., 1987; Binder, et al., 1995):
- *ABCD rule of dermatoscopy*: it is a semi-quantitative simplification of pattern analysis method. It is based on the evaluation of ABC, and different dermatoscopic structures within the lesion (Nachbar, et al., 1994). Each of the 4 criteria is scored with conversion factors, given the Total Dermatoscopic Score (TDS). It is the model used in the CHP.
- *7-point checklist*: is a quantitative variation of pattern analysis that uses a simplified point system and fewer criteria, which are divided into major and minor criteria (Argenziano, et al., 1998; Johr, 2002; Carli, et al., 2003; Pagnanelli, et al., 2003

- *Menzies method*: is a simplified algorithm based on asymmetry and color criteria and pattern analysis. Lesions are divided into benign and melanoma.

When comparing the different paradigms, the 7-point checklist and Menzies method had the highest, while pattern analysis had the lowest level of sensitivity (Rao and Ahn, 2012).

2.4.3) Biopsy

Techniques

There are two main techniques for biopsy:

- excisional biopsy (complete surgical excision) - considered the method of choice (Harris and Gumport, 1975).
- incisional biopsy (e.g. punch and shave biopsies) – is an acceptable option in certain circumstances, such as a facial or acral location or low clinical suspicion (Zager, et al., 2011). One to three millimetres margins are required in most atypical melanocytic lesions (Bichakjian, et al., 2011).

Every biopsy, of any lesion suspicious for melanoma, should

i) assure sufficient tissue to make a histologic diagnosis and

ii) precisely establish the depth of tumour, which influence the initial diagnostic evaluation, the margins of surgical resection, and the correctness of sentinel lymphadenectomy (Warycha, et al., 2009).

Histological evaluation

- standard histopathologic analysis is achieved with hematoxilin & eosin staining

- immunohistochemistry

In order to help in diagnosis confirmation, HMB-45 (Wick et al., 1988) and S-100 antibodies (Nakajima et al., 1988) are used. However, none has proved to be completely reliable, due to staining of other tissues and/or not identifying some types of melanomas (amelanotic and desmoplastic) nor the metastatic lesions (Wick et al., 1988). Hence, other factors are analysed to proper diagnosis, staging and treatment.

- Other characteristics

Other factors are than used, among them: ulceration presence, mitosis quantification, histologic regression and gene mutation identification (ex: BRAF) (Callender, et al., 2011; Carvajal, et al.,

2011; Thompson, et al., 2011). In addition, the identification of unusual melanoma subtypes (ex: nevoid, spitzoid, and desmoplastic) may influence the extent of surgery (Maurichi, et al., 2010).

Sensitivity and Specificity

Biopsies sensitivity and specificity are good but not excellent:

- Sensitivity: 71%, for ≤ 6 mm melanomas (Friedman, et al., 2008).
- Specificity: study results vary from 5:1 (Carli, et al., 2004) to 500:1 (Cohen, et al., 1991)

Therefore, new diagnostic aids which would increase biopsies' sensitivity and specificity are necessary (Ferris an Harris, 2012).

2.4.4) Pre-operative metastatic evaluation

Pre-operative metastatic evaluation is determined mainly by the stage of the disease.

- melanoma in situ or invasive lesions <0.5mm: no laboratory or radiologic metastatic evaluation is required.
- melanomas 0.5-4.0mm thick: chest radiograph and routine blood chemistries (including LDH) primarily as a baseline, although the risk of distant metastases is minimal (<3%).
- patients with melanomas >4 mm; 2-4mm with ulceration or mitoses; intra-lymphatic metastasis should be evaluated with computed tomography (CT), fluorodeoxyglucose (FDG)-based positron emission tomography (PET) CT scans, and magnetic resonance imaging (MRI) of the brain (Levine and Shapiro, 2012)

2.4.5) Recent diagnostic techniques advances

In addition to the established methods previously presented, there are new methodologies for skin cancer diagnosis, as (Ferris and Harris, 2012):

- Confocal Scanning Laser Microscopy
- Multispectral Imaging
- Electrical Impedance Spectroscopy
- Fiber Diffraction
- Tissue Elastography
- Noninvasive Genomic Detection

2.5) Staging

The American Joint Committee on Cancer (AJCC) is the main staging system for melanoma, with the Breslow thickness being the principle component to determine the prognosis (Balch, et al., 2009). This staging system is based on TNM (tumor, regional nodes, distant metastasis)

classification (Table II) and creates four clinical and pathologic stages (Table III) (Balch, et al., 2010a).

Tumour (T)

Describes the state of the primary tumor by thickness, presence of ulceration, and mitotic rate (Breslow, 1970; Payette, et al., 2009).

Tumor/Breslow thickness (measured from the melanoma's top of the granular layer down to the lowest tumor cell) determines T classification in T1 to T4 (Table II).

Although the tumour thickness is the main prognostic factor, with survival decreasing as the depth increases, the mitotic rate and the ulceration further subcategorize the Breslow thickness increasing its prognostic accuracy:

a - no ulceration in all T categories or $< 1/mm^2$ mitoses in tumors in the T1 category;

b - ulceration in all T categories or $\geq 1/mm^2$ mitoses in tumors in the T1 category.

Table II – TNM melanoma classification (Wisco and Sober, 2012).

T		
Classification	**Thickness (mm)**	**Ulceration / Mitosis**
Tis	NA	NA
T1	≤1	**a**: Without ulceration and mitosis $<1/mm^2$ **b**: With ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2	**a**: Without ulceration **b**: With ulceration
T3	2.01-4	**a**: Without ulceration **b**: With ulceration
T4	>4	**a**: Without ulceration **b**: With ulceration
N		
Classification	**Number of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	**a**: Micrometastasis a **b**: Macrometastasis b
N2	2-3	**a**: Micrometastasis a **b**: Macrometastasis b **c**: In-transit metastases/satellites without metastatic nodes
N3	≥4 matted nodes, or in-transit metastases/satellites with	

	metastatic nodes	
M		
Classification	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, of nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Mitotic rate is determined by identifying the area of the dermis with the highest number of mitotic figures (the hot spot), counting the number of mitotic figures in the hot spot and in adjacent fields, until an area of 1 mm^2 has been evaluated and reporting the number of mitoses per square millimeter (Balch, et al., 2010a).

Ulceration is considered to be present if there is a

- full-thickness epidermal defect;
- reactive changes, such as fibrin deposition and neutrophils;
- effacement of the surrounding epidermis ;
- reactive hyperplasia in the absence of trauma or recent surgical procedure.

Regional Nodes (N)

Nodal involvement is classified (Table II) by the number of nodes in N1-N3 and whether the nodal involvement is

microscopic (*a*): diagnosed after sentinel lymph node biopsy;

macroscopic (*b*): defined as clinically detectable nodal metastases confirmed pathologically.

Furthermore, intra-lymphatic metastasis also contributes to N staging. Patients with intra-lymphatic metastases are classified as

N2c – if don't present nodal metastases

N3 – if present concomitant nodal metastases.

Intra-lymphatic metastasis was defined as metastases within the (Balch, et al., 2009):

i) regional lymph nodes (satellites): microscopic satellites metastases or clinical satellite metastases);

ii) lymphatic vessels: in-transit metastases,

and was associated with poor prognosis (Day, et al., 1981).

Satellites (around a primary tumour)

- Microscopic satellites metastases: discontinuous group of melanoma cells (> 0.05 mm in diameter) located ≤0.3 mm from the invasive tumour mass but separated from it by normal dermis or panniculus not affected by fibrosis or inflammation (Gershenwald, et al., 2010). They have a highly recurrent locorregional involvement and lower survival rates.

- Clinical satellite metastases: tumor located no further than 5.0 cm from the primary lesion

In-transit metastasis

Metastases between a primary melanoma site and the regional lymph node, located at a distance more than 5.0 cm from the primary tumor site, but proximal enough to the draining lymph node. It has a 5-year survival of 69%

Lymph node positivity is normally evaluated by hematoxylin and eosin stained sections, but it can also be determined by IHC stain if at least one melanoma-associated marker (human melanin black [HMB-45], Melan-A/MART-1) is positive (Ohsie, et al., 2008).

Table III – TNM Melanoma Stages (Wisco and Sober, 2012).

Stage	**T**	**N**	**M**
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b; T2as	N0	M0
IIA	T2b; T3a	N0	M0
IIB	T3b; T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a; N2a	M0
IIIB	T4b	N1a; N2a	M0
	T1-4a	N1b N2b N2c	M0
IIIC	T4b	N1b N2b N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

M - Distant metastases classification

Melanoma is capable of metastasising to any distant site. The most common locations are the skin, soft tissues, lung, liver, brain, bone, and gastrointestinal tract (Balch, et al., 1983; Balch, et al., 2010a)

M is sub-divided, based on the anatomic metastatic site (Neuman, et al., 2008):

M1a: distant skin/subcutaneous tissue/distant lymph nodes

M1b: the lungs

M1c: any other visceral site

An elevated serum lactase dehydrogenase (LDH) upstages patients to M1c level.

If the LDH is elevated above a laboratory's reference standard, survival rates decrease, despite of the site of the metastases.

Approximately 10% of patients present with metastatic disease in the absence of an identified primary melanoma (Reintgen, et al., 1983).

When the primary site is unknown, staging is based on the location of the initial metastatic disease (Rutkowski, et al., 2010):

Stage III: metastatic disease is found in the skin, subcutaneous tissue, or in a lymph node;

Stage IV: metastatic disease in a visceral site.

2.6) Treatment

2.6.1) Localized diseased (Stage I & II)

Surgery

The primary treatment for cutaneous melanoma is surgical excision with histologically negative margins (Bichakjian, et al., 2011). Although the excision margin width being determined by primarily lesion thickness (Table IV), ≥ 2cm margins do not have a significant impact on local recurrence (12%) and 5 years survival (55%) (Heaton, et al., 1998).

Mohs Micrographic Surgery (MMS) can be an option for melanoma in situ in H and M areas (Area H: central face, eyelids, eyebrows, nose, lips, chin, ear and periauricular skin /sulci, temple, genitalia, hands, feet, nais, ankles, and nipples/areola; Area M: Cheeks, forehead, scalp, neck, jawline and pretibial surface) (Ad Hoc Task Force, 2012). Additionally, MMS with immunohistochemistry in fixed or frozen tissue, may offer lower recurrence rates and better survival than surgical excision (Hui, et al., 2012).

Table IV - Excision margins relation with primary melanoma thickness.

Melanoma thickness (mm)	**Excision margins (cm)**
In situ	0,5
<1	1
≥1	2
very thick lesions or if satellite metastases are present	3

Adjuvant therapy

Although there is little evidence of efficacy, with a high risk for patients and with very few centres performing it, there is references to the use of adjuvant therapy in the treatment of localized diseased (Stage I & II).

- Interferon-α

Pegylated IFN-α (PegIFN-α) is recommended (II, B) in patients with micrometastases and primary ulcerated melanomas (Dummer, et al., 2012).

- Radiotherapy

It should be considered (III, B) in case of inadequate resection margins of lentigo maligna melanoma or melanoma metastases (Dummer, et al., 2012).

Sentinel lymph node biopsy (SLNB)

The identification of clinically occult nodal metastases is the most important independent predictor of prognosis in patients with stage I and II melanoma (Gershenwald, et al., 1999). However, although the risk for regional lymph node metastases is correlated with tumour thickness (Schmidt, et al., 2009) (Table V), studies did not demonstrate an increase in survival with prophylactic lymph node dissection (Sim, et al., 1978).

Table V – Association between melanoma thickness and the risk for lymph node metastasis.

Melanoma thickness	**Risk (%)**
In-Situ	None
<1mm	<5
1-4mm	20-25
>4mm	50-75

Therefore, sentinel lymph node biopsy (SLNB) can be performed in the evaluation of clinically negative regional lymph nodes in patients with ≥ 0.85mm thick melanoma without clinical or radiologic evidence of regional lymph node or distant metastases (Table VI) (Piris, et al., 2012).

Sentinel node detection can be achieved with the use of (Liu, et al., 2008):

- isosulfan blue dye, or
- lymphoscintigraphy with technetium-99 labeled sulfur colloid, followed by intraoperative identification using a g-sensor probe scanner.

Lymphoscintigraphy performed before surgery must demonstrate the lymphatic drainage pathway and regional nodal drainage basin in order to allow the precise location and excision of the correct node (Gershenwald, et al., 2011).

Table VI- Sentinel lymph node biopsy (SLNB) recommendations,

Melanoma thickness (mm)	**SLNB**
<0.76	No
0.76-0.85 negative ulceration, regression, or mitoses positive ulceration, regression, or mitoses	 No Yes
>0,85	Yes

SLNB should <u>not</u> be performed if:

- lymphoscintigraphy does not clearly demonstrate a regional lymph node drainage basin and sentinel node,
- in patients with confirmed regional nodal or distant metastases,
- in patients with limited life expectancy from melanoma or associated medical conditions

Histopathologic analysis of the sentinel lymph node is achieved by the evaluation of hematoxylin-eosin and immunohistochemical-stained sections (Scolyer, et al., 2008). For immunohistochemistry several antibodies are used:

- S100
- Melanoma Antigen Recognized by T-cells 1 (Mart-1)
- Melanocyte antigen (Melan A);
- Human Microphthalmia-associated transcription factor (MITF);
- HMB-45.

Intra-operatively, the sentinel node can be sent for frozen section, or immunostaining examination. However, the evaluation of intra-operative frozen section is less sensitive than of formalin-fixed tissue and, therefore, is not recommended (Scolyer, et al., 2005).

If sentinel lymph node does not contain metastasis, the remaining lymph nodes are unlikely to contain melanoma and no additional regional surgery is recommended (Reintgen, et al., 1994).

If sentinel lymph node do have metastases, although the risk of additional nonsentinel lymph node metastasis is low (<15%), it is recommended complete regional lymph node dissection.

Complications of SLNB are rare (4-10%) and include (Veenstra, et al., 2011):

- dye reactions (<1%),
- wound complications,
- seroma/hematoma.,
- lymphedema (<5%),
- false-negative sentinel node (5%–15%).

Regional disease control can be estimated by recurrence rates in the lymph node basin. However, even though sentinel lymph node biopsy allows better staging, regional disease control (Piris, et al., 2012) and lower recurrence rate in comparison with patients with lymphadenectomy for clinically palpable tumor (<10% vs 10-50%) (Gershenwald, et al., 1998), the benefit of sentinel lymph node mapping has not been clearly shown and some authors do not consider sentinel lymph node biopsy not to have a therapeutic advantage (Kanzler, 2010).

2.6.2) Loco-regional disease (Stage III)

A palpable lymph node should be considered an indication of metastasis. Diagnosis is achieved by biopsy (fine-needle aspiration, or excisional if the fine-needle aspiration biopsy is not available or results are indeterminate) (Basler, et al., 1997; Doubrovsky, et al., 2008). Patients with regional lymph node metastases should undergo toracoabdominopelvic CT scanning (with intravenous contrast) or FDG-PET scanning and brain MRI, to exclude the presence of further metastases.

In patients with cytologically or histologically detected regional nodal metastases, complete lymphadenectomy should be performed (III, C). Treatment of non-resectable metastases of the limbs may be achieved with isolated limb perfusion (e.g. melphalan and/or TNFα) (III, C) or radiotherapy (Dummer, et al., 2012; Levine and Shapiro, 2012).

Survival diminishes (10 to 50%) with palpable lymph node metastases, in number and extension (Callery, et al., 1982)

2.6.3) Metastatic disease (Stage IV) (Dummer, et al., 2012)

Stage IV melanoma patients should be screened for mutations (BRAF, NRAS, c-Kit, GNA11, GNAQ) and their case discussed in an interdisciplinary tumour board in order to decide the appropriate treatment, which may include:

- New systemic therapies, which have demonstrated good antitumor activity, namely:
  - immunotherapy (ipilimumab or anti-PD1 antibodies),
  - selective BRAF inhibitors (vemurafenib and dabrafenib),
  - c-Kit inhibitors,
  - MAPK/ERK kinase (MEK) inhibitors.

  Ipilimumab and vemurafenib (preferable if BRAF V600 mutation) are first-line therapies (II, B).
- Cytotoxic drugs as dacarbazine (the reference), taxanes, platin derivatives, cytokines (IFN, IL-2), may be used if new targeted are not available.
- Surgery of visceral metastases may be appropriate in patients with good performance and isolated tumor manifestations.
- Palliative radiotherapy should be considered in symptomatic brain or localized and painful bone metastases.

2.6.4) Treatment of Local recurrence

Local recurrence reflects the stage of the primary lesion, not the failure of the primary excision. A subcutaneous nodule within 2–5 cm to a primary excision site (satellite metastasis), or *en route* to a regional lymph node (intransit metastasis) should be considered a recurrence or progression (Levine and Shapiro 2012).

Fine-needle aspiration biopsy or excisional biopsy of the nodule, for diagnosis, and CT or MRI and FDG-PET scans for search of systemic metastases, should then be performed

Complete surgical resection is the standard treatment the (margins are not defined). However, there is 67% of additional recurrence, being associated with disease progression, and death (Hafstrom, et al., 1991).

2.7) Follow-up

Although detection should occur as early as possible (Dummer et al., 2011), and the existence of the risk of melanoma relapse - 8% within 2 years after diagnosis (Titus-Ernstoff et al., 2006), and appearance of other skin tumours (Farshad te al., 2002), it is still unproven that clinically monitorization leads to improved survival rates. Additionally, most relapses are detected by the patients. Therefore, there is no consensus on optimal frequency of follow-up visits neither on the utility of imagiology and blood tests (Nieweg and Kroon, 2006).

If a protocol should be indicated, recommendations based on the relapse risk profile over time propose (Dummer et al., 2012) (Table VII):

- Patients should be informed to avoid solar or artificial UV exposure, sunburns, and to perform regular skin and peripheral lymph nodes self-examinations (Bichakjian, et al., 2011).
- Clinic control every 3 months during the first 3 years and every 6–12 months thereafter; intervals between controls tailored according to individual risk may reduce false-positive findings (Turner et al., 2011).
- In patients with thick primary tumours, lymph nodes affection, or metastases, CT-scan may lead to an earlier diagnosis relapses (Bastiaannet et al., 2009).
- S-100 rising serum is the most specific for disease progression (Beyeler et al., 2006).

Table VII: ESMO recommendations for melanoma follow-up (Dummer et al., 2012). y: year, Y: perform; N: not applicable.

	Stage 0, I & II			**Stage III**	**Stage IV**
Clinic Control	**Tis-T1**	**T2-T3**	**T4**		
First year after diagnosis	2/y	4/y	4/y	4/y	4/y
Second year after diagnosis	1/y	3/y	4/y	4/y	4/y
Third year after diagnosis	1/y	2/y	3/y	3/y	3/y
Fourth year after diagnosis	1/y	2/y	3/y	3/y	3/y
Fifth year after diagnosis	1/y	2/y	2/y	2/y	2/y
For life	1/y	1/y	1/y	1/y	1/y
S-100	N	N	N	N	Y
CT Scan	N	N	2/y	2/y	2/y
Self Examination	Y	Y	Y	Y	Y
Sun & UV avoidance	Y	Y	Y	Y	Y

2.8) Prognosis

The 5-year melanoma survival has increased in the last decades, with prevention and early detection having relevant effects. However, melanoma-specific survival decreases with several factors (Balch, et al., 2009; Pollack, et al., 2011):

- sex: men (86.8%);
- age: ≥ 65 years (83.2%);
- stage: metastasized (15.7%); thicker than 4.0 mm (56.6%);
- location: scalp/neck (82.6%);
- unspecified/overlapping lesions (41.5%), the least favorable prognosis;
- histologic subtypes: nodular (69.4%) and acral lentiginous melanomas (81.2%).

Size

Prognosis worsens with tumour size, mitotic rate and ulceration

Survival rates at 5-years are:

- 97% in patients with T1a melanoma and 53% in patients with T4b melanoma (Balch, et al., 2002; Balch, et al., 2010a).
- lower with increasing mitotic rate (Wisco and Sober, 2012).
- the same of the next T category, if ulceration is present in tumours of lower T category (Wisco and Sober, 2012).

Regional Nodes (N)

The overall 5-year survival decreases with presence of positive regional nodes and if they have metastases, micro (67%) or macro (43%) (Balch, et al., 2010b). Stratifying:

1 positive node: 71% Vs 50%

2 positive nodes: 65% Vs 43%

3 positive nodes: 61% Vs 40%

≥ 4 positive nodes: 36% 5-year survival independent of microscopic or macroscopic disease.

Additionally, the presence of intra-lymphatic metastases increases the risk of regional recurrence and has 69% of 5-year survival (Balch, et al., 2010).

Metastasis

The prognostic value of the M is the presence or absence of distant metastasis, with the differences of M categories being insignificant for the TNM staging and prognosis (Lee, et al., 2009).

Regression

Regression is the absence of melanoma cells within, or immediately adjacent to, a melanoma; being this area flanked, on one or both sides, by viable melanoma cells (Ronan, et al., 1987). Regression was associated with increased likelihood of metastasis, being important for prognosis (Clark, et al., 1989).

Tumour-infiltrating lymphocytes

It can occur an infiltration of cytotoxic T lymphocytes in the vertical growth phase of the tumour, which was described as (Busam, et al., 2001):

- brisk: lymphocytes diffusely infiltrate throughout the tumour;
- non-brisk: focal or multifocal infiltration;
- absent: there are no lymphocytes infiltrating the tumour.

It has been reported that patients with a brisk infiltrate had a better prognosis than patients without tumour-infiltrating lymphocytes (Clemente, et al., 1996). However, this parameter has not been validated for staging,

Lymphovascular invasion

Lymphovascular invasion was indicated as the presence of tumour cells adherent to the lumen vessel wall or merged with fibrin (Piris et al., 2012). It can also occur in other levels:

- uncertain vascular invasion: tumour cells are adjacent to the endothelium of the vessel wall but without luminal involvement;
- extravascular migratory metastasis / angiotropism: tumoral cells surround the perivascular compartment (Barnhill, et al., 2004).

Although this characteristic has not been considered in the AJCC staging system, it is a relevant predictor of metastasis (Petersson, et al., 2009).

Considering that surgical excision, the main treatment to melanoma, did not have significant alterations in the last decades, the 5-year survival progress can be mostly attributed to earlier detection (Russak and Rigel, 2012). Thus, and also because the cost of treating is dramatically higher in late-stage melanoma, the detection of melanoma at an early stage is extremely important, giving prevention an essential role.

2.9) Prevention

2.9.1) Primary prevention

There is still no consensus, with different references presenting different recommendations. While some advise avoiding the sun, others advise enjoying a moderate amount of sun exposure.

The American Cancer Society recommends (Berwick et al., 2009):

- avoidance of
  - sun, between 10 and 4 PM;
  - artificial UV sources, always (ex: tanning beds)
- when sun cannot be avoided - use of umbrellas, protective hats, clothing, and sunscreen factor (≥ 15).

However, the role of sunscreen in melanoma prevention remains controversial (Mulliken, et al., 2012), it is still not clear if sunscreens provide protection from developing melanoma, or if they increase the risk for skin cancer (Gorham, et al., 2007). This is also due to the fact that individuals use of sunscreens wrongly, namely using them to prolong their exposure to the sun.

Additionally, there is also no consensus in sunscreens ability to reduce nevi formation, which is a putative precursor lesion for melanoma (English, et al., 2005; Whiteman, et al., 2005; van der Pols et al., 2006).

Therefore, the most consistent and robust protection from UVR and melanoma is clothing. The physical barrier provided by hats, long sleeves, and long pants is an ideal protective agent against the sun. (Autier et al., 1998; Bauer, et al., 2005; English, et al., 2005)

2.9.2) Secondary prevention

Patient education, including the ABCDE of melanoma is an important part in early diagnose. Thus, regular self-examinations of the skin should be encouraged (Abbasi, et al., 2004; Rigel, et al., 2005; Berwick, et al., 1999; Pollitt, et al., 2009)

Although there are no randomized trials supporting a widespread population-based screening for melanoma, Geller and colleagues (2002) suggested total skin examination (including the hands, plantar skin, webspaces, and mucous membranes) of those at highest risk:

- white men ≥ 50 years. The group who most often has deep lesions and where half of the melanoma-related deaths occur;
- persons with a family history of melanoma or with multiple or atypical nevi;
- those with a previous diagnosis of melanoma.

Furthermore, in 2007 Goldberg and colleagues indicated five factors (HARMM) that would increase the probability for melanoma detection through visual examination at screenings:

- History of previous melanoma,
- Age over 50,
- Regular dermatologist absent;
- Mole Changing;
- Male gender.

With individuals with high risk (4 or 5 factors) being 4.4 times more likely to have melanoma than those with low risk (zero or one factor).

Chapter 3

Materials and Methods

C) Materials and Methods

Study

This was a retrospective study of primary coetaneous melanoma cases diagnosed in the Oporto Hospital Centre (CHP) between 2006 and 2012.

The study was performed with the approval of Ethic for Health Commission and the Administration Board of the CHP. During the study patients' anonymity was maintained.

Data

In the study there were used one hundred and forty eight cases referenced as primary melanoma by the Pathology Service of the CHP between 2006 and 2012.

The analysis focused on main epidemiological parameters: total number of cases, gender, age, tumour location, histological type, stage, follow up, profession, skin phenotype, total number of melanocytic nevi, presence of dysplastic nevi, type of sun exposure, artificial UV radiation exposure, frequency of sunburn, and history of skin cancer.

Information was obtained using *Sistema de Apoio ao Médico* (Administração Central do Sistema de Saúde, PT) software and consulting the physical processes in the central archive of the CHP.

The World Health Organisation (WHO) International Classification of Diseases (ICD) it is the "gold-standard" classification of the WHO member states (WHO, 2014). For the purpose of this study we adapt the ICD-10 classification as presented in Table VIII.

Table VII: Relation between the anatomic location here presented and classification and codification (CID-10) used by the Anatomopathology Service of the CHP.

CID-10	**Anatomic Location**
C44.2	Skin of ear and external auricular canal
C44.3 & C44.0	Skin of face and lip
C44.4	Skin of scalp and neck
C44.5	Skin of trunk (including anal margin and skin, and skin of breast)
C44.6	Skin of upper limb (including shoulder)
C44.7	Skin of lower limb (including hip)
C44.9	Skin, unspecified
C51.9	Skin of vulva
C69	Eye and Annexe (conjunctive, choroid, cilliary body, orbit, eye NS)

Statistics

Data were analysed using Excel 2003 software (Microsoft Cop., Redmond, WA), with the results being expressed as total number of cases, percentage of cases or average ± standard deviation when comparing the average age of patients in the different anatomic locations, histological types and melanoma stages.

Statistical analysis was performed using SPSS 21.0 software (SPSS Inc., Chicago/IL). Prior to parametric analysis, the homogeneity of variance was confirmed by Levene's test, the overall differences were studied through one-way analysis of variance (ANOVA) and the inter-group variations were assessed with Post-Hoc Tukey test. Categorial non parametric variables were analyzed with Binomial or Chi-squared test. Statistical significance was accepted when p was < 0.05.

Chapter 4

Results

D) Results

In order to assess if the international pattern of increase in the number of diagnosed cases of melanoma (Erickson and Driscoll, 2010) also occurred in the area of action of our hospital, we studied the number of diagnosis between 2006 and 2012.

Data analysis revealed an increased of the number of cases diagnosed after 2009 and that this augment was due more to the increase in number of cases diagnosed in men than in women (Fig. 1).

It was also possible to observe that the number of primary melanoma cases in women seemed to be higher than in men (Fig. 1).

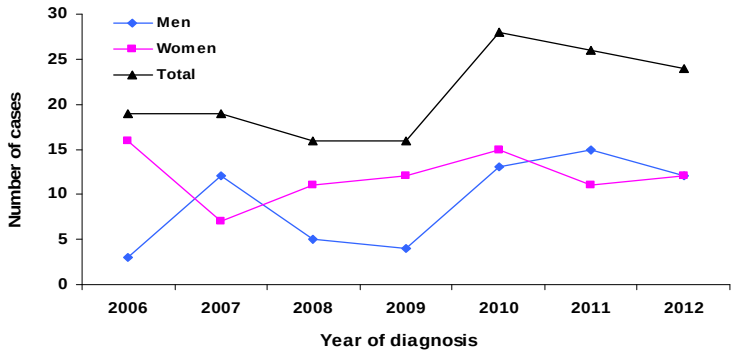

Figure 1. Graphic representation of the evolution on the number of diagnosis of primary melanoma in CHP between 2006 and 2012. Total: evolution of the total number of cases diagnosed between 2006 and 2012; Men: evolution of the number of cases diagnosed in men; Women: evolution of the number of cases diagnosed in women.

Confirming the impression given by our first analysis (Fig. 1), we observed, from a total number of 148 cases, a higher number of diagnoses of primary melanoma occurring in women than in men (Fig. 2).

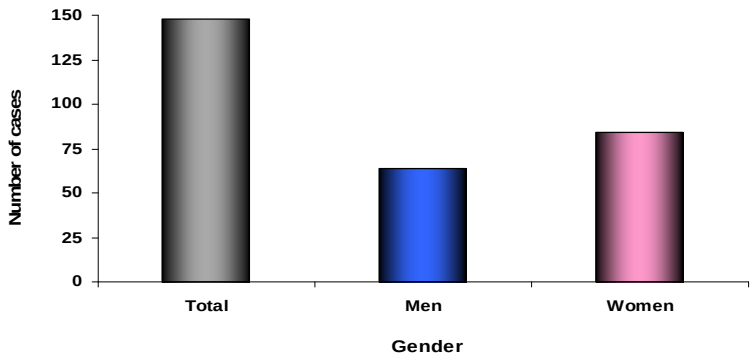

Figure 2. Graphic representation of the total number of primary melanoma cases diagnosed in the CHP between 2006 and 2012 and the number of cases in men and in women.

So that we could assess if, in our patients, melanoma risk increased with age, as previously described (Rigel, 2010), we studied the number of diagnosed patients per cluster of age.

We observed an increase in the number of diagnosis with age, until reaching a peak in the group of 60-69 years old. Women maintain that pattern, however, the maximum number of diagnosis in men occurs previously, in the group of 50-59 years old (Fig. 3).

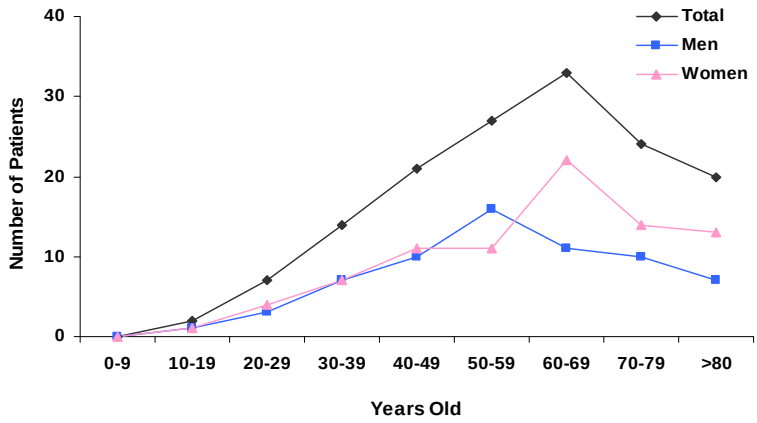

Figure 3. Graphic representation of the relation between the number of the diagnosis of primary melanoma with the age at which the diagnosis occurred. Total: total number of diagnosis; Men: number of diagnosis in men; Women: number of diagnosis in women.

When indexing the number of patients to the national demography per gender (Fig. 4) it is possible to observe an increase of the incidence of cases with age. Interestingly, the peak at 60-69y at women and 50-59y at men, observed when analysing the number of patients (Fig. 3), continues to occur.

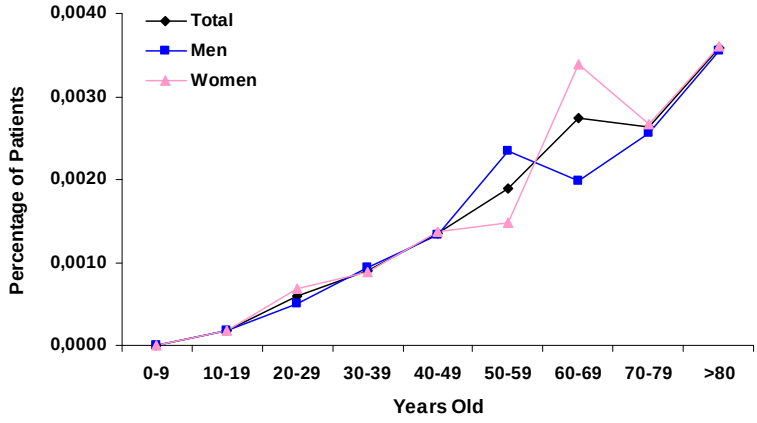

Figure 4. Graphic representation of the percentage of patients at each age group per national demography per gender.

In order to determine if, in the CHP's melanoma patients, the anatomic distribution of melanoma changes with sex and age, as previously described (Garbe and Leiter, 2009), we analysed the possible relation between these variables.

Our study revealed that the anatomic distribution of primary melanoma in the CHP is in accordance with the international observations: men present a higher incidence of melanoma on the trunk and women on the lower limbs (Fig. 5). It was also possible to see that, on total, there is a higher number of diagnosis of primary melanoma of the lower limbs followed by primary melanoma of the trunk (Fig. 5).

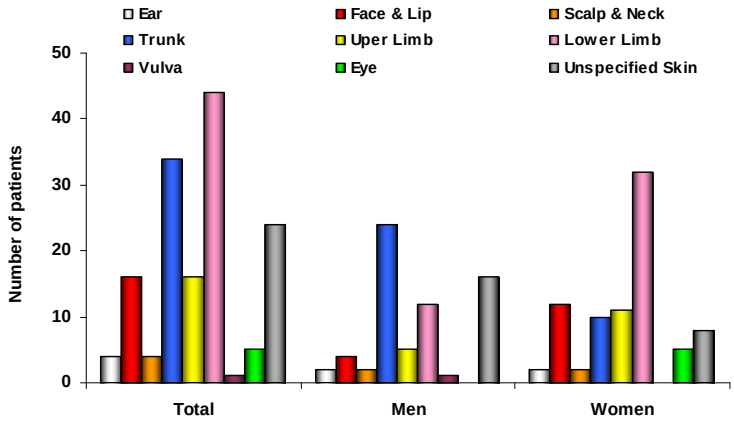

Figure 5. Graphic representation of anatomic distribution of primary melanoma diagnosed in the CHP, total, on men and on women.

However we did not observed an alteration of the anatomic distribution with age (Fig. 6)

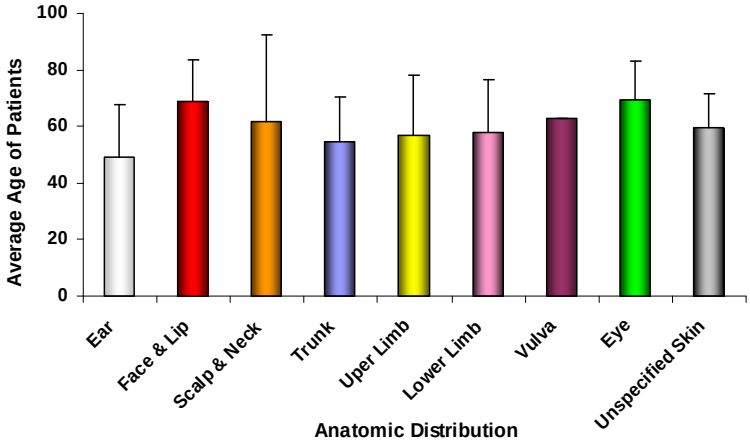

Figure 6. Graphic representation of the relation between patients' age and anatomic distribution of primary melanoma diagnosed in the CHP.

So that we could determine if the proportion of the melanoma histological types previously indicated (superficial spreading > nodular > lentigo maligna > acral lentiginous; Watson et al., 2011) also happens in CHP's referenced population, we assessed melanoma's differentiated incidence.

Our results showed the superficial spreading melanoma has having the highest incidence, being followed by the nodular type, both in men and in women (Fig. 7). Interestingly, the number of female cases was higher in all histological types with the exception of the nodular melanoma (Fig. 7).

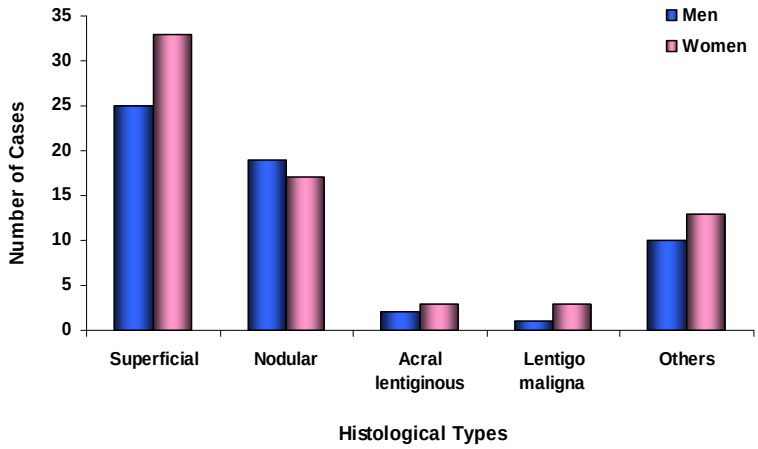

Figure 7. Graphic representation of the melanoma histological types diagnosed in the CHP. Others: other types of classification given by the anatomopathology department to the cases, including dysplastic nevi.

It was possible to verified that there was no differences between the average age of patients between histological type, neither between men and women in each histological type (Fig. 8).

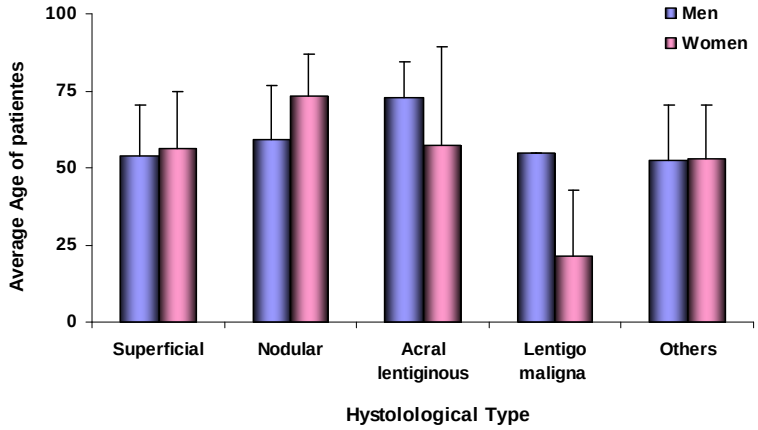

Figure 8. Graphic representation of patients' average ages for each the melanoma histological type in men and in women.

It is known that the incidence of the melanoma's stages it is not homogeneous (stage I > II > III > IV) (Mouw et al., 2008; Shack; et al., 2008; Birch-Johansen et al., 2008; Cancer Research UK, 2014). In order to assess if the same happened in melanoma's patients diagnosed in the CHP we study this parameter.

We observed (Fig. 9) the same relation between stages (stage I > II > III > IV) previously described for the UK. Moreover, our analysis indicated that the proportion of the histological types

presented in Fig. 6 is maintained in every stage, with the exception of stage II where the nodular type has the highest incidence (Fig. 9 A). We also observed that tumours ≤ 1mm were the ones with more cases (Fig. 9 B).

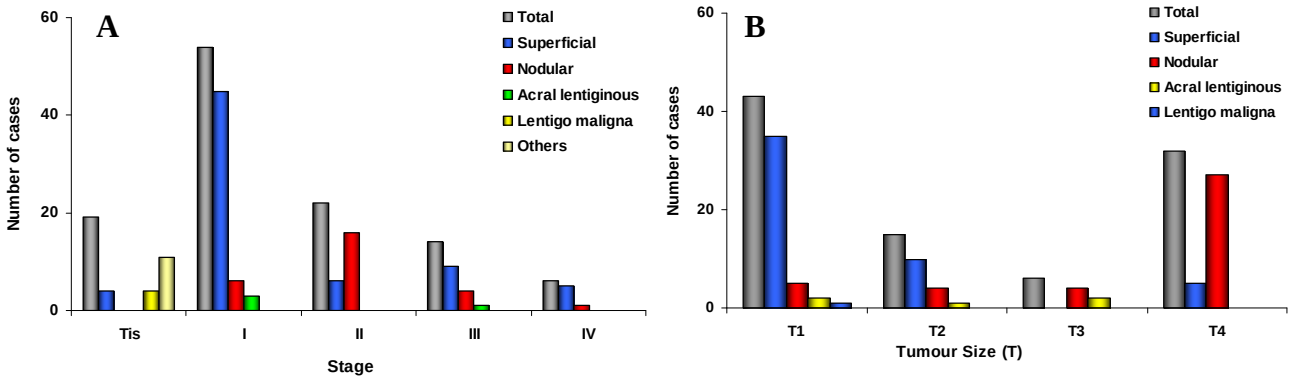

Figure 9. Graphic representation of the number of **A)** melanoma stages and **B)** Tumour size (T) for each histological type.

Additionally, our results also show that women present a higher number of stage 0, I and II melanoma than man, but in the following stages the opposite occurs (Fig. 10 A). Women seem to have more cases than men in all Tumour sizes, with the exception on T4 (Fig 10.B)

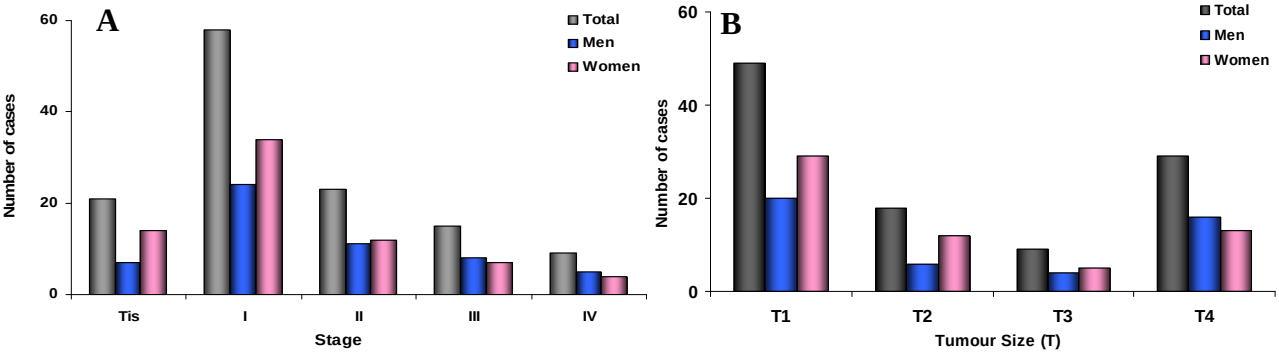

Figure 10. Graphic representation of the number of **A)** melanoma stages, **B)** Tumour size, in total and for each gender.

Our analysis of the data also included the study of a possible relation between tumour thickness and stage and patient's age, as previously described (Jamal, et al., 2011). Although there is an apparent tendency to the incidence of higher stages and thicker tumours at older ages, our results did not showed significant differences between the average ages of each stage an tumour sizes(Fig. 11)

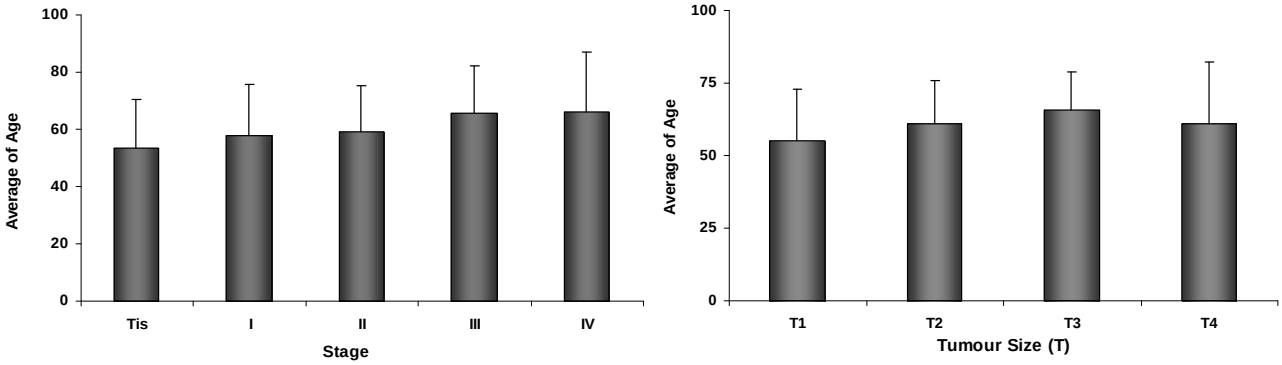

Figure 11. Graphic representation of the average ages of patients in each **A)** melanoma stage, and **B)** Tumour size.

Being an important part of melanoma's protocol, patients' follow-up it is essential to detect relapses and potentiate patients' survival. So that we could determine if CHP's melanoma's protocol allows international's rates of survival (97,3 %; Howlader et al., 2009) we studied the outcome registered at patients' last consultation at the moment of the data recollection

The analysis of the CHP's data between 2006 and 2012 seems to indicate a 2,4% rate of mortality, and an average age of death of 72 years old. Compatible with a 97,6% rate of survival, we also saw that the majority of patients had been discharge or were with appropriated physical and dermatoscopic parameters (Fig.12). Furthermore, as previously indicated (Balch, et al., 2002; Balch, et al., 2009; Balch, et al., 2010a Pollack, et al., 2011) gender seemed to be a factor influencing the outcome, considering that the female cases were higher in all classes of the follow-up, with the exception of the "not-appropriated" one (Fig.12).

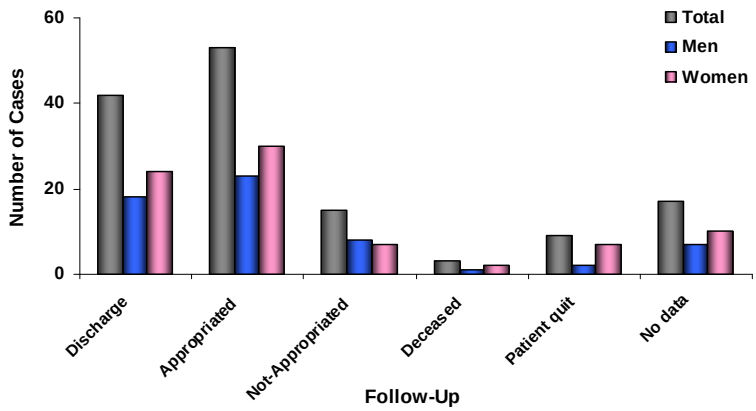

Figure 12. Graphic representation of patients' evaluation in their last register consultation at the moment of the date recollection.

Compatible with the highest incidence of cases occurring in the trunk and lower limbs (Fig. 5), the majority of patients with "discharge" or "appropriated" physical and dermatoscopic parameters were those with primary melanoma in the trunk and lower limbs (Fig. 13)

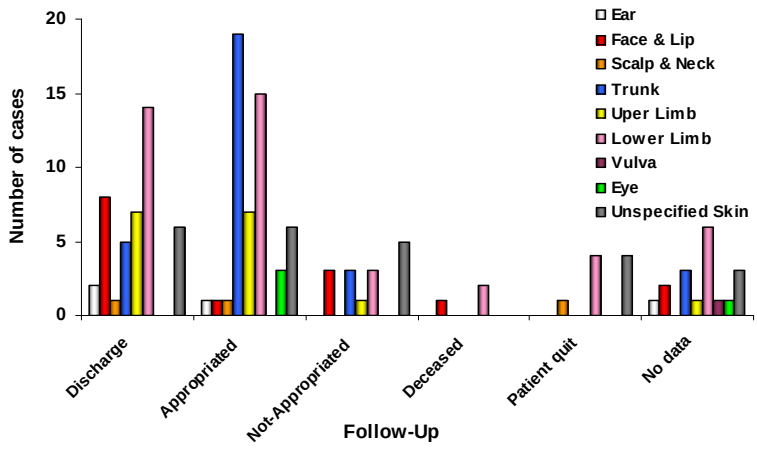

Figure 13. Graphic representation of patients' evaluation in their last register consultation at the moment of the date recollection, for each anatomic location.

The outcome of the follow-up presented above (Fig. 12) occurred at all stages, with the exception of stage IV were the majority of patients had "not-appropriated" physical and/or dermatoscopic parameters (Fig. 14A). Independently of tumour size, the highest number of cases had an "appropriated" evaluation. (Fig. 14B)

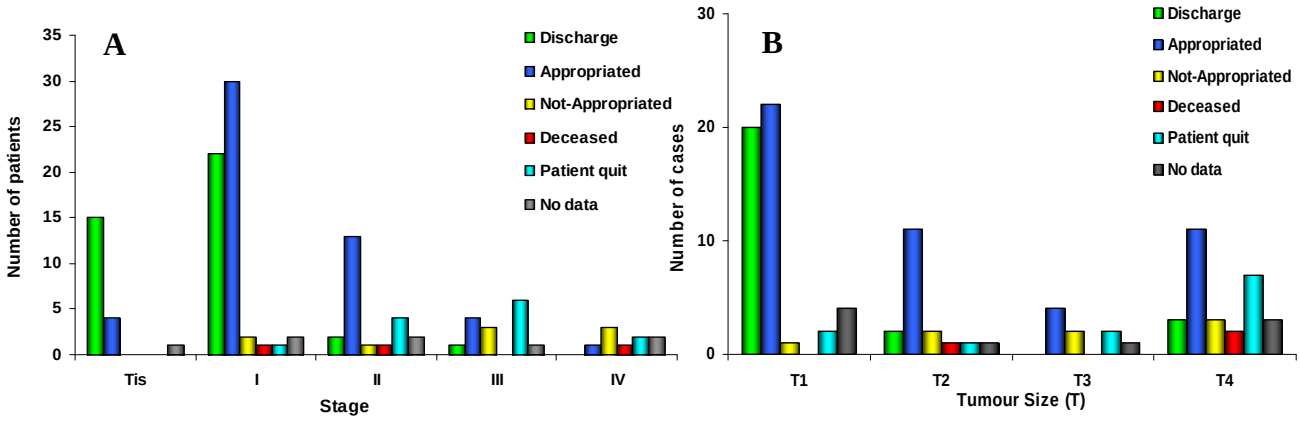

Figure 14. Graphic representation of patients' evaluation in their last register consultation at the moment of the date recollection for each **A**) histological stage, and **B)** Tumour Size.

The majority of patients that were discharged or that presented an "appropriated" evaluation had superficial melanoma, whereas patients that deceased, quit the consultation or treatment or presented a "not-appropriated" physical and dermatoscopic parameters had nodular melanoma (Fig .15).

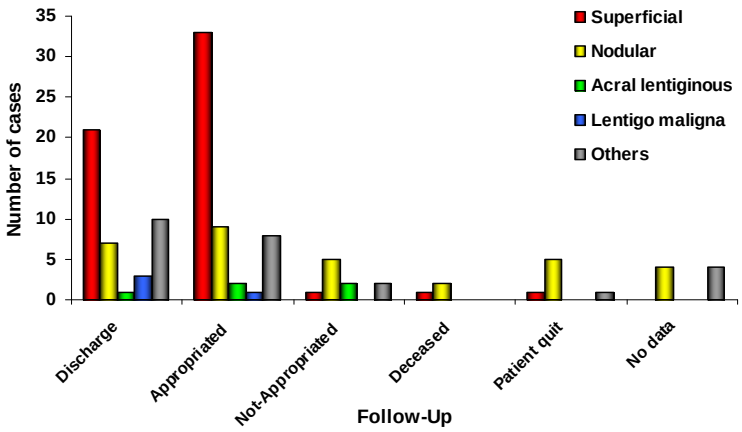

Figure 15. Graphic representation of patients' evaluation in their last register consultation at the moment of the date recollection for each melanoma type.

Chapter 5

Discussion

E) Discussion and Conclusions

The appearance of melanoma is a multifactor process where both personal characteristics and environmental factors contribute. Studies indicate that malignant melanomas are associated with heavy sun exposure in low phototype populations (Armstrong and Kricker, 1993). Therefore, it is natural hat the highest incidence rates in the world occur in Australia and New Zealand, both nations having being colonized by North European countries and with very high sun intensity (Ferlay, et al, 2008).

It is also known that intermittent intense sun exposure is the leading form of UV inducing melanoma (Armstrong, 1988). Therefore, it is not strange that in the European Union the highest incidences of melanoma arise in Sweden and Denmark due to disproportionate sun exposure during holidays at southern countries (IARC, 2008). Interestingly, on the contrary to the North America, in the European countries, the rates of melanoma are higher in women than in men, with Portugal being no exception (Cancer Research UK, 2011).

Melanoma incidence is increasing rapidly worldwide (Erickson and Driscoll, 2010). However, there is no agreement in the reasons responsible for this occurrence. Some reports indicate that this may be due to the i) higher awareness of patients and physicians, ii) increased surveillance and detection, or iii) new classifications (Qin et al., 2005; Welch et al., 2005). Others studies indicate that the increase in incidence occurs among all Breslow thickness, and also in mortality rates, defending that the melanoma epidemic is real (Linos et al., 2009; Hollestein et al., 2012; Little and Eide, 2012). They also support that this may occur because outdoor occupations were replaced by indoor ones, leading to a decrease of chronic solar exposure, which is protective for melanoma, and an increase in intermittent sun exposure, which is a risk factor to melanoma (Gallagher et al., 1989).

In order to contextualize the epidemiological results of our study it is necessary to be familiar with the Portuguese demography. According to the National Institute of Statistics, the Portuguese population is decreasing since 2010, being constitute in 2012 by 10.487.289 persons, of which 4.995.697 were men and 5.491.592 were women (INE, 2013). The national higher number of female population also occurs in Oporto district (RON, 2006).

INE's 2013 report also indicates that the population is aging, mainly due to a decrease in the birth-rate but also because of an increase in the life expectancy. Thus, the cluster of population with higher percentage, for men and women, is the one of 40-49 years old.

The analysis of the incidence of primary melanoma diagnosed in the CHP between 2006 and 2012 showed an increase in the number of diagnosis in this period, namely after 2009, and also in comparison with previous studies on the same population (Ferreira et al., 2007). This occurred in both gender, but more pronouncedly in men. In this particular case this result may be influenced by the new classification of the dermatology service of CHP as reference centre for melanoma. This implicates that the cases that were diagnosed and treated in other hospitals started to be sent to the CHP increasing the number of cases diagnosed per year.

The study of the melanoma occurrence per gender over time also gave the impression that, in overall, the incidence was higher in women than in men. This tendency was confirmed when analysing the global incidence per gender in the CHP between 2006 and 2012. It was possible to observe a higher number of female patients diagnosed with primary melanoma than male patients, something that had been observed also between 1996 and 2006 (Ferreira et al., 2007).

This result could be due to a higher number of female population in Portugal. However, when having this factor into account and analyzing percentages, the incidence rate is still higher in women (0,0015%) than in men (0,0013%), which is in accordance with the previous studies for the European (Cancer Research UK, 2011) and Portuguese population (Ferreira et al., 2007; Alves et al., 2007).

Melanoma risk is known to increase with age (Rigel, 2010, Cancer Research, 2014) and to be associated with intermittent sun / UV radiation exposure over lifetime (Armstrong et al., 2001), which, by its turn is, correlated with NRAS mutations (Gandini et al., 2005). In the UK the incidence rates of melanoma increase with age, but the average number of cases per year is higher at 60-69 years old, for both men and women (Cancer Research, 2014).

In accordance with UK's data, our study revealed an increase of primary melanoma rates with age and that the number of diagnosis was higher in the group of patients at 60-69 years old. However, it was also possible to observe that, although the incidence rate increase with age, there was a peak in the rates at 50-59 years old for men and at 60-69 years old for women. Considering that there is no apparent epidemiological, clinical nor pathological explanation for this occurrence, further investigations are need in this subject.

The majority of malignant melanoma is located in sun exposed anatomical sites but some are internal or in anatomical sites not exposed to sun. Additionally, the anatomic distribution of melanoma is related with sex and age. While in men it occurs more on the trunk, in women it is preferentially located in the lower limbs (Garbe and Leiter, 2009). Below 50 years old the incidence

is higher at the back, while over 50 years old it is higher above the neck (Elwood and Gallagher, 1998).

Our study indicated that, although there was not a relation of the anatomic distribution with age, men presented a higher incidence of melanoma on the trunk and women on the lower limbs, which is in accordance with the international reports and with previous studies on the same population (Ferreira et al., 2007). The gender differences in anatomic distribution of melanoma may represent the sun exposure differences, generally fitted with the sex differences in general clothing patterns and hair cover (Bulliard et al., 2007). Moreover, melanocytes are asymmetrically distributed on the body skin and might differ in their response to sun exposure accordingly to anatomical location (Green, 1992).

Melanoma subtype classification is mainly based on histological appearance and biological behaviour (Clark et al 1969). Superficial spreading melanoma (SSM) is the most common type of melanoma, namely in young people and occurs in locations that are intermittently exposed to sunlight (Whitman et al., 2011). There are studies indicating for BRAF mutations occurring more commonly in SSM, while NRAS is associated with NM (Whiteman et al., 2011). Nodular melanoma is the second most common type of melanoma, occurring more in males in the 5^{th} and 6^{th} decades of life, often on body sites that are intermittently exposed to sunlight (Whitman et al., 2011). Lentigo maligna melanoma (LMM) is a rare form of melanoma, which is associated with high levels of accumulated sun exposure, being most common in the face (90%), and in elderly people (Whitman et al., 2011). Acral lentiginous melanoma arises more often on the palm of the hand, sole of the feet or under the nails of elderly and in non-white people (Duncan, 2009).

In the USA in 2004 and in the CHP in 2006 the proportion of melanoma histological types were SM > NM > LM > ALM > other types (Jemal te al., 2011; Ferreira et al., 2007).

Our study indicates that, in the cases diagnosed in the CHP between 2006 and 2012, superficial spreading melanoma has the highest incidence, being followed by the nodular type, both in men and in women. Furthermore, women present higher indexes in all histological types, with the exception of the nodular melanoma. These results are in accordance with international literature and with previous studies on the same population (Ferreira et al., 2007); however, we did not observed a relation between the age of the patients and the melanoma's histological type, as previously described (Whitman et al., 2011).

The American Joint Committee on Cancer (AJCC) created four (I–IV) clinical and pathologic stages based on the standard TNM (tumor, regional nodes, and distant metastasis) classification. Reports indicate that the majority of cutaneous melanoma are stage I melanoma (stage I > II > III >

IV), with this proportion being maintained in both genders (Birch-Johansen et al., 2008, Cancer Research UK, 2014). Furthermore, women have more cases at stage I than men, with the opposite occurring at the following stages (Cancer Research UK, 2014).

Our study indicated the same proportion between melanoma stages as previously described (stage I > II > III > IV) (Ferreira et al., 2007; Cancer Research UK, 2014). Furthermore, it was also possible to see that the proportion of the histological types referred above (SM > NM > LM > ALM) is maintained in every stage, with the exception of stage II where the nodular type has the highest incidence. This may be due to the capacity of NM to be similar to other possible diagnosis and, by that reason, making it difficult early detection, previously described (Mar et al., 2012).

Furthermore, there were more cases of thinner melanomas, which is in accordance with the observation that in developed countries the majority cutaneous melanoma has <1 mm (Whitman et al., 2011).

Interestingly, women presented more cases than man in every tumour size with the exception of sizes ≥ 4mm (T4) and presented a higher number of melanoma's stage 0 and I than man, with the opposite occurring in the stages III and IV. These results can be related with the fact that i) at diagnosis the NM's median thickness being known to be greater than that of SSM (Mar et al., 2012), and ii) in men this is the histological type with higher incidence (Whitman et al., 2011).

The incidence of tumour thickness is related with patient's age (Jamal, et al., 2011), with the occurrence of thicker tumours being higher above 65 years old. Although our results indicate an apparent tendency to the incidence of higher stages and thicker tumours at older ages, this was not significant.

Despite the lack of consensus on the protocol for the follow-up of patients treated for primary melanoma (Nieweg and Kroon, 2006) the CHP follows the ESMO guidelines (indicated in the Introduction chapter). For the proposal of this study, to analyse the outcome of the treatment and the progression of the patient we used the information registered in the last evaluation of the patients at the moment of this study.

Patients' survival is known to be influence by gender, age, melanoma's anatomic location, subtype and stage (Balch, et al., 2002; Balch, et al., 2009; Balch, et al., 2010a; Pollack, et al., 2011). In 2009 the melanoma's rate of survival was calculated around 97.3% per year, with a median age at death of 68 years old (Howlader et al., 2009). We here observed a rate of mortality of 2,4%, and an average age at death of 72 years old, which is in accordance with the literature. Results also indicated that the higher number of patients, at their last register consultation, had been discharge or

were with “appropriated” physical and dermatoscopic parameters, which is in accordance with a survival rate of 97,6% and with previous reports for the same population (Ferreira et al., 2007).

Furthermore, we saw a higher number of female patients in almost all classes of follow-up, something that could be related with the higher total number of female patients. However, in the classification “not-appropriated” of the follow-up the number of male patients was higher than of female patients, which could be due to man presenting a higher number of nodular melanoma and in higher stages. This is consistent with the reports indicating that NM contributes significatively to melanoma deaths (Criscione and Weinstock, 2010; Shaikh et al., 2012), because it is not detected early and due to its four times faster growth phase (Chamberlain et al., 2003; Liu et al., 2006).
Supporting this view, our results indicate that in patients with “not-appropriated” physical and/or dermatoscopic parameters or that have deceased, the melanoma subtype with more cases was the nodular melanoma; whereas the majority of patients that were discharged or that presented an “appropriated” evaluation had superficial melanoma, which is know for having a better prognosis (Whitman et al., 2011).

In agreement with the relation between higher stage and worse prognosis (Wisco and Sober, 2012; Cancer Research UK, 2014) our results indicate that the proportion of appropriated>not-appropriated> deceased between the follow-up classes occurred all diagnostic stages. The exception occurred at stage IV where the higher number of patients had “not-appropriated” physical and/or dermatoscopic parameters.

Studies have shown that melanoma on trunk, head, or neck conferred a worse prognosis than at an extremity (Balch et al., 2001), and that between the ones of axial location (trunk, head, or neck) melanomas on the scalp and neck had a worse survival (Pollack et al., 2011). In accordance with the literature, we observed that in patients discharged or with “appropriated” physical and dermatoscopic parameters the lower limbs was the anatomic location with more diagnosed cases.

It was of notice that 6.5% of patients quit the consultation. Even tough the good results obtained in the survival of patients, it is worrying that 6.5% quit their consultation, treatment or follow-up. Questions should be raised why patients have this attitude. In which stage were these patients? Did they quit because, as they were in low stages, they though they did not need treatment or follow-up? Did they die, because of melanoma or other causes? Was there any aspect of the patient-institution/doctor relation that potentiated this attitude? More studies are needed to find these answers and ameliorate this parameter.

Also interestingly was the fact that in 10% of the cases there was no data about patients follow-up. Moreover, there was also observed that the majority of the clinical processes had an almost total absence of registered clinical information regarding patients' anamnesis. This associated with the i) the encrypted handwriting of the majority of the clinicians, ii) total disorganization of patient's processes and iv) difficulty to obtain the processes, derailed the possibility to present robust results about melanoma risk factors (eg: phototype, sun exposure and total nevi number) that were also part of our study. From the files obtained (118) only 22 had relevant information for the study. From these, descriptive analysis indicated that the majority of patients (15) presented primary melanoma on a pre-existing nevus. From the clinical processes with information regarding personal or family history of skin cancer (9) only 3 present family precedents of skin cancer.

There are several possibilities that may lead to this observation: i) which are the criteria to define follow-up; ii) which service was responsible for the follow-up of these patients? iii) where should the services have written their notes?; iv) what was the role played by the informatization of the system in this? v) is there lack of time for the consultations? vi) is there a deficit of organisational culture from all of the involved parts? Independent of the many possible factors that may lead to this outcome this is something that can not be ignored. Therefore, more investigation should be performed to better understand the reasons underneath this result and to point measures to adjust it.

Conclusions

The analysis of the melanoma cases diagnosed in the CHP between 2006 and 2012 indicated that the representative patient is a woman between 60 and 69 years old with a superficial spreading melanoma localized in the lower limbs, which, at the time of diagnosis, is at stage I. This patient will be discharge or will have a good evolution in her follow-up, with a survival chance of 97.2%.

Although i) the diagnostic techniques need improvement in sensibility and specificity, ii) there is no much options to treatment, and iii) there is no international accordance in the best protocol for the follow-up of these patients, our results show that in the CHP the standing procedure for diagnosis, treatment and follow-up are among the best in the world allowing survival rates of 97.2%, with the majority of patients being discharge or having good evolution on theirs physical and dermatoscopic parameters.

It is also of notice that i) 6.5% of patients quit the consultation, ii) 10% of the cases there was no data about patients follow-up, and iii) in the majority of cases there was no information about patients anamnesis in their processes. This indicates that there is still room for improvement namely in the organizational aspects of the system, which may lead to even better clinical results in the future.

Chapter 6

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