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ΜΠΣ: «ΝΕΟΠΛΑΣΜΑΤΙΚΗ ΝΟΣΟΣ ΣΤΟΝ ΑΝΘΡΩΠΟ: ΣΥΓΧΡΟΝΗ ΚΛΙΝΙΚΟΠΑΘΟΛΟΓΟΑΝΑΤΟΜΙΚΗ ΠΡΟΣΕΓΓΙΣΗ ΚΑΙ ΕΡΕΥΝΑ»

Dermoscopy as a technique for the early identification of melanoma. Current status and future perspectives

Ο ρόλος της δερματοσκόπησης στην έγκαιρη διάγνωση του μελανώματος. Παρούσα κατάσταση και μελλοντικές προοπτικές

ΚΑΠΝΙΑΡΗ ΕΙΡΗΝΗ

ΜΕΤΑΠΤΥΧΙΑΚΗ ΦΟΙΤΗΤΡΙΑΑ

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Η παρούσα μελέτη εκπονήθηκε στο πλαίσιο των σπουδών για την απόκτηση του Μεταπτυχιακού Διπλώματος Ειδίκευσης στη

ΝΕΟΠΛΑΣΜΑΤΙΚΗ ΝΟΣΟΣ ΣΤΟΝ ΑΝΘΡΩΠΟ: ΣΥΓΧΡΟΝΗ ΚΛΙΝΙΚΟΠΑΘΟΛΟΓΙΚΗ ΠΡΟΣΕΓΓΙΣΗ ΚΑΙ ΕΡΕΥΝΑ

που απονέμει η Ιατρική Σχολή του Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών.

Η ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

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Στους γονείς μου Θανάση και Θεοκτίστη που αποτέλεσαν για μένα παράδειγμα και λιμάνι σε όλη μου τη ζωή. Στον Προκόπη μου και τη Μυρτώ μας γιατί χωρίς αυτούς τίποτα δε θα είχε αξία! Τους ευχαριστώ για την κατανόηση και τη συμπαράσταση και τους αφιερώνω τη μελέτη αυτή.

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Abbreviations

ABCD:	Asymmetry, Border, Color, Diameter
ALM:	Acral Lentiginous Melanoma
AMM:	Amelanotic Malignant Melanoma
CASH:	Color, Achitecture, Symmetry, and Homogeneity algorithm
CM:	Cutaneous Melanoma
CSLM:	Confocal Scanning Laser Microscopy
DDM:	Difficult to Diagnose Melanomas
EGF:	Elevated, Firm, Growth
HMM:	Hypomelanotic Malignant Melanoma
LM:	Lentigo Maligna
NM:	Nodular Melanoma
NPD:	NonPolarized light Dermoscopy
PCD:	Polarized light Contact Dermoscopy
PD:	Polarized Light Dermoscopy
PNCD:	Polarized light NonContact Dermoscopy
RCM:	Reflectance Confocal Microscopy
RR:	Relative Risk
SSE:	Skin Self Examination
SSM:	Superficial Spreading Melanoma
UV:	Ultra Violet

Introduction

Cutaneous melanoma (CM) is one of the six most common malignancies among men and women. It affects all ages and sexes with an increasing annual incidence of about 3%. The patient's prognosis is very good if melanoma is diagnosed at an early stage but in case of a CM with metastases only a median survival of some months can be achieved. The challenge for the physicians involved is to achieve an early identification of cutaneous melanoma. Given that an early cutaneous melanoma may mimic a benign nevi, diagnosis may be difficult for even an expert dermatologist, whereas biopsying every suspicious for the naked eye lesion could be a proposal but very time consuming and expensive for the patients and the health system as well.

Dermoscopy is a non invasive, time saving, cost effective method for examining skin lesions, which continues to gain profit in different fields of dermatology (pigmented lesions, inflammatory lesions, parasitic invasions, trichoscopy). In pigmented lesions, dermoscopy helps the differential diagnosis between a benign nevus and an early cutaneous melanoma. Thus, the real challenge is not only to recognize a melanoma but also to get the chance to see it; a challenge that only dermoscopy could possibly face.

The aim of this review is to summarize the basic knowledge on melanoma and focus on the role of dermoscopy in its early diagnosis.

Definition of melanoma

Melanoma is a malignant tumor that arises from melanocytic cells. It primarily affects the skin (cutaneous melanoma - CM) and rarely the eye (uvea, conjunctiva and ciliary body), meninges and various mucosal surfaces. CM is the most dangerous form of skin tumors and causes 90% of skin cancer mortality. It is usually heavily pigmented, but can be also hypo or even amelanotic.[1]

Epidemiology

General

CM is the fifth most common malignancy in men and sixth in women responsible for the 4% of all cancer deaths and 6 of every 7 skin cancer related deaths even though it accounts for less than 5% of skin tumors.[2, 3] During the last decades CM has shown increasing incidence rates in many countries with white populations and has developed from a very rare disease into a cancer with growing importance; one person dies every hour from melanoma in the United States.[4, 5]

Figure 1. Common cancer types and estimated new cases (*www.seer.cancer.gov*)

	Common Types of Cancer	Estimated New Cases 2014	Estimated Deaths 2014
1.	Prostate Cancer	233,000	29,480
2.	Breast Cancer (Female)	232,670	40,000
3.	Lung and Bronchus Cancer	224,210	159,260
4.	Colon and Rectum Cancer	136,830	50,310
5.	**Melanoma of the Skin**	**76,100**	**9,710**
6.	Bladder Cancer	74,690	15,580
7.	Non-Hodgkin Lymphoma	70,800	18,990
8.	Kidney and Renal Pelvis Cancer	63,920	13,860
9.	Thyroid Cancer	62,980	1,890
10.	Endometrial Cancer	52,630	8,590

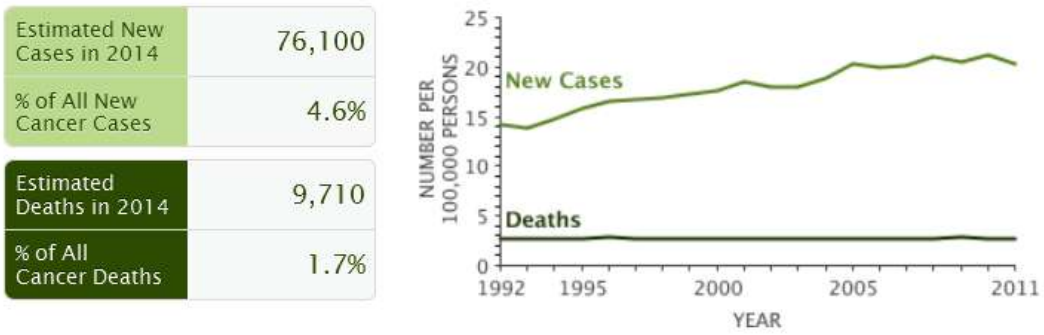
Incidence

The American Cancer Society estimates that during 2013 about 76,000 new cases of CM will be diagnosed and 9,480 people are expected to die.[6] Based upon data obtained between 2004 and 2006, the lifetime probability of developing CM in the United States is estimated to be 1 in 37 for men and 1 in 56 for women.[7] The annual increase of CM incidence varies between populations but is estimated between 3% and 7%. These estimates suggest a doubling of rates every 10 to 20 years.[4] The cancer statistics in the United States reported 6 new cases per 100,000 people in 1970 s and 18 per 100,000 in 2000; thus demonstrating a threefold increase in

incidence rates. For the same period in Europe the increase was from 3 to 4 cases to 10 to 15 per 100,000 which was very similar to the one in the United States.[4]

Some investigators have suggested that the reported increase in CM incidence results at least in part from of an increasing number of skin biopsies and significant variability in the histological interpretation of early evolving lesions.[5, 8, 9] However, this explanation does not account for the increase in CM mortality rates, particularly in older men. Others have speculated that the increasing incidence of CM is related to a rise in screening leading to the detection of thinner, more indolent lesions.[5, 8, 10] However, a study of SEER data (1992-2004) from non-Hispanic whites found increasing incidence of CM of all thicknesses and among all socioeconomic levels.[10] These results suggest that screening accounts for some, but not all, of the increase in CM incidence. Finally, another significant part of this rise may be related to a change in sun seeking behavior as more people are exposed to natural or even artificial UV radiation.[11]

Figure 2. Incidence of melanoma and death rates (*www.seer.cancer.gov)*



Geography

The frequency of CM is closely associated with the skin color and varies in different geographical zones. Incidence rates of CM in whites are five times higher than in Hispanics and 20 times higher than in African Americans.[4, 11] Overall, the lifetime risk of getting CM is about 2% (1 in 50) for whites, 0.1% (1 in 1,000) for blacks, and 0.5% (1 in 200) for Hispanics.[6] The highest incidence rates are reported in Australia and

New Zealand, with 30 to 60 cases per 100,000 inhabitants and year. In these countries, CM is one of the most frequent cancer types whereas Japan is the country with the lowest rates of CM.[4] In Europe the highest incidence rates appear in Scandinavian countries, but significant increases of incidences are also found in central and southern Europe. The Mediterranean countries have the lowest incidence rates. The reason for this north–south gradient is a darker skin type (type III–IV according to Fitzpatrick) in the Mediterranean populations.[4] Mackie *et al* also hypothesized that this gradient may be related to sun exposure behaviors, and in particular to the tendency of Northern Europeans to intense, intermittent sun exposure.[12]

As for the mortality rates of CM they were increasing until the 1980s in most European countries as well as North America, Australia and New Zealand with a peak in 1988 to 1990. Thereafter things seem to start changing. Mortality rates are still rising in several European countries for middle-aged adults more favorable among women. However, they have stabilized for young adults. This seems to be related with changing patterns of sunshine exposure and sunburn in younger generations as well as better and earlier diagnosis of CM. A trend towards thinner and less invasive melanomas in both central Europe and Australia has also been observed during recent decades.[4]

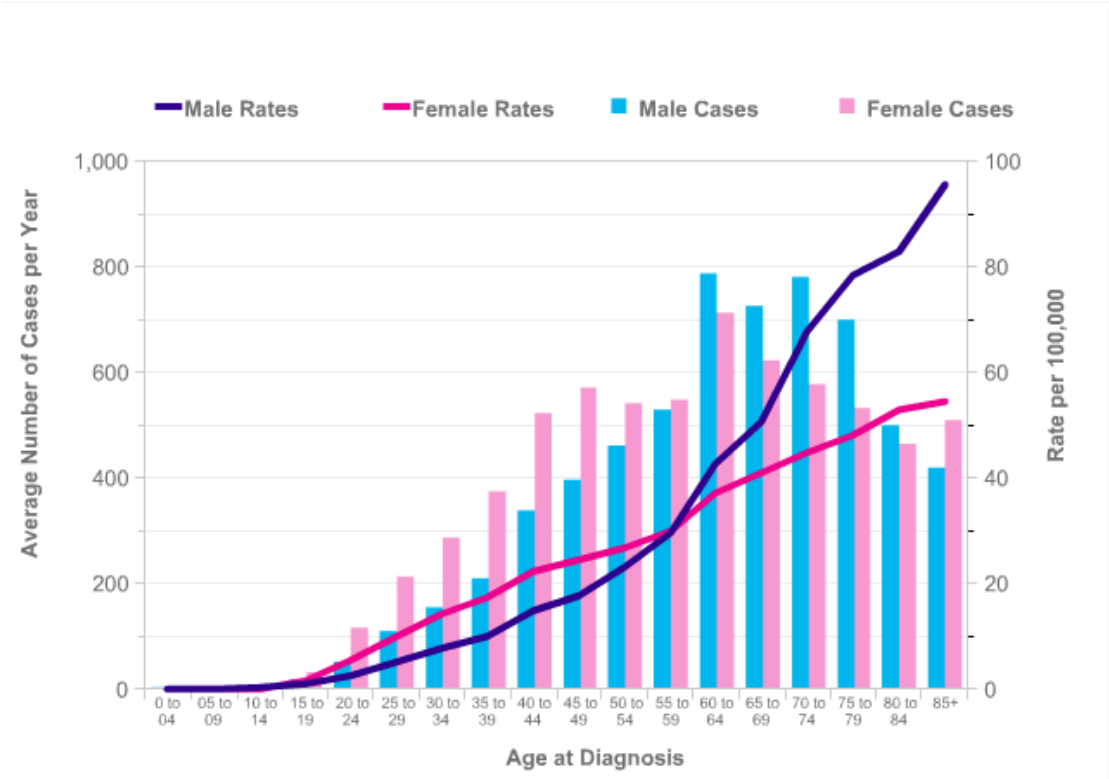
Figure 3. Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex (*SEER 18 2007-2011*)

Sex and age

The male/female ratio varies in melanoma databases in different countries. In countries with a high CM incidence, such as Australia and the United States, a preponderance of men is observed. In countries with a lower incidence, such as Great Britain, a higher ratio of women patients with melanoma can be found. In Germany in the time of low incidence rates in the 1970s, almost two-thirds of CM patients were women; whereas in the 1990s, the ratio of both sexes equalized.[4]

In contrast to non-melanoma skin cancer, CM is diagnosed at an earlier age. The median age is about 55 years, almost a decade before most solid tumors arise, which means that 50% of all CMs are already diagnosed before this age[4, 5]. Nevertheless, the age-specific incidence is slightly increasing with older age and reaches the highest incidence rates in individuals aged older than 65 years[4].

Figure 4. Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Population, UK, 2009-2011 (*www.cancerresearchuk.org*)



Anatomic location

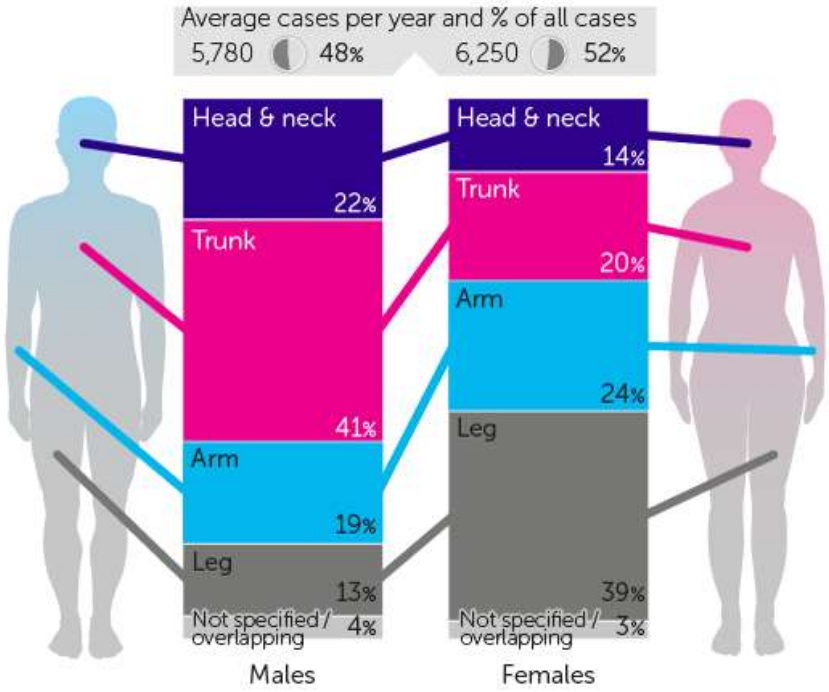
The anatomic location varies according to sex. In men, 55% of the tumors are localized on the trunk, with 39% on the back; in women, 42% are localized on the lower extremity, with 24% on the lower leg followed by 25% on the trunk. CM localized on the head and neck region and the upper extremity follow and are nearly equivalent in both sexes. A very similar site distribution was found in most countries with inhabitants of white origin such as in Europe, the United States, and Australia.[4]

Gender differences in body site distribution of melanoma lesions have been thought to be a result of inherent differences between males and females. Differences in clothing, hair style, occupation, sun-seeking behavior, and preventive measures and seeking medical care have all been considered as potential reasons for the higher incidence of lesions on the lower extremities in women and lesions of the head, neck and truncal areas of the body in men. However, the reason(s) for the observed gender differences may go beyond societal differences among males and females. Speculations of a relationship between steroid hormones and melanoma arose when population studies revealed that females have a survival advantage over males, which was evident between 1973 and 1997 when males had a rate of death from melanoma that was twice as high as that of females. Furthermore, the natural history of malignant melanoma in women has been reported to be rare before puberty, rise steeply through child-bearing years and decrease during menopausal years, thus implicating the involvement of estrogen.[5]

The site-specific incidence of melanoma varies according to age. The incidence of melanoma localized on the trunk and on the lower extremity decreases with advancing age, whereas a significant increase of melanoma localized on head and neck areas can be found in older patients. Nearly 80% of melanomas in patients aged 80 years and older were found on head and neck areas. Melanomas developing at different body sites are associated with distinct patterns of sun exposure. Melanomas of the head and neck are associated with on-going patterns of sun exposure, whereas trunk melanomas are associated with intermittent patterns of

sun exposure, supporting the hypothesis that melanomas may arise through divergent causal pathways.[3, 5]

Figure 6. Percentage distribution of CM cases diagnosed on Parts of the Body by sex (*www.cancerresearchuk.org*)



Adolescents and young adults

CM is the second most commonly diagnosed cancer (after lymphomas) and the most lethal form of skin cancer among adolescents and young adults under the age of 30 years in the United States.[7]

The incidence of melanoma in this group appears to be higher in adolescent and young adult women. 68,000 new cases of melanoma were diagnosed in the United States among young women between 20 and 29 years old.[8] One factor probably related to it is female sex hormones and a second one a higher intermittent exposure to UVR via outdoor or even indoor tunning.[14]

The body site distribution of melanoma in adolescents and young adults differs somewhat from that of older adults. In both sexes, the most common anatomic site

is the trunk counting for nearly half (46.7%) of melanomas in young males and 37% in females. This fact suggests once more the role of intermittent sun exposure as the trunk is a normally unexposed body site nevertheless with high incidence of short, intense bursts during summertime.[14]

Risk Factors

Although a discussion of risk factors for CMM is important, it also is critical to differentiate behavioral versus heritable factors. To date it is widely accepted that a person's total risk of melanoma is determined through the interplay between genetic factors and exposure to sunlight.[2]

Known Phenotypic Risk Factors

Nevi

Typical nevi

Most of typical nevi occur in photo exposed areas and are linked to cumulative sun exposure during the first decade of life. The number of typical nevi cited as the cut off for increased melanoma risk is 50 to 100 nevi which is associated with a relative risk (RR) of 5 to 17. [10]

Atypical nevi

The term atypical nevus, also called dysplastic nevus, is used to describe dysplasia underlying a benign congenital or acquired nevus. Individuals with atypical nevi have an associated 3- to 20- fold elevated risk of developing CM compared to the general population. Of all melanomas, approximately 10 to 20 percent arise within atypical nevi. The elevated risk depends on the number of the atypical nevi and varies with the person's sun exposure. UVR may act as both an initiator of new nevi (through sunburn) and a promoter of nevus growth whereas patients with atypical nevus syndrome are more sensitive to sunlight. Families with multiple cases of malignant melanoma often

exhibit the dysplastic nevus syndrome, a syndrome characterized by multiple atypical moles that continue to appear in adulthood.[2, 11, 15]

Hair and eye Colour

Comparisons made between different eye groups and dark eye color group found elevated relative risks in the groups with the light colors (1.47 for the blue, 1.61 for the green and 1.52 for the hazel). Similar were the results for the hair color comparing different colors to dark hair. Red hair were found to have a RR of 3.64, blond 1.96 and light brown 1.62.[16]

Family History

Approximately 5-10% of melanoma occurs in families with hereditary melanoma predisposition. About 40 % of familial melanoma is associated with chromosome 9p. Worldwide, approximately 20-40% of kins with familial melanoma harbour germline mutations in the CDKN2A gene, located on chromosome 9p21, which encodes two different proteins, p16INK4 and p14ARF, both involved in regulation of cell cycle progression and induction of senescence. There are geographical variations in the incidence of CDKN2A mutations. The risk of melanoma in CDKN2A mutation carriers varies between populations and is higher in regions with high sun exposure and high incidence of melanoma in the general population. Another melanoma susceptibility gene, CDK4, accounts for only small number of families with germ mutations on chromosome 12q14, encoding a cyclin dependent kinase which normally interacts with p16INK4A. Relative risk to cutaneous melanoma depends on anatomic differences such as hair colour. These differences could be attributed to gene variability.[6]

Comorbidity

Xeroderma pigmentosum (XP)

XP is another inherited disease that affects the skin's ability to repair UVR damage, also increases the risk for developing skin cancers, particularly at an earlier age. XP is

characterized by sun sensitivity (severe sunburn, persistent erythema and marked fricle like pigmentation in the face at ages earlier than 2), ocular involvement (photophobia, keratitis) and increased risk of cutaneous malignancies. Nowhere is the linkage between UVR damage and carcinogenesis more clearly demonstrated than in patients with XP, in whom the normal DNA repair machinery is faulty. XP has been classified by complementation group (XP-A, XP-B, XP-C, XP-D, XP-E, XP-F, XP-G) based on research laboratory testing. The XP complementation groups are associated with biallelic mutations in nucleotide excision repair (NER) genes: XPA, ERCC1, ERCC3 (XP-B), XPC, ERCC2 (XP-D), DDB2 (XP-E), ERCC4 (XP-F), and ERCC5 (XP-G). In addition XP is associated with mutations in the DNA bypass polymerase POLH. In these individuals, UVR exposure leads to a high incidence of malignant melanoma and other skin cancers.[11, 17]

Endometriosis

A prospective epidemiologic study has shown a statistically significant increase of melanoma in women with endometriosis (RR 1.6).[18]

Parkinson 's disease

Parkinson's disease has been associated with an increased risk for melanoma compared to the general population (standard incidence ratio 1.95, 95% CI 2.4-2.6). Although early case reports mentioned levodopa (a common therapy for Parkinson disease) as a potential etiologic factor, an increased risk for melanoma precedes the diagnosis and treatment of the neurologic disorder.[19]

Personal History of Nonmelanoma Skin Cancer

Individuals who have had basal cell or squamous cell skin carcinomas appear to have not only an increased risk of developing melanoma, but also an increased risk of dying from it.[20] Although the risk is highest in the first year after the initial diagnosis, there is a progressive increase over the time, estimating the risk of developing a second melanoma from 2 to 11% at five years.[10]

Childhood Cancer History

Childhood cancer survivors have a six-fold increased risk of developing subsequent neoplasms when compared to the general population. We sought to describe the occurrence of melanoma as a subsequent neoplasm among adult survivors of childhood cancer. Survivors of childhood cancer have an approximate 2.5-fold increased risk of melanoma. Early screening and prevention strategies are warranted.[20]

Personal History of melanoma

It is well documented that personal history of melanoma is one of the strongest risk factors for melanoma. Although the risk is higher in the first year after the initial diagnosis, there is a progressive increase over time. Estimates of the risk of developing melanoma range from 2 to 11 percent at five years. [10]

Pregnancy and Hormones

Pregnancy generally does not increase the subsequent risk of having melanoma and there is no increased risk of melanoma developing during pregnancy. Patients expressing estradiol receptors in melanoma cells have been reported to have a better prognosis. On the other hand, there is little evidence that significant changes in nevi occur during pregnancy.

As for the role of hormones, normal and malignant pigment cells are known targets for many hormones. Besides alpha-melanocyte-stimulating hormones and the steroidal hormones estrogen, testosterone, and glucocorticoids, other factors produced by epidermal cells can stimulate melanocytes. Among these factors are the prostaglandins, vitamin D3, ETAF (epidermal cell-derived thymocyte activating factor), and interleukin-1. A relationship between the biological behaviour of melanoma and sex hormones action has been identified in several areas of research. These observations include different survival prognoses for females and males, the rarity of melanoma incidence in prepubescent children and effects of exogenous

hormones. Estrogen, estradiol and progesterone receptors have been observed in human melanomas and, consequently, melanoma seems to be associated with female hormones.[6]

Vitamin D

The sun exposure is the major risk factor for developing melanoma. On the other hand, sunlight is necessary for the synthesis of Vit D on the skin. There is evidence that Vit D might play a protective role in melanoma promoting cell survival, inhibiting tumor growth and improving skin's intrinsic defense against skin cell UV damage. In order to achieve sufficient levels of Vit D only a relatively minimal exposure to sunlight is required, not enough to harm the skin causing skin cancer.[21]

Known Exogenous or Iatrogenic Factors

Sun Exposure

Although a direct causal relationship between solar ultraviolet (UV) radiation and melanoma cannot be demonstrated experimentally, the evidence from indirect studies is overwhelming and leaves little doubt that UV exposure is a major risk factor for melanoma:

Clinical and epidemiologic evidence demonstrates higher rates of melanoma in people with extensive or repeated intense exposure to sunlight. Intermittent exposure and sunburn in adolescence or childhood were strongly associated with an increased risk of melanoma, while occupational exposure did not confer an increased risk. The majority of melanomas develop on sun-exposed skin, particularly in areas that are more susceptible to sunburn. Individuals with naturally dark skin or whose skin darkens easily upon sun exposure have lower rates of melanoma, supporting the concept that greater penetration of UV light into the skin results in a higher risk.[22]

Adjusted for skin type, the geographic incidence of melanoma is highest in equatorial areas and decreases proportionately with distance from the equator, with its correspondingly lower level of UV exposure.[18] Ultraviolet B radiation (UV-B, wavelengths 290 to 320 nanometers) appears more closely associated with the development of melanoma than UV-A (wavelengths 320 to 400 nanometers). This is supported by the higher incidence of melanoma in equatorial regions than in latitudes farther from the equator, as UV-B radiation is most intense at the equator while UV-A intensity varies less across latitudes. Although UV-B appears to be more important than UV-A as a risk factor, a causal link to UV-A exposure is also supported by data from patients using tanning beds and or treated with PUVA for psoriasis.

The pattern and timing of sun exposure appear to be important for skin cancer. Non-melanoma cancers are associated with cumulative sun exposure and occur most frequently in areas maximally exposed to the sun (e.g., face, dorsal hands, forearms). In contrast, melanomas tend to be associated with intense, intermittent sun exposure and sunburns and they frequently occur in areas exposed to the sun only sporadically (e.g., the back in men, the legs in women). This association with intermittent sun exposure may not be true for all body sites; for example, melanomas of the head and neck are more frequent in patients with high occupational sun exposure[10].

Indoor Tanning/ Artificial Sunlamps and ionizing radiation

Lamps used for sun tanning emit wavelengths in the short end of the UVA range. Despite claims from the tanning industry, artificial tanning is not a safe or useful way to increase systemic vitamin D levels. Many studies indicate a significantly increased risk of cutaneous melanoma subsequent to sunburn/sunlamp exposure, especially among individuals who are young, Caucasian, and female. A European study showed that 40 hours of sun bed use resulted in a 55% increased risk for melanoma.

More than 40 kinds of skin diseases such as sclerotic skin disease, vitiligo, atopic dermatitis, localized scleroderma e.t.c. can be treated with artificial UVR by three

types of phototherapy, namely, broadband UVB phototherapy, narrowband UVB phototherapy, and UVA phototherapy. Phototherapy combined with chemicals such as oral methoxsalen (psoralen) in combination with UVA radiation (PUVA) provides a highly effective therapy for psoriasis and many other skin conditions such as vitiligo. However, PUVA is carcinogenic and increases melanoma risk. This risk is greater in patients exposed to high doses of PUVA. It appears to be increasing with the passage of time, and should be considered in determining the risks and benefits of this therapy.

It is also suggested that people exposed to ionizing radiation, e.g., nuclear industry workers, subjects near nuclear test blasts, survivors of the atomic bombings of Japan, airline pilots and cabin attendants, recipients of medical radiation, and radiological technicians may be at increased risk of developing melanoma.[6]

Organ Transplant Recipients

Medically induced immunosuppression, common in organ transplantation recipients, is well documented in the literature as a significant skin cancer risk factor.[12] Among patients with melanoma treated before transplantation, recurrences are frequent, and usually occur within five years. Waiting at least five years between the treatment of melanoma and transplantation may reduce the risk of recurrent disease.[23]

Pharmaceutical agents

A connection between TNF-alpha inhibitors and melanoma has been proposed. However, additional studies are necessary to determine whether treatment with TNF-inhibitors influences the risk for melanoma.[24] Also, studies have suggested the preventive role of NSAID'S (non-steroidal anti-inflammatory drugs) against many human malignancies including melanoma.[25]

Subtypes

Four different subtypes of melanoma can be identified clinically and histologically[1]:

1. **Superficial spreading melanoma** (SSM) begins with an intraepidermal horizontal or radial growth phase, appearing first as a macule that slowly evolves into a plaque, often with multiple colours and pale areas of regression. Secondary nodular areas may also develop. A characteristic histologic feature is the presence of an epidermal lateral component with pagetoid spread of clear malignant melanocytes throughout the epidermis.[1] The majority of SSMs arise de novo and only about 25% are associated with a preexisting nevus. SSM can occur in any anatomic location, but has a predilection for the back in men and lower extremities in women.
2. **Nodular melanoma** (NM), in contrast, is a primarily nodular, exophytic brown-black, often eroded or bleeding tumour, which is characterized by an aggressive vertical phase, with a short or absent horizontal growth phase. NM is most difficult to diagnose at an early stage. While the great majority of SSM and lentigo maligna (LM) melanomas are diagnosed at less than 1mm of thickness, at least half of all NM are greater than 2mm. When present, an epidermal lateral component is observed histologically within three rete ridges at the maximum.[1] It may resemble blood blisters, hemangiomas, dermal novi or polypi.[6]
3. **Lentigo maligna melanoma** (LM) arises often after many years from a lentigo maligna (melanoma *in situ*) located predominantly on the sun-damaged faces of elderly individuals. It is characterized histologically by a lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction and histological features of chronic sun exposure (solar elastosis).[1]
4. **Acral lentiginous melanoma** (ALM) is typically palmoplantar or subungual. In its early intraepidermal phase, there is irregular, poorly circumscribed pigmentation; later a nodular region reflects the invasive growth pattern.[1] ALM is the most common type of CM among dark skinned individuals who are at lower risk for more sun related melanoma subtype. **Subungual**

melanoma: arises from the nail matrix and usually presents as a longitudinal brown or black band, with or without nail dystrophy. Sometimes, it presents as a subungual mass with various degrees of ulceration and nail plate destruction.

5. Mucosal melanoma arises from melanocytes located in mucosal membranes lining respiratory, gastrointestinal and urogenital tract. Although the majority of mucosal melanomas originate from the mucosa of the nasal cavity and accessory sinuses, oral cavity, anorectum, vulva and vagina, they can arise in almost every part of mucosal membranes. Mucosal melanomas are rare, but they are known to behave more aggressive and have less favorable prognosis compared to other melanoma subtypes. Most of mucosal melanomas occur in occult sites, which together with the lack of early and specific signs contribute to late diagnosis, and poor prognosis. Because of their rareness our knowledge about their pathogenesis and risk factors is insufficient, and also there are not well established protocols for staging and treatment of mucosal melanomas.[26]

6. Unusual variants:[27, 28]

Amelanotic and **hypomelanotic melanoma** (AMM and HMM) represent 2% of all melanomas presenting without or with little pigmentation and being very difficult to be diagnosed.

Desmoplastic melanoma is a rare variant of melanoma first described in 1971 which could be mistaken for a scar, a fibroma, a basal cell carcinoma or a fibromatosis. Clinically it appears as a cutaneous or mucosal pigmentation overlying a palpable dermal or submucosal nodule. They are related to a lesser risk of metastatic disease than conventional melanomas of same depth. Histologically, the invasive tumor cells have a spindled morphology and are associated with a striking desmoplastic stromal response.

Nevoid malignant melanoma describes a heterogenous group of lesions showing histological features closely recapitulating a benign nevus and a cell population manifesting apparent maturation of cells with descent in the dermis. The lesions behave like invasive melanoma.

Minimal deviation melanoma is a type not universally accepted. These tumors share an architectural growth pattern that simulates vertical growth phase melanoma but lack the cytologic features diagnostic of malignant transformation and have better prognosis compared with other melanomas at similar depth.

Malignant blue nevus is a rare lesion usually arising in a background of cellular blue nevus. The clinical hallmarks include rapid enlargement, ulceration and change in color. This tumor is considered to have an aggressive behavior and metastizes in the majority of patients.

Balloon cell melanoma is a rare form of vertical groeth phase melanoma. It is characterized by priliferation of neoplastic ballon cells in a background lesions of SSM. Lesions appear as soft, rubbery or firm nodules with a polypoid or papillomatous contour whose cut surfaces are grayish, white or beown. The prognosis is similar with other types of melanoma with similar depths.

SSM is the most frequent subtype composing nearly 59% of all CM, followed by NM at 21%, LM at 11% and acrolentiginous melanoma at 4%[4]

Recent molecular studies have shown the genetic heterogeneity of melanoma, with distinct molecular signatures identified in tumors at different anatomical locations and with different associations with reported sun exposure. Intermittent sun exposure melanoma is mainly located on trunk and extremities and frequently carries a BRAF mutation. Chronic sun exposure melanoma is located mainly in the head and neck region and has a moderate frequency of NRAS mutations. Non-sun-

related melanomas are located on acral and mucosal sites and carry a low frequency of CKIT mutations.[1]

Prognostic factors and staging

About 90% of melanomas are diagnosed as primary tumors without any evidence of metastasis. The tumor-specific 10-year-survival for them is 75–85%. The most important histological prognostic factors for primary melanoma without metastases are:[1, 29]

1. Vertical tumour thickness (Breslow's depth); as measured on histological specimen with an optical micrometre. Tumor thickness is the most important prognostic factor. Depth of invasion was first reported as a prognostic factor in melanoma by the pathologist Alexander Breslow in 1970. Currently, it is included in the AJCC staging guidelines for melanoma. [1, 29, 30]

Table 1. Tumor depth in association with 5 year survival. Survival figures from British Association of Dermatologist Guidelines 2002

Tumor Depth	Approximate 5 year survival
<1mm	95-100%
1-2mm	80-96%
2.1-4mm	60-75%
>4mm	50%

2. **Ulceration.** Melanoma ulceration is defined as the combination of the following features: full-thickness epidermal defect (including absence of stratum corneum and basement membrane), evidence of host response (i.e. fibrin deposition, neutrophils), and thinning, effacement or reactive hyperplasia of the surrounding epidermis.[1] Survival rates for patients with an ulcerated melanoma are proportionately lower than those of patients with a nonulcerated melanoma of equivalent T category but remarkably similar to those of patients with nonulcerated melanoma of the next highest T category.[30]
3. **Mitotic rate** (number of mitosis/mm^2); appears as a powerful and independent prognostic factor in several population studies.[1] Multiple threshold of mitotic rate were examined statistically, and the most significant correlation with survival was identified as a threshold of at least 1/mm^2. Mitotic range has replaced Clark's level of invasion as a primary criterion for defining T1b stage of melanoma. [30]
4. **Level of invasion** (Clark's level) is only of independent significance for thin tumors (<1 mm thickness).[1]

   Five anatomical levels are recognized, with worsening prognosis at higher levels:

   Level 1 Melanoma confined to the epidermis (in situ)

   Level 2 Invasion to the papillary dermis

   Level 3 Invasion to the junction of the papillary and reticular dermis

   Level 4 Invasion to the reticular dermis

   Level 5 Invasion to the subcutaneous fat

Patient age, Sex and anatomic site of Primary Melanoma are also independent prognostic factors. There is a significant and consistent step down of survival based on increasing decades of life. In addition to this, patient's sex (males with poorer prognosis than women) and the anatomic location (trunk, head and neck with poorer prognosis than extremities) correlate significant with survival.[1, 29]

Melanomas can metastasize either by the lymphatic or by the haematogenous route. About two-thirds of metastases are originally confined to the drainage area of regional lymph nodes. A regional metastasis can appear as:

- Micrometastases in the regional lymph nodes identified via sentinel lymph node biopsy. In contrast to macrometastasis, micrometastasis is not clinically recognizable neither by palpation nor by imaging techniques.
- Satellite metastases (defined as up to 2 cm from the primary tumor).
- In-transit metastases (located in the skin between 2 cm from the site of the primary tumor and the first draining lymph node).
- Clinically recognizable regional lymph node metastases.

The 10-year-survival is 30–70% for patients with micrometastasis, 30–50% for patients with satellite and in-transit metastases and 20–40% for those with clinically apparent regional lymph node metastases.[1] For the patients with metastatic nodes the actual number of nodal metastasis is the most significant factor for the outcome as survival decreases significantly with increasing nodal involvement. The best grouping is one versus two to four versus over four metastatic nodes.[29]

Distant metastases have a grim prognosis with a median survival in untreated patients being only 6–9 months, although there is considerable variation depending on internal organ involvement and serum levels of lactate dehydrogenase (LDH). Distant melanoma spreads in an unpredictable fashion with widespread metastasis to any organ but in particular skin, lung, brain, liver and small bowel.[31] In 2009, the AJCC proposed a new TNM classification and staging for melanoma; it has now also been accepted by the UICC.[20] This new system now forms the cornerstone for classifying melanoma.[1]

<u>In summary:</u>

(1) tumor thickness and ulceration are the most powerful predictors of survival in patients with localized melanomas (stages I and II), whereas level of invasion has a significant impact only within the subgroup of thin melanomas.

(2) the number of metastatic nodes, tumor burden (microscopic v macroscopic), and presence or absence of melanoma ulceration are the most powerful predictors of survival in patients with nodal metastases (stage III).

(3) the anatomic site of distant metastases are the most significant predictor of survival in patients with distant metastases (stage IV).

The current melanoma staging system was substantially revised in 2001 for the sixth edition of the Cancer Staging Manual, on the basis of an analysis of 17,600 patients in the American Joint Committee on Cancer (AJCC) Melanoma Staging Database.[30]

Table 2. TNM staging Categories for CM

T classification of primary tumor for melanoma		
classification	**thickness**	**Ulceration/Mitoses**
Tis		no tumour invasion
Tx	No information	Stage cannot be determined
T1	≤1.0 mm	a: No ulceration, no mitosis b: Ulceration or mitotic rate ≥1/mm^2
T2	1.01–2.0 mm	a: No ulceration b: Ulceration
T3	2.01–4.0 mm	a: No ulceration b: Ulceration
T4	>4.0 mm	a: No ulceration b: Ulceration

[a] Tumour thickness or information on ulceration not available or unknown primary tumor

N classification of the regional lymph nodes for melanoma

N	No of involved lymph nodes	Extent of lymph node metastases
No	o	o
N1	1	a: Micrometastases* b: Macrometastases**
N2	2–3	a: Micrometastases b: Macrometastases c: Satellite or intransit metastases
N3	≥4, satellite or in-transit metastases plus node involvement	

*Micrometastases are diagnosed after sentinel lymph node biopsy

** Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically

M classification of distant metastases for melanoma

M	Site	Serum LDH
M0	0	0
M1a	Skin, subcutaneous tissue or lymph node	Normal

M1b	Lungs	Normal
M1c	All other distant metastases	Normal
	Any distant metastasis	Elevated

Table 3. Melanoma Staging

Clinical staging*				***Pathologic staging****			
	T	**N**	**M**		**T**	**N**	**M**
0	Tis	N0	M0	**0**	Tis	N0	M0
IA	T1a	N0	M0	**IA**	T1a	N0	M0
IB	T1b	N0	M0	**IB**	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	**IIA**	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	**IIB**	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	**IIC**	T4b	N0	M0
III	Any T	N>N0	M0	**IIIA**	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0

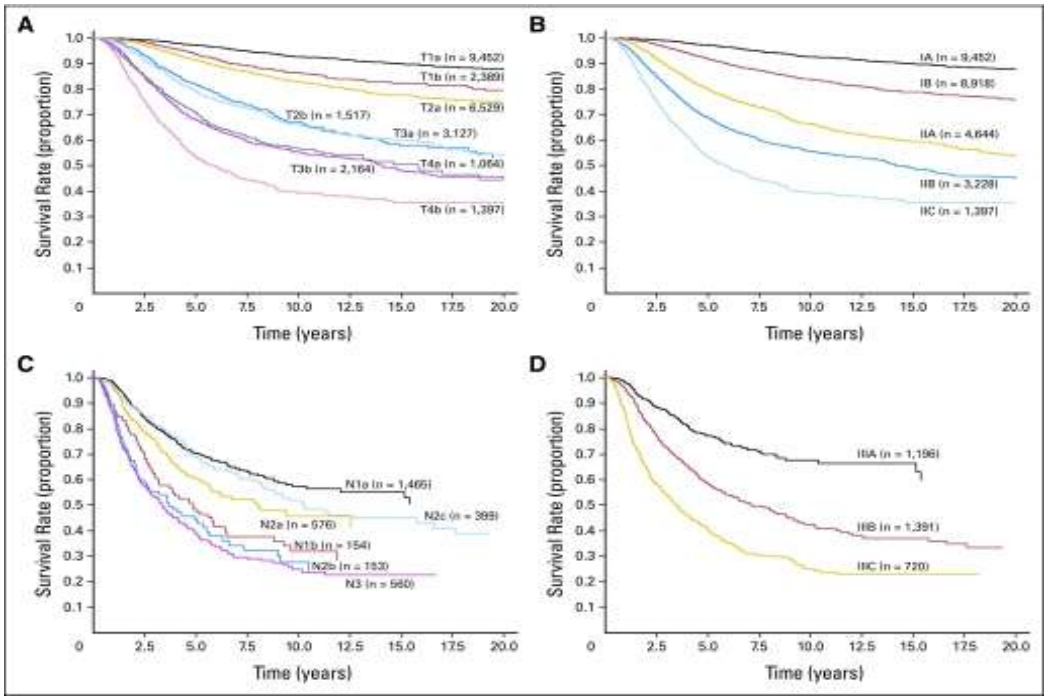
					T1-4b	N2b	MO
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	**IV**	Any T	Any N	M1

*Clinical staging includes microstaging of CM and clinical/radiological evaluation of metastases.

**Pathologic staging includes microstaging of CM and information about regional lymph nodes after partial or complete lymphadenectomy

Compared with all cancers CM remains one with a relatively high 5 year survival. Only prostate, thyroid and testis have a better 5 year survival rates. The important thing is that CM survival has steadily improved during the last decades increasing from 82% to 91% between 1979 and 2012.[2]

Figure 7. Survival Curves from the American Joint committee on Cancer Melanoma Staging Database



Diagnosis

As the incidence of CM is increasing faster than any other potentially preventable cancer, the importance of early diagnosis cannot be underestimated. Detection of melanoma

early in its evolution is of crucial importance. CM typically grows initially horizontally within the epidermis (in situ) and in time penetrates into the dermis (invasive melanoma). The vertical depth has been shown in multivariate analyses to be the factor that best correlates with prognosis.[32] Fortunately, there has been a steady improvement in survival over the past decades with the 5year relative survival rising from 82.6% for the interval 1975-1979 to 93.1% for cases diagnosed in 2002.[32] As primary treatment for CM –surgical excision- has not changed during the last years, this improvement can be primarily attributed to earlier detection.

The standard method to evaluate a skin lesion and rule out melanoma is the biopsy and histopathological examination. However, the challenge is to identify as early as possible the lesions that have the possibility of being a melanoma.

Basic Factors on Early Diagnosis

The past 30 years there has been a significant evolution in the diagnosis of early melanoma. Several factors have contributed to a marked improvement in detection of CM at an early, curable stage. Before the 1980s, there has been little change in identifying melanoma, as the diagnosis was made by identifying clinically macroscopic features. Melanomas were often recognized only when they were large, ulcerated and fungating. By that time, prognosis was poor. Overall melanoma incidence and mortality continued to increase in the United States and elsewhere, making the early recognition of melanoma an important public health priority.

In 1985, recognizing the need to educate physicians and the public to recognize melanoma at its early clinical presentation, researchers at New York University devised the ABCD acronym (Asymmetry, Border, Color, and Diameter). The ABCD criteria were intended to be a simple tool that could be implemented in daily life, a mnemonic “as easy as ABC” to alert both laypersons and healthcare professionals to the clinical features of early melanoma. Later on the letter E for Evolving was added to ABDC criteria, especially important for the diagnosis of nodular melanoma. Other melanoma early diagnosis

paradigms have been developed to enhance early diagnosis. The most recognized of these are the Glasgow 7-point checklist and the "ugly duckling sign".

In an attempt to detect melanoma earlier and to incorporate the ABCDs into national public and professional education campaigns, individual and mass evaluation programs were initiated in the mid 1980s. Skin self-examination (SSE) was encouraged by many organizations for all individuals but especially for those at highest risk for melanoma. In addition, nationwide mass screenings have been undertaken. The first Monday in May has been recognized as Melanoma Monday with associated public education events undertaken each year.

In the 1990s, light-based visual technologies were adopted to augment the early diagnosis of melanoma. It had been demonstrated that diagnostic accuracy could be improved through the use of surface microscopy, which allows an observer to examine pigmented skin lesions covered by a drop of oil and a glass slide through a stereo microscope, but this technique was time consuming and subjective. To obtain these benefits with an approach that was more easily used in the clinical setting, dermoscopy (also known as dermatoscopy or epiluminescence microscopy) was developed and is now a well established method that uses a hand-held lighted magnifier to analyze skin lesions by observing newly defined and descriptively named subsurface structures, eg, dots, streaks, veils, networks. Later on, computerized approaches have been used to augment the efficacy of dermoscopy in a variety of formats and have been shown to have better results than those of manual dermoscopy.

Currently, new techniques seem to gain profit in the diagnosis of melanoma, some of them in institutional setting. Confocal Scanning Laser Microscopy (CSLM), Reflectance Confocal Microscopy (RCM), Diagnostic Ultrasound, Bioimpedance measurements and Tape Stripping present new non invasive methods that will probably help in the early diagnosis of melanoma.

Clinical Diagnosis

The clinical recognition of melanoma may be challenging even for the most experienced dermatologist. However, several clinical features of skin lesion are suggestive of melanoma and prompt referral to a specialist or biopsy. Three diagnostic aids have been identified to help clinicians (and lay people) identify suspicious lesions: the ABCDE rule, the revised Glasgow 7point checklist and the "ugly duckling" sign.

ABCDE rule

The ABCD acronym for melanoma screening was devised in 1985 to provide the lay public and primary health care professionals with a useful and memorable mnemonic to aid in the early recognition of potentially curable cutaneous malignant melanoma. The now well known parameters of Asymmetry, Border irregularity, Color variegation and Diameter greater than 6mm are used globally in medical education to provide simple parameters for identification of lesions that may need to be further examined by a specialist. Since their description nearly 20 years ago, evidence has accumulated that the addition of E for Evolving will improve and enhance the ability to recognize melanomas at earlier stage (especially for nodular melanoma). As evolving lesions are defined those noted to have changed in size, shape, symptoms (itching, tenderness), surface (bleeding) or shades of color.

The sensitivity and specificity of ABCDE mnemonic vary when they are used individually or in combination, and the risks of over or under referral must be balanced accordingly. Specialist evaluation may result in further workup via dermoscopy, biopsy or both. [33]

Glasgow seven point checklist

The first seven point checklist was developed in 1985. The points were, in order: sensory change, diameter of 1cm or greater, growth of the lesion, an irregular edge, irregular pigment with different shades of brown and black, inflammation and crusting, oozing or bleeding. The advice offered was that in practice melanomas were likely to have three or more of these features. The positive impact of this

campaign was evaluated through the fact that from 1986 onwards a significant shift in favor of thin lesions with good prognosis was shown.

From 1985 to 1989 a retrospective review of patient with melanoma has taken place and the set of criteria was subsequently revised. The revised Glasgow seven point checklist includes three major and four minor criteria. The major signs include change in size, shape, colour of a new or preexisting lesion. The remaining four -inflammation, crusting or bleeding, sensory change and diameter 7mm or more are the minor features.

The presence of a major feature is an indication for referral; the additional presence of any of the minor criteria reinforces the need for referral.[34]

The ugly duckling sign

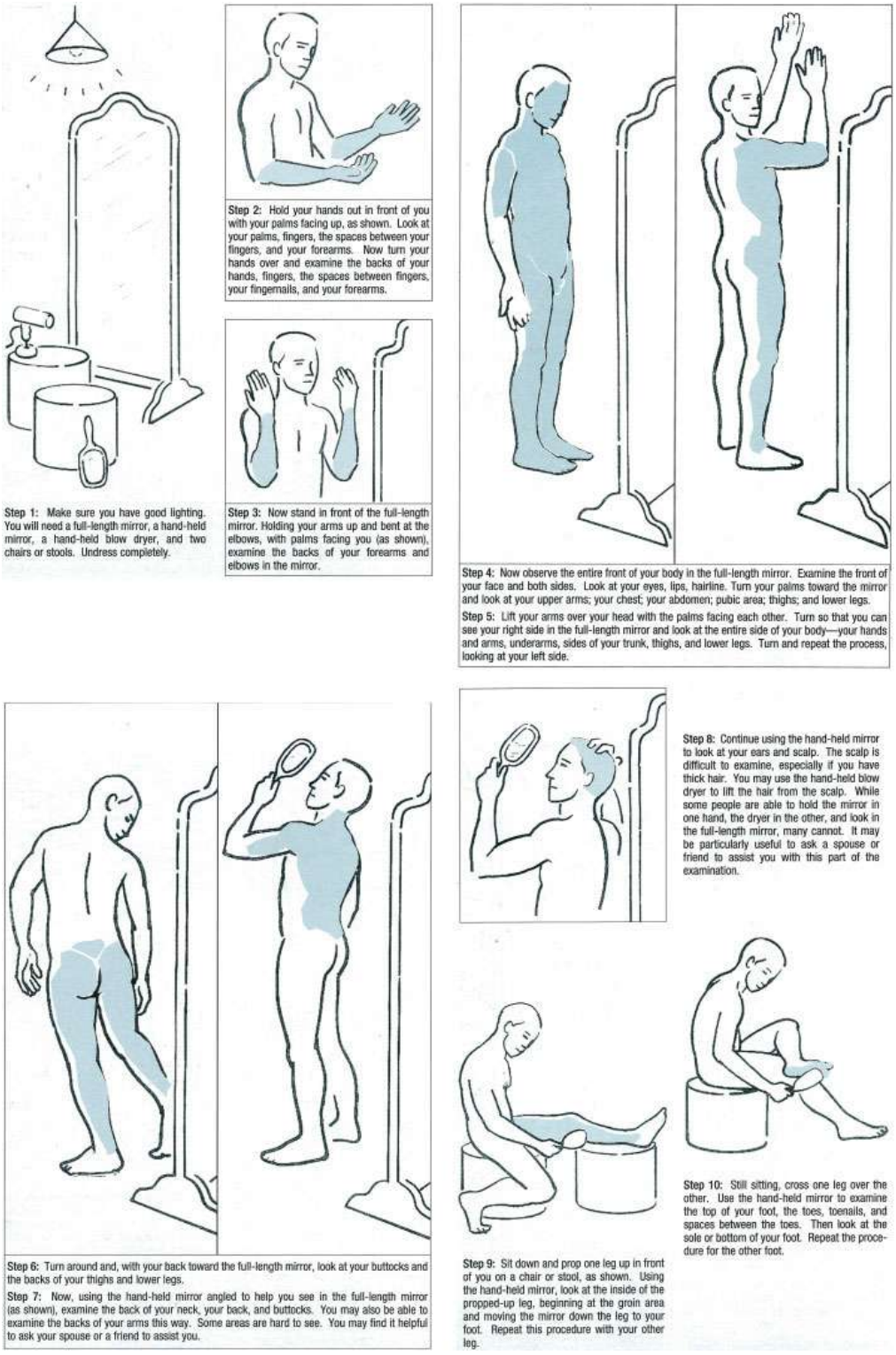
In 1998, Grob, et al introduced the ugly duckling concept-the observation that nevi in the same individual tend to resemble one another, and that MM often deviates from this nevus pattern. This clinical realization pointed to the importance of not just evaluating the morphology of the lesion in question, but also comparing it to that of surrounding lesions, looking for an outlier in the background of similar-appearing moles. For example, the outlier lesion can be larger and darker than the surrounding moles, or conversely, small and red in the background of multiple large dark moles.[34]

Skin self examination (SSE)

SSE is a simple, convenient method of screening for CM and precancerous lesions for all individuals but especially for those at high risk for developing CM. Instructing patients to perform regular SSEs is important for several reasons. Melanomas are commonly detected by patients, although it is far more common for dermatologists to detect second primary tumors. Persons undergoing skin self-examination were found to be more aware of melanoma and to have the lesions they detected be thinner when biopsied versus persons who did not practice this approach. The main predictors of thorough skin self-examination performance are having been advised to do so by a physician, availability of a partner to help, and availability of a wall and hand-held mirror. The use of photographic

examples of lesions with the ABCDE characteristics enhances the effectiveness of the procedure.[32]

Figure 8. Skin self examination *(Malignant melanoma: Prevention, early detection, and treatment in the 21st century. (CA Cancer J Clin 2000;50: 215-236)*



Dermatoscopy

Dermatoscopy (also known as dermoscopy, surface microscopy, epiluminescence microscopy and amplified surface microscopy) is an in vivo noninvasive method of skin imaging which uses optical magnification, fluid immersion and light (with either low angle of incidence or cross polarized) allowing the visualization of pigmented cutaneous lesions right to the starting edge of the reticular dermis.[35, 36] Dermatoscopy represents a link between clinical and histological examination. Its use increases the diagnostic accuracy but this method has a major drawback being highly user-dependant. This method is not time consuming as time for dermoscopic evaluation of nevi is only double that the one required for a naked eye examination (142 vs 70 seconds)- still under 3 minutes.

Argenziano et al had proposed three possible explanations of the fact that dermoscopy allows earlier melanoma diagnosis: (I) with dermoscopy we can see earlier signs that are not visible in naked eye examination yet, (ii) clinicians are now more concerned with rigoroous checking by dermoscopy of clinically banal-looking lesions; and (iii) an improved attitude of clinicians to follow up their patients with digital dermoscopy.[37]

History

The 1980s can be considered as the heyday of dermoscopy, with the definition of criteria of dermatoscopy and the first Consensus Conference on Skin Surface Microscopy; however, the origins of this method go back in 1663 when Christophorus Kolhaus used a “microscope” to see small vessels in the nail fold. In 1878 Abbe described the use of immersion oil in light microscopy, whereas Hueter in 1897 reported examination of lower limb capillaries using a magnifying glass and artificial light.[38, 39]

In the 19th century, Unna suggested the term “diascopy” after examining a case of lupus vulgaris with a glass lens over the patient’s skin surface. In 1920, a German dermatologist called Johann Saphier, was the one to introduce the term “dermatoscopy” as he published series of cases using a new diagnostic tool,

produced by Zeiss. It was the first dermoscopic binocular microscope with a built-in light source which allowed Saphier to make some very interesting morphological observations on anatomical skin structures. However, surface microscopes were relatively large and unwieldy, thus not very popular among physicians. This problem was solved in the United States by Goldman in the 1950s, where the first portable dermoscope was produced. Goldman was the first dermatologist to use this technique for the evaluation of skin pigmented lesions. In 1971 Rona Mackie established the benefits of dermatoscopy in the differential diagnosis of benign vs malignant skin lesions. These investigations continued by many European groups leading to the First Consensus Conference on Skin Surface Microscopy that took place in Hamburg in 1989. [35, 39]

In 1990 Kreusch and Rassner published the first Dermoscopy Atlas and in 2001 took place the first World Dermoscopy Congress in Rome. From 2000 to the present, Dermoscopy has gained profit and is widely spread all over the world with many courses, books, publications and symposia. Specifically, more than 1060 articles on dermoscopy were published between 2000 and 2009 whereas only 100 were published through 1999.[40] In 2003 took place the founding of the International Society of Dermoscopy by H. Peter Soyer, Rainer Hofmann-Wellenhof and Giuseppe Argenziano in order to promote clinical research in dermoscopy and represent a clinically oriented international organization with a thrust towards helping and improving education in dermoscopy.[35, 39]

Definition-Technique

The handheld device used in Dermatoscopy is called dermatoscope. Dermatoscope traditionally consist of a magnifier, a non polarized light source and a transparent plate.[52] The device generates a beam of light that fall in a 20^{o} angle on skin surface. Placing a liquid (oil, water, gel or glycerin) between the epidermis and the glass reduces light reflection allowing the visualization of the lesions characteristics (pigmented network, vascular pattern, color distribution) resulting from the presence of melanin and hemoglobin in the different skin layers.[35, 41]

The most common immersion fluids in dermoscopy are synthetic oil, ultrasonographic gel, alcoholic disinfectants or, simply - water. Ultrasonographic gel seems to be the best immersion fluid - it is inexpensive, efficient, and ensures a good adhesion of the dermoscope to the lesion - making it possible to analyse not only flat melanocytic nevi but also those of verrucous type, possessing crypt-like depressions. When using USG gel, less pressure is required to obtain a better visibility of the vascular structures within the lesion. Furthermore, the gel facilitates dermoscopic revision in difficult-to-access regions such as the flexures of extremities and interdigital spaces. Ultrasonographic gel assures appropriate immersion while avoiding any staining on the dermoscope's optical systems (as well as patients' garments) while being rather inexpensive. ECG gel should be avoided, as it may leave permanent stains on the dermoscope's optical system, especially on its rubber elements.[42]

There are two different types of dermatoscopes: the original, non polarized version and the newer using polarized light. Until recently, dermoscopes used only nonpolarized light sources to illuminate the skin, requiring a liquid interface and direct contact between the scope and the skin. With this approach, the amount of light reflected, refracted, and diffracted at the skin surface was reduced, thereby allowing the observer to visualize structures below the stratum corneum. Nonpolarized dermoscopes have been the standard for dermoscopy training and courses as so as for capturing dermoscopic images for textbooks and manuscripts. However, new commercially available dermoscopes that exploit the properties of cross-polarized light have been recently introduced. Unlike nonpolarized light dermoscopy (NPD), polarized light dermoscopy (PD) allows visualization of deep skin structures without the necessity of a liquid interface or direct skin contact with the instrument. These instruments offer the capability of viewing the skin with (polarized light contact dermoscopy [PCD]) or without (polarized light noncontact dermoscopy [PNCD]) a liquid interface and direct skin contact.[43]

Although all 3 modalities (NPD, PCD, and PNCD) yield overall similar images, subtle differences do exist.[56] Generally, non-polarized are superior in visualizing blue-white

areas, milia-like cysts and comedo like openings whereas polarized are found to be better for assessing vascular structures and shiny white streaks that could be a sign of fibrosis. If required and is potential, the two different dermatoscopes can be used in conjunction to increase the sensitivity and specificity of detection[47, 56] In order to combine the benefits of both types, dermoscopes with dual light-sources (non-polarized and polarized) have now been designed.[42]

Figure 9. Different types of dermatoscopes

The usual magnification provided by the dermatoscope is 10-fold, but digital dermatoscopes are available with magnifications of up to 70-fold.[35] Photographic documentation can be easily performed with a dermoscopic attachment to a digital camera and data are moved in a computer allowing easy storage, retrieval and follow up of pigmented skin lesions. For dermatologists with less experience technology offers the possibility of computer assistant diagnosis for malignant melanoma or telemedicine and expert consulting.[39]

The dermatoscope, despite its ease of handling is not just a magnifying glass as it allows the superimposition of skin layers. On the other hand, the image taken is much different than the one of histopathology, where the visualization is total, with the ability to observe deeper layers. It is usual to compare the visualization provided by the dermatoscope to an aerial view of the skin, as from an helicopter, whereas, in histopathology, a deeper view is obtained, comparable with that produced by a

submarine.[35] Dermoscopy therefore represents a valuable tool between these two areas.

Dermoscopic criteria

The dermoscopic evaluation of a lesion is performed in two steps. Differentiating melanocytic from nonmelanocytic lesions is the focus of the first-step algorithm. Once the lesion is identified to be a melanocytic one, the decision has to be made whether it's a benign, suspicious or malignant one. To determine this, several different approaches are more used. The most widely used include: pattern analysis; ABCD rule; Menzies method; and the 7-point checklist. These 4 diagnostic algorithms have been validated in the Consensus Net Meeting on Dermoscopy. Through this Internet meeting, 40 experienced dermoscopists independently evaluated 108 pigmented skin lesions. Interobserver agreement was good to excellent for all 4 algorithms. In addition, these diagnostic algorithms have been validated with statistical methods to aid in the delineation between benign and malignant pigmented skin lesions.[44, 45]

Figure 10. Two step procedure for the classification of pigmented skin lesions. Adapted from Argenziano G et al. J Am Acad Dermatol 2003;48

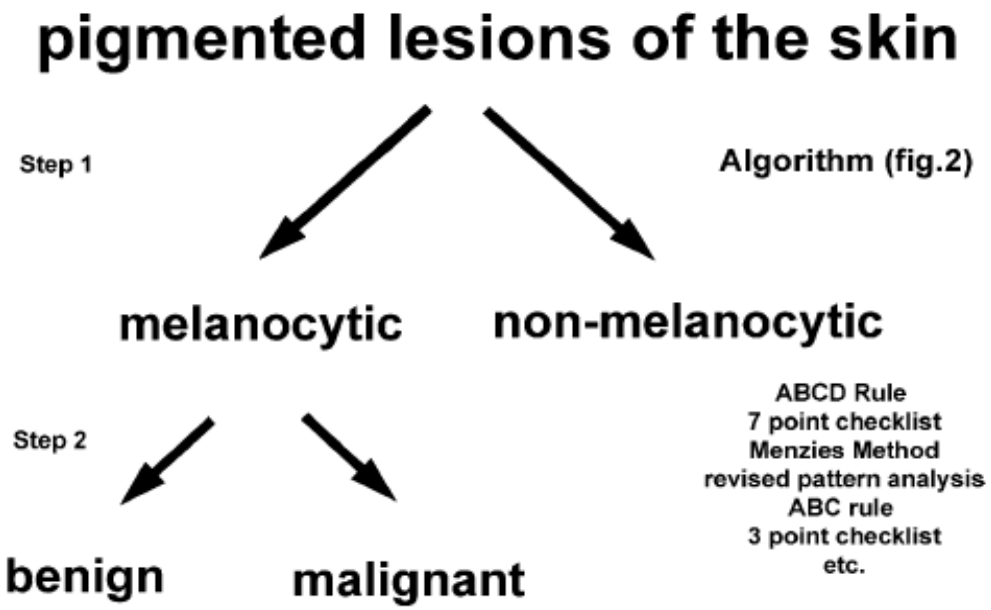
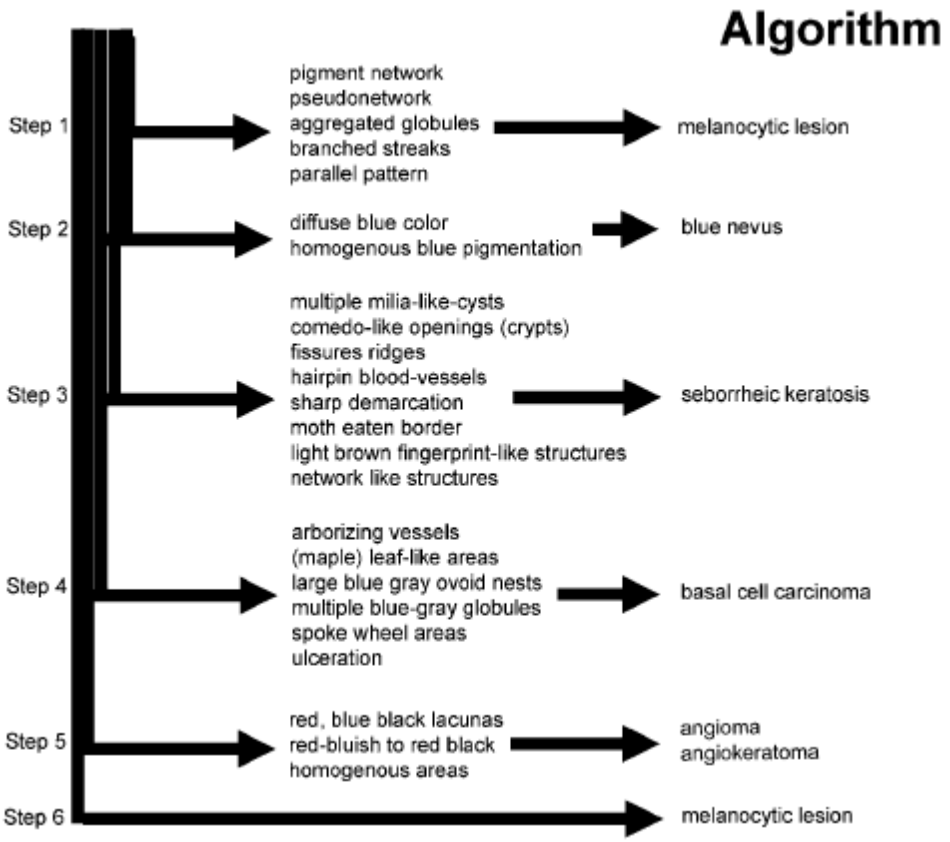


Figure 11. Algorithm for the determination of melanocytic versus nonmelanocytic lesions according to the proposition of the Board of the Consensus Netmeeting. Adapted from Argenziano G et al. J Am Acad Dermatol 2003;48:679-93



Color

Color is a dermoscopic criterion useful in the interpretation of a doubtful pigmented lesion. Several colors can be observed in the dermoscopy, depending on the location of melanin in the different skin layers.Table 4 shows the representation of different colors observed during routine dermatoscopy.[35] Common colors are light brown, dark brown, black, blue, blue-gray, red, yellow, and white. The most important chromophore in melanocytic neoplasms is melanin. The color of melanin essentially depends on its localization in the skin. The color black is due to melanin located in the stratum corneum and the upper epidermis, light to dark brown in the epidermis, gray to gray-blue in the papillary dermis and steel-blue in the reticular dermis. The color blue occurs when there is melanin localized within the deeper parts of the skin

because the portions of visible light with shorter wavelengths (blue-violet end of spectrum) are more dispersed than portions with longer wavelengths (red end of visible spectrum). The color red is associated with an increased number or dilatation of blood vessels, trauma, or neovascularization. The color white is often caused by regression and/or scarring.[39]

Table 4. Dermoscopy – color and location of melanin

Color	**Representation**
Black	Melanin in the spinous layer
Light or dark brown	Melanin in the dermal-epidermal junction and horny layer
Gray-bluish	Melanin in the papillary dermis
Blue	Melanin in the reticular dermis
White	Fibrosis or lesion regression (white must be lighter than the color of the lesion periphery)
Red	Hemoglobin inside the vessels

Pattern analysis

Pattern analysis is based on:

1. The general appearance of pigmented skin lesions, which may be uniform or heterogeneous, the profile of the pigmented skin lesions, which may appear within the level of the surrounding skin, elevated or depressed, and the surface, which may correspond to that of the surrounding skin or may be smooth or rough
2. The pattern of pigmentation, including color, intensity, depigmentation, and particular pigment patterns, such as the so-called pigment network, brown globules, and black dots

3. The margin of pigmented skin lesions, which may be regular or irregular, the latter sometimes characterized by specific pigment patterns that we have termed pseudopods and radial streaming.[46]

The global patterns are as follows: reticular pattern (predominant pigmented net: benign melanocytic lesion); globular pattern (prevalence of globules: compound and intradermal nevi); rectangular street pavement pattern –parallelepipeds (boxed-in globules: highly specific of compound and intradermal nevi); pointillist pattern (regular brown or gray-bluish dots at the base of the skin color: compound and intradermal nevi); homogeneous pattern (homogeneous pigmentation in the lesion: if blue, highly suggestive of blue nevus); parallel pattern (junctional palmoplantar nevi); pattern in star "burst" (radial streaks or pseudopods regularly distributed in the periphery of the lesion: Reed's nevus); multicomponent pattern (three or more areas of the lesion with different dermoscopic characteristics: highly specific of cutaneous melanoma); unspecific pattern (commonly found in cutaneous melanoma); and nonestablished pattern (possible melanoma).

The local patterns are as follows: pigmented net (if typical, benign melanocytic lesion; if atypical, probable melanoma); dots and globules (if regular, benign melanocytic lesion; if irregular, probable melanoma); streaks (if regular, benign melanocytic lesion – Reed's nevus; if irregular, probable melanoma); bluish veil (melanoma); regression areas (white or with blue dots, as "black pepper grains" – melanoma); hypopigmentation is a nonspecific criterion; area without structure (symmetric, benign melanocytic lesion; asymmetric, probable melanoma).

Finally, characteristics related to location should be considered. Face: typical pseudonet (benign melanocytic lesion); granular ring structures (melanoma); gray pseudonet (melanoma); rhomboid structures (melanoma); asymmetric pigmentation of the follicles (melanoma). Palms and soles: parallel furrow pattern (acral nevus); lattice pattern (acral nevus); fibrillary pattern (acral nevus); parallel ridge pattern (melanoma).[43, 57, 58]

Dermoscopic structures

Several structures, such as globules, dots, pseudocysts, pseudopods and crypts can be observed during dermatoscopy being more or less indicative of certain diagnoses. Table 5 shows all structures observed as well as their representation.[35, 39]

Table 5. Structures observed by dermatoscopy and their representation

Structures	Representation
Pigmented net	Melanin at the dermal-epidermal junction. Honeycomb type tissue with lines corresopnding to melanin and holes to papillary dermis. In melanocytic lesions with two exceptions: dermatofibroma and extra nipple
Clustered globules	Presence of clustered melanin. In melanocytic lesions
Ramified streaks	In radial growth of cells containing melanin. Fringe type structure at the periphery of the lesion. In melanocytic lesions. If asymmetric suggestive of melanoma, if in the entire lesion may represent the pattern of spitz nevus
Dots	Rounded structures with <1mm in diameter. In benign lesions in the center of it. When in the periphery represent an active lesion or even a melanoma. Black or brown: horny or granular layer Gray-blue: melanophages in the dermis Black pepper: melanoma
Areas with no structure	Not specific of melanocytic lesion
Blue metallic areas	Homogenous blue: blue nevus Brown areas: junctional activity or combined nevi
Horny pseudocysts	Pale-yellow circular areas: seborrheic keratoses (intraepidermal keratin accumulations)
Follicular pseudo-openings	Seborrheic keratoses or papillomatous nevi
Red-bluish lake	Increased and dilated vascular spaces pahtognomonic of hemangioma
Maple leaf like structures	Bulbar extensions of brownish to gray-bluish color. Nests of pigmented epithelial nodules of basal cell carcinoma
Pseudopods	Exremities of radial streaks suggestive of invasive melanoma usually heavy pigmented

Blue whitish veil	Reveals presence of orthokeratosis and compact aggregation of pigmented cells in the dermis. In invasive melanoma
Depigmentation areas	In regression of pigmented lesions – fibrosis of invasive melanoma
Fissures and crypts	Similar to the surface fo human cortex, typically in seborrheic keratoses
Fingerprint like pattern	In seborrheic keratoses and solar lentigo. Fine compact strings of brown-white coloration
Vascularization	Is described below
Large ovoid blue grayish nests	Not closely connected to the body of the pigmented tumor. Intradermal epithelial masses indicative of pigmented BCC
Radial areas	Similar to the spokes of a bibycle wheel found in the periphery of BCCs
Ulceration	In the evolution of BCC and later in invasive melanoma

Dots/Globules: Dots and globules are sharply circumscribed, usually round or oval, variously sized, and more or less clustered with various shades of brown and grey-black. They correlate with aggregations of pigmented melanocytes, melanophages or clumps of melanin within the cornified layer, the epidermis, the dermoepidermal junction or the pappilary dermis. The color of the globules depends on the depth of them in the skin. In benign lesions dots and globules are regular in size and shape, and evenly distributed. In melanoma, irregular dots and globules are usually located at the periphery, are of different size and shape and are asymmetrically distributed.[37]

Streaks: the architectular distribution of the streaks is more important than the morphology of a single streak in the management of pigmented skin lesions. Streaks are bulbous and often kinked or finger-like projections seen at the edge of the lesion. The range in color from light brown to black, and can also be called radio streaming, radial streaks and pseudopods. They correspond to pigmented junctional nests of melanocytes that are disposed like tubules to be parallel to the skin surface. The presence of irregular streaks, particularly when they are unevenly distributed in

a pigmented skin lesion is strongly associated with melanoma. However, irregular streaks can also be observed in Spitz or Reed nevi.[37]

Regression: Regression structures are often located in the flat part of the lesion and appear as white scar like areas, blue areas or a combination of them. The blue areas , also called peppering, are zones with small multiple blue-gray dots that correspond to a variable number of melanophages in the pappilary dermis. Fibrosis and melanosis are commonly found together in a combination of white and blue areas in the same lesion. Regression structures when found are a valuable tool in differentiating benign from malignant lesions.[37]

A melanocytic lesion will have a dermatoscopy presentation with aggregated globules, pigment network, branched streaks, homogenous blue pigmentation or a parallel pattern (palms, sols, mucosa). If the lesion appears with comedo like plugs, multiple melia like cysts and comedo like openings, irregular crypts, light brown fingerprint like structures, or fissures and ridges (brain like appearance), is suggestive for seborrheic keratosis. A basal cell carcinoma will appear with arborizing blood vessels, leaf like areas, large blue-gray ovoid nests, multiple blue-gray globules, spoke-wheel areas or ulceration. The presence of red or red-blue to black lagoons indicates a hemangioma or angiokeratoma. [35, 39]

Granularity

Braun et al made an evaluation on the significance of granularity for melanoma diagnosis. It appeared in the 26.5% of the benign lesions and in 93% of melanomas. An irregular, peripherally situated or in association with red or white color was statistically high associated with the diagnosis of melanoma and these lesions should definitely be removed. In the prospective part, granularity was found to have 85% sensitivity and 99% specificity for the diagnosis of melanoma.[47]

Vessels

Vascular pattern has gained more importance in the last years and has become a strong dermoscopic criterion. In histological examination it is not possible to appreciate the morhological features of vessels as histology provides only a vertical

view. Dermoscopy on contrast provides a horizontal view, allowing the identification of a wide variety of vascular patterns. When using contact dermoscopy one should be very careful in order to apply the minimun pressures needed otherwise the vessels will be compressed. The best way to examine blood vessels is using either noncontact polarized dermoscopy or ultrasound gel for immersion.[48, 49]

Vascular patterns generally show up better in hypopigmentated or nonpigmentated lesions or in lighter areas of pigmented tumors. Vessels located in the dermis are generally pink and appear out of focus whereas those found closer to the surface are bright red and focus. There are three essential features that should be analyzed when evaluating the vascular pattern of a lesion: vessel morhology, architectural arrangement and presence of additional data that may help to narrow the diagnosis.[48, 49]

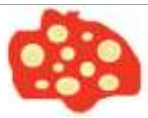
Vascular pattern, structures and architecture[48]

Vascular patterns show up better in hypopigmented or nonpigmented lesions or in lighter areas of pigmented lesions. Their evaluation during dermoscopy depends strongly on the optical system and the examination technique used (immersion fluid, magnification power). Heomoglobin is a pigment found in the erythrocytes of the vascular lumen. Vessels located in the dermis are generally pink and appear out of focus due the effect of the dispersion of light through the dermal connective tissue; those found closer to the surface by contrast are bright red and in focus. Other important factors are patient phototype, age, lesion location as well as certain anatomic areas.

There are three essential features that should be analyzed: vessel morhology, architectural arrangement and additional features.Several different vascular patterns are identified in dermoscopy with most important being comma vessels, hairpin vessels, glomerular vessels, arborizing vessels, crown vessels, the strawberry pattern, milky red areas or globules and lacunae being presented on Table 6.

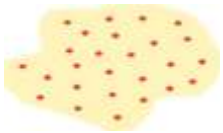
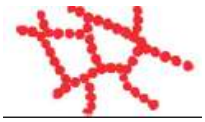
Table 6. Vessel morphology (Vascular patterns in Dermoscopy, Martin, Bella Navaro, Jorda. Actas Dermosifiliogr. 2012;103(5): 357-375)

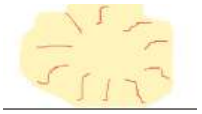
Vascular Pattern	Description	Interpretation	diagram
Arborizing vessels or telangiectasias	In-focus large -caliber vessels that branch into finer secondary vessels	- Basal cell carcinoma - Adnexal tumors	
Hairpin vessels	Vessels that double back on themselves and are seen as loops when they are oblique to the surface of the lesion; in keratinizing tumors, they are surrounded by a hypopigmented halo	- Regular: seborrheic keratosis - Irregular: melanoma, Spitz nevus, and keratoacanthoma	
Crown vessels	Thick, linear curved lines with little branching and occasionally one end that is thicker than the other	-Sebaceous hyperplasia - Molluscum contagiosum	
Comma vessels	Barely branching peripheral vessels that do not cross the center of the lesion	- Compound or dermal nevus	
Dotted vessels	Small-caliber reddish vessels that resemble a pinhead	- Spitz nevus - Melanoma - Inflammatory lesions	
Glomerular vessels	Larger-caliber reddish dots formed by tortuous capillaries curled up into a ball or resembling the glomerular apparatus of the kidneys	- Bowen disease - Stasis dermatitis	
Corkscrew vessels	Linear irregular spiral vessels areas containing atypical linear vessels	- Melanoma - Melanoma metastasis	

Milky red areas/globules	Out-of-focus pink-reddish oval or polygonal areas containing atypical linear vessels	- Melanoma	
Strawberry pattern	Structureless erythematous areas with heterogeneous whitish areas forming a type of pseudonetwork	Melanoma Superficial basal cell carcinoma	
Linear irregular vessels	Straight vessels varying in shape and size	Melanoma	
Polymorphous vessels	Different vascular morhologies in the same lesion	Melanoma Carcinomas	

The identification of the architectural arrangement will provide essential clues for differential diagnosis of lesions with same vessels but different arrangement as seen on Table 7.

Table 7. Vessel distribution patterns (Vascular patterns in Dermoscopy, Martin, Bella Navaro, Jorda. Actas Dermosifiliogr. 2012;103(5): 357-375)

Vascular pattern	Description	Example	Diagram
Regular	Vessels distributes evenly through the lesion	Spitz nevus	
String of pearls	Dotted vessels arranged linearly in a pattern that resemles a string of pearls	Clear cell acanthoma	

Clustered	With a tendency to group together in a lesional area	Bowen disease	
Radial	Presence of vessels only at the periphery of the lesion without crossing the center	Sebaceous hyperplasia	
Branching	Large vessels that branch into smaller	Basal cell carcinoma	
Irregular	Vascular polymorhism	Melanoma	
Rope ladder pattern	Short slightly dilated loops that emerge from the edges of the scar and cross it completely	Scar	

ABCD rule

The ABCD rule of dermatoscopy, described by Stolz et al in 1993 was based on an analysis of 157 pigmented skin lesions (Table 8). [39]

The melanocytic lesion is divided with two perpendicular axes and its asymmetry is assessed (not only with regard to form, but also to the disposition of the structures in the lesion). If asymmetric in both axes, it will score 2.6; if asymmetric in only one of the axes, it will score 1.3; if totally symmetric, it will score zero.

The borders are also observed, dividing the lesion with four axes, giving a total of eight borders. The abrupt end of the pigmentation or the net is evaluated, with a score of zero if the pigmentation gradually fades towards the periphery. Each abrupt border scores 0.1.

There are six possible colors in dermoscopy (black, dark brown, light brown, gray-bluish, white, and red), and each color found scores 0.5.Finally, there are five different possible structures in ABCD dermoscopy (pigmented net, clustered globules, ramified streaks, amorphous area, and dots), and the score is 0.5 for each structure.

The higher the score, the greater the probability for the melanocytic lesion to be highly suspicious of melanoma (> 5.45); if above 4.75, the lesion is considered as suspect, as a dysplastic nevus, and, in this case, an excision should be assessed; if the total score is less than 4.75, the melanocytic lesion is considered to be benign.[35, 44]

Table 8. ABCD rule of dermoscopy according to Stolz et al

		Points	**Weight factor**	**Subscore range**
Asymmetry	Complete asymmetry aymmetry in 1 axis asymmetry in 2 axis	0 1 2	1,3	0-2,6
Border	8 segments, 1 point for abrupt cut off of pigment	0-8	0,1	0-0,8
Color	1 point for each color white red light brown dark brown black blue-grey	1-6	0,5	0,5-3
Differential structures	1 point for every structure pigment network structureless areas dots globules streaks	1-5	0,5	0,5-2,5
Total score range: 1,0-8,9				

Rule of seven points

In 1998 Argenziano et al described the 7point checklist based on the analysis of 342 pigmented skin lesions. They distinguished 3 major (2points) and 4 minor (1 point) criteria (Table 9). If the total score is below three, the lesion is considered to be benign, but, if equal or higher than three, the lesion is diagnosed as melanoma. The major criteria include an atypical pigmentary net, blue-whitish veil, and atypical vascular pattern. The minor criteria include radial streaks and pseudopods, irregular pigmentation, globules and irregular spots and regression patterns.

Table 9. The 7 point checklist (Argenziano et al. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. Arch Dermatol. 1998 Dec;134(12):1563-70

Criteria	**7 point score**
Major criteria • atypical pigmented network • blue white veil • atypical vascular pattern	 2 2 2
Minor criteria • Irregular streaks • Irregular pigmentation • Irregular dots/globules • regression structures	 1 1 1 1

Rule of three points

This method was developed as a screening method, especially for beginners dermatoscopists with little training in order to avoid misdiagnosing melanoma.[35] The presence of two or three of the criteria is suggestive for a suspicious lesion that must be excised. The characteristics include:

- Asymmetry of color and structure in one or two perpendicular axes
- Atypical network (pigmented network with irregular holes and thick lines)
- Blue-white structures

Menzies' method

In this method, introduced in 1997 by Menzie, the clinician is required to identify 11 surface microscopy features, divided in two negative and nine positive. The negative ones define the lesion as benign, and are the symmetry and a single color. The positive are blue-white veil, multiple brown dots, pseudopods, radial streaming, scar -like depigmentation, peripheral black dots/globules, multiple (5 - 8) colors, multiple blue/grey dots and broadened network. The presence of a positive feature, added to the absence of a negative one, is sufficient for the diagnosis of cutaneous melanoma (Table 10).[35, 39, 50]

Table 10. Mezie'method for diagnosis of invasive melanoma[50]

Negative features (Cannot be found)	Symmetry or pigmentation Presence of only one single colour
Positive features (At least one feature found)	Blue-white veil Multiple brown dots Pseudopods Radial streaming Scar -like depigmentation Peripheral black dots/globules Multiple (5 - 6) colors Multiple blue/grey dots Broadened network

CASH method

The **C**olor, **A**chitecture, **S**ymmetry, and **H**omogeneity (CASH) algorithm for dermoscopy includes a feature not used in prior algorithms, namely, architecture. The CASH algorithm is a simplified version of pattern analysis, and hopefully more attuned to less experienced dermoscopists.

Architectural order/disorder is defined as follows.

- No/mild architectural disorder: The arrangement of the dermoscopic structures and colors in the lesion is orderly or only slightly disarranged.
- Moderate architectural disorder: The orderly distribution of structures and colors seen in lesions with no/mild architectural disorder is somewhat disorganized in that structures lose their uniformity and orderly placement.
- Marked architectural disorder: The dermoscopic structures and colors are disorganized so that their positioning within the lesion is often chaotic.

The scoring system assigns points as follows:

1. Color: 1 point for each of the following colors: light brown, dark brown, black, red, white, blue
2. Architectural disorder: 0 = none/mild, 1 = moderate, 2 = marked
3. Symmetry: the shape of the lesion and dermoscopic structures within the lesion; 0 = biaxial symmetry, 1 = monaxial symmetry, 2 = biaxial asymmetry
4. Homogeneity/heterogeneity based on the number of dermoscopic structures: 1 point for each of the 7 following structures: network; dots/globules; streaks/pseudopods; blue-white veil; regression structures [gray areas with or without peppering; scarring]; blotches [structureless regions of any color occupying [10% of the area of the lesion]; and polymorphous blood vessels [including dotted and irregular linear].

A total CASH score (TCS) is calculated for the lesion. The cut point for this method is eight meaning that lesions with scores of 8 or more are suspicious for malignancy.[45]

Table 11. Comparison of sensitivity and specificity CASH algorithm with other dermoscopic algorithms[45]

Algorithm	Sensitivity	Specificity
CASH	98%	68%
ABCD rule	97.9%	90.3%
Menzies method	92%	71%
7-Point checklist	85%-93%	45%-48%
Pattern analysis	83%	83%

Fairytales and dermoscopy

The ugly duckling sign

Hans Christian's Andersen tale speaks about a duckling born grey, different from its brothers. Regarding in Dermatology every person's nevi usually resemble each others like brothers. The ugly duckling is the one that is different. After a complete examination the physician can easily identify a common profile of most nevi. A nevi that does not follow this pattern is easily distinguished and should be very carefully examined even if the dermoscopy features indicate a benign nevi.[49]

Little red Riding Hood

This sign comes from another fairytale in which the wolf pretended to be a little girl's grandmother but was distinguished by his enormous teeth. In dermoscopy this sign is used to describe a lesion that at first glance looks benign but when examined carefully with the dermatoscope shows features of melanoma.[49]

Beauty and the Beast

This feature has recently been described. As "beauty" are described the benign lesions, which fit into eight categories/ patterns (Table 12) and are characterized by symmetry of pattern, structure and color. One of these rarely, if ever, will encounter a melanoma that mimics one of these benign patterns. Melanoma is defined as

"Beast" and almost invariably displays at least some degree of asymmetry in pattern, color and structure.[49]

Table 3 Patterns of benign melanocytic nevi[49]

• Diffuse reticular pattern
• Patchy reticular pattern
• Peripheral reticular central homogeneous pattern
• Structureless (homogeneous) pattern
• Peripheral reticular and central globular pattern
• Peripheral globular and central reticular pattern
• Globular pattern
• Symmetric multicomponent pattern

Additional dermoscopic tests

The adhesive tape test

A dark (black or brown) homogenous area involving the central part of a nevus can be obtained, called black lamella, corresponding histopathologically to a cornified layer containing large amounts of melanin granules. After careful removal, a reticular area typical of the acquired nevi becomes more visible. The adhesive test is used to confirm that the ugly duckling sign is only temporary. It involves the repeated sticking of an adhesive tape to the lesion, and then tearing it off, which results in the removal of the central hyperkeratotic black lamella.[42]

The ink furrow test

The pigment of the acral nevi is mainly located within the furrows of skin markings whereas melanoma shows pigmentation in the ridges. Sometimes it is difficult to distinguish the location of the pigmentation and this test will indicate it making the differential diagnosis easier. Liquid ink is applied on the skin and remained for a few seconds. Subsequently, the ink is easily removed using a cotton swab. This wiping will only remove the ink from the ridges, leaving stable the one in the furrows being easily observed during dermatoscopisis.[42]

Exceptions

Difficult to diagnose melanoma (DDM)

DDM have been reported at 5-10%. Among them are featureless melanomas, which lack the melanoma specific criteria, nodular melanomas simulating benign tumors, amelanotic or hypopigmented melanoma and others with uncharacteristic dermoscopic features. In some of them the only clue could be patient's report of change during the last months.

Recent studies have shown tha DDMs are of higher prevalence among women than men, whereas the risk for DDM increases with the reduction of Breslow depth. Most of cases with DDM are early melanomas or *in situ* lacking the melanoma specific criteria mentioned above.

The diagnostic problem is not always solved using histopathology as DDM can make this complex and difficult. In these cases, dermatoscopy is a valuable tool helping as a predictor for diagnostic disagreement among dermatopathologists.[37]

Nodular melanoma: Blue-black and EGF rule

The classical dermoscopical criteria are described in the context of superficial spreading melanoma. NM represents a biologically aggressive, rapidly growing, potentially lethal tumor that lacks of the classic clinical and dermoscopical features. A published Victorian study of patients' perceptions of the presenting symptoms and signs of NM compared with those of SSM has demonstrated how contrasting these subtypes may appear. Nodular melanomas were mostly symmetrical (80%), with a regular border and of single colour (78%), the majority (55%) being amelanotic. They were also more likely to be elevated (90%), weeping, crusted or tender in comparison to SSM. Nodular melanomas are mostly red or pink in colour and if present, pigmentation is usually evenly distributed throughout the lesion. They are raised from the outset and grow progressively as a round nodule. Lesions that are persistently growing for more than a month are suspicious for NM and require an urgent response.[51]

Argenziano et al has mentioned the role of the presence of both black and blue color (BB) involving at least 10% of the lesion's surface. This combination means that the pigment is not only present in the mid-deep dermis (blue color), as is sometimes seen in blue nevi and haemangiomas, but also in atypical melanocytes within the epidermis (black colour). The BB feature is scored as negative when the black structures are clearly recognized as comedo-like openings (seborrhoeic keratoses) or lacunae (haemangiomas). Using both the BB rule and the standard dermoscopic criteria we achieve a 90.6% positive value for malignancies and a 93.2% negative predictive value for melanoma. [52]

A suggested aide memoire for the clinical features of NM might be 'EFG'. EFG refers to a recently developed mnemonic rule that outlines the most frequent clinical characteristics of NM, i.e. a lesion that is Elevated and Firm, with a history of rapid and progressive Growth. However, the diagnostic accuracy of the EFG criteria is still unknown.[51, 52, 53]

Acral lentiginous melanoma (ALM)

Pigmented lesions on palms and soles cannot be examined using the common dermoscopical rules. In these cases, characteristics related to location should be considered. Palms and soles have a particular anatomy which is characterized by marked orthokeratosis and the presence of sulci (furrows) and gyri (ridges). The sweat ducts join the surface at the summits of the gyri. In fact, the pigmentation follows the skin markings of palms and soles, giving an asymmetrical appearance with an irregular and notched edge to all even benign lesions.[54]

The three most common types occurring in the foot are SSM, nodular and ALM. ALM is rare but represents the predominant melanoma type in extremities with a misdiagnosis rate of about 20%. Specific dermoscopic patterns have first been described by Saida *et al* and Malvehy and Puig. The two most prevalent dermoscopic features are parallel ridge pattern and irregular diffuse pigmentation. The parallel ridge pattern shows band-like pigmentation on the ridges of the skin markings. In irregular diffuse pigmentation randomly distributed brownish or grayish black

pigmentation with highly variable shades is mentioned. These two clues are highly indicative of malignancy and their presence indicates the necessity for biopsy.[47, 55]

Facial lesions (lentigo maligna-LM)

The face has a very particular anatomic architecture especially concerning the dermoepidermal junction where rete ridges are shorter. That is why facial lesions often do not exhibit a regular pigment network. Dermoscopy shows a broadened pigment reticulation which is called a "pdeudonetwork". This does not correspond to the projection of pigmented rete ridges. It is due to a homogenous pigmentation which is interrupted by the surface openings of the adnexal structures.

The differential diagnosis of a pseudonetwork is solar lentigo, seborrhoeic keratosis, lentigo simplex, melanoma in situ, lichen planus-like keratosis, and pigmented actinic keratosis.[39]

Dermoscopy diagnosis of lentigo maligna based on criteria defined by Stolz *et al*. has a 89% sensitivity and a 93% specificity. At least one of the classical Stolz criteria is present in 87% of cases: hyperpigmented follicular opening (51%), annular-granular pattern (42%), pigmented rhomboidal structures (69%), obliterated hair follicles (13%). Pralong *et al*. decribed also three original criteria: increased density of the vascular network (58%), red rhomboidal structures (40%) and target-like patterns (41%). About 68% of lentigo maligna melanomas were characterized by the presence of at least three colours. 45% of cases revealed the presence of regression, among which dominated peppering (35%) and the presence of white scar-like structureless areas (10%).[56]

Dermoscopy of a large-size LM typically reveals several of the above criteria, allowing a straightforward diagnosis. However, at earlier stages, dermoscopic criteria of LM have not yet fully developed. Interestingly, all the classic LM criteria have a common denominator, namely, the gray color, which can be detected even before the formation of the characteristic LM structures, such as circles or rhomboids. Grey color is the single most sensitive feature for the dermoscopic recognition of early

facial melanoma and its presence should always prompt the clinician to perform a biopsy.[57]

Nail melanomas

The use of dermoscopy in the examination of nail lesions was introduced in 2002 but it was in 2007 that Braun et al suggested a simplified diagnostic algorithm for the management and diagnosis using nail dermoscopy. The use of a gel (ultrasound gel, cosmetic gel or hand sanitizer) as an immersion fluid is recommended as it fills the gap between the curved nail and the dermoscopy contact plate. Equally to the classic dermoscopy, the first step is to determine whether the lesion is melanocytic or not (bloof or fungus).

In nail hyperchromia the pigmentation is homogenous, without the granular aspect of the melanin inclusions in the nail plate.

Subungual hematoma appears as red to red-black pigment depending on the time that has already passed. Reddish to reddish black globules are identified at the proximal end of the pigmentation and streaks at the distal one. Clinically, a hematoma will progressively grow out distally as the nail plate grows. Thus, the hematoma can happen either after a trauma or due to neovascularization, so the presence of sublingual blood does not rule out the diagnosis of melanoma. If it does not grow with the nail plate and remains stable at the same position, one should pay more attention at this lesion.

Infection of the nail with Trichophyton rubrum var nigricans can also cause pigmentation. Although difficult to treat, it will fade progressively after successful treatment of the fungal infection.

Once the lesion has been identified as melanocytic by the presence of melanin inclusions in the nail plate, the next step is to determine the pigmentation color. A grey color usually indicates pigmentation due to ethnicity, drug or a lentigo. The brownish color characterizes melanocytic proliferation. In that case one has to find out whether it’s a benign or a malignant lesion. A benign lesion consists of narrow, brown lines with a regular pigmentation pattern, homogenous in color, regular spacing and thickness. On the other hand, irregular brown bands with irregular

pigmentation, disruption of parallelism, multiple colors, irregular spacing and thickness are suggestive of a nail malignancy.

The following signs and symptoms could also indicate the presence of a nail malignancy:

1. any isolated pigmentation developing during the fourth to sixth decade of life.
2. any nail pigmentation that develops on a previously normal nail plane.
3. any pigmentation that alters in size
4. any pigmentation on the thumb, index finger or large toe.
5. any lesion in a person with a history of melanoma.
6. any lesion in association with nail dystrophy.
7. the presence of Hutchinson sign (pigmentation in the periungal skin).[49, 58]

Amelanotic and hypomelanotic malignant melanoma (AMM and HMM)

AMM and HMM lesions represent approximately 2 to 8% of all melanomas, presenting without or with little pigmentation, respectively. This fact makes this type of tumor difficult to diagnose. Dermatoscopy is a major tool allowing the visualization of different structures and above all determining the characteristic vascular structures which play an important role in setting the suspicion of melanoma.[27]

In dermatoscopy AMM appear with no melanin pigmentation whereas HMM may represent as partially pigmented lesions with melanin pigmentation area of less than 25% of total surface area; or as light colored lesions with only light brown, light blue or light grey pigmentation occupying more than 25% of total surface area-but with no dark brown, deep blue or black pigmentation found.[27]

Vascular pattern is another important clue increasing the level of suspicion for AMM or HMM, depending of melanoma's invasion level. Melanoma can initially show dotted vessels and as the thickness increases, presenting with vascular polymorphism (hairpin and linear-irregular vessels associated with milky-red areas, reticular depigmentation and chrysalis-white, shiny streaks).[71] Chrysalis streaks are

shiny and white corresponding to collagen alterations in the papillary dermis and can be seen only with polarized light dermoscopy.[48]

Rarely, a region of necrosis may appear in the lesion representing a dermoscopic pitfall. In such cases, dermoscopic examination may reveal whitish-yellow areas resembling the milia like cysts usually seen in seborrhoeic keratosis, papillomatous nevi or basal cell carcinoma. Milia like cysts should not distract from the correct diagnosis in the presence of vascular patterns indicating MM.[59]

According to Menzies *et al*., the vascular dermoscopic criteria for diagnosis of amelanotic melanoma include: blood vessels in the central part of the lesion, hairpin vessels, milky red-pink areas, more than one shades of pink, and a combination of dotted and linear irregular vessels.[56]

Mucosal melanoma

Evaluating pigmented lesions located on the mucosa is considered as a problematic task because of the high rates of lesions mimmicking melanoma, the very low rates of the latter and the lack of pathognomonic signs capable to differentiate benign lesions from malignant ones. In order to obtain a larger number of cases the International Dermoscopic Society conducted a multicenter, observational study including lesions from lips, labia, glans, praeputium and other areas. Evaluators were asked to score the dermoscopic patterns and colors. The conclusion of this large study was that the combination of blue, gray, or white color with structureless zones is the strongest indicator for melanoma. Early signs include presence of structureless zones and grey color, while multiple patterns and additional colors, especially blue or white may represent late stage signs. [60]

Sensitivity and Specificity

Dermoscopy has been shown to increase diagnostic sensitivity for melanoma by up to 35% when compared to clinical diagnosis with an unaided eye.[36] Depending on the individual experience of the clinician, a sensitivity of up to 92% and a specificity of up to 99% have been documented for the detection of cutaneous melanoma by dermoscopy. A recent large meta-analysis showed a diagnostic improvement for the

diagnosis of melanoma up to 16% (sensitivity values with and without dermoscopy being 90 and 74% respectively).[60] Among dermatologists, dermoscopy has become a routine examination technique in Europe and is with gaining acceptance worldwide.[41, 61, 62, 63]

The diagnostic performance of dermoscopy is improved when the diagnosis is made by a group of examiners in consensus. A consensus diagnosis may not be always possible, but electronic transmission of dermoscopic images can potentially involve two or more experts making the diagnosis easier and more accurate.[63]

The number needed to excise (NNE) is one of the most important factors to evaluate accuracy of melanoma detection. It is calculated as the number of melanocytic lesions excised for every confirmed melanoma. NNE value varies according to clinician expertise ranging from 20 to 40 for general practitioners to 4 to 18 for dermatologists at specialized clinics. Two metanalyses have shown that when used by experts, dermoscopy is associated with a significant improvement of sensitivity for melanoma as well as improvement of NNE value by decreasing the number of unnecessary excisions of benign lesions.[60, 64, 65]

During the last years, as computer hardware became more and more available and affordable, digital dermoscopy devices have been developed and rapidly integrated into the clinical setting. These offer the advantage of computer storage and retrieval during later examinations of patients and even computer-assisted diagnosis. Despite the high cost, digital examination offers a number of advantages, especially for patients with a high number of atypical nevi and a personal or family history of melanoma. In these cases, incipient melanomas can be identified by detection of intralesional changes, for instance enlargement or architectural changes.[41, 66]

Digital Dermoscopy follow up

Sequential digital dermoscopy imaging is crucial in identifying melanomas lacking the specific criteria of malignancy. Choosing short or long term follow up depends on several parameters.

Generally, a short, three months follow up remains the correct interval to diagnose featureless melanoma. It is also recommended as the optimal period for high risk patients as those with familiar atypical mole syndrome and multiple melanoma syndrome, whereas 6-12 months follow up is better for petients with atypical mole syndrome.[67, 68]

Patient's compliance is a huge challenge in the field of digital dermatoscopy follow up. Short term follow up has shown to be the best strategy to optimize patient's compliance. The reason is probably the major concern for a lesion to be checked after only 3 months.[67] On the other hand, because of the low rate of patients undergoing follow up, many physicians often feel forced to make more aggressive management, indicating excisions of lesions that could otherwise be monitored.[68]

However, not all the changes observed in the digital follow up are considered suspicious. In long term follow up the following changes are NOT considered as suspicious:

- increased or decreased diffuse pigmentation
- change in the number or distribution of brownish globules
- decrease in the number of black dots
- resolution of inflammatory reaction
- replacement of parts of the pigment network with light brown diffuse pigmentation.

The risk of melanoma is present in the following changes:

- change in shape
- asymmetric growth
- change in color
- reduction in size

- occurrence of any structures indicating melanoma.

As for short term follow up the strategy is different. Any change in the lesion should be considered suspicious with only exceptions mentioned below:

- increase or decrease of horny pseudocysts
- increased or decreased diffuse pigmentation without structural changes
- symmetrical increase in the size of the nevus with multiple peripheral globules. [68]

Argenziano *et al* described a series of patients diagnosed with melanoma after long term follow up with minimal dermoscopic changes. These slow growing melanomas hardly change over time, with a minimal change in diameter. These melanomas appeared to become more disorganized, revealed a loss of network in favor of structureless areas, and developed new colors including black, grey, blue, red and white.[65, 68] Such observations support the theory that not all melanomas behave the same way; some of them grow rapidly, with high capacity to metastasize, whereas others remain almost stable, growing very slowly and are often detectable only after repeated follow up visits.[67]

Avoiding missing melanoma: Management Rules

Most melanomas are easily diagnosed clinically and dermoscopically using the classical criteria. The challenge for the dermatologist is the way to achieve early diagnosis when morphology is not enough to recognize melanoma. Argenziano *et al* has proposed a simple 7 step rule outlining the need for a more general approach combining clinical and dermatological examination.[65]

Step 1: Look basically all lesions

This rule is priceless in order to detect early melanomas as these will be definitely excluded in a routine dermoscopy of clinically worrisome lesions and dermoscopy findings appear earlier than the clinical ABCD criteria.

People with multiple nevi should also be examined in such a base as melanoma may be masqueraded among the many benign moles (Beauty and the Beast sign).

Opponents of the method argue that examining all the lesions will be very consuming having no fair, as it has been shown that using a polarized light handheld instrument the total examination spends only 2 min.

Step 2: Undress high risk patients

While a certain amount of melanomas are detected by the patient and relatives, the rest remains to be identified by the clinician. Adding the fact that most melanomas are presented in covered body areas, it is easy to understand the need of a full naked body examination. This need becomes more urgent at high risk patients such as old ones (over 60 years old), younger with multiple navi (over 50), patients with a history of melanoma, other skin cancer or family history of first degree relatives with melanoma or people over 50 years old with chronic solar damages.

Step 3: Use the 10 sec rule in a single lesion

The strong majority of skin neoplasias exhibit characteristic morphological characteristics. Studying these characteristics and gathering dermoscopic experience one can easily recognize most lesions in 10 sec or less. On the other hand, a small proportion of lesions have a non typical morphology, resulting in a diagnostic dilemma expressed by a prolonged dermoscopic examination. These are positive in the 10 sec rule, which raises a diagnostic uncertainty and the choice of excision should be strongly discussed. This step refers to people with solitary or few lesions and not ones with atypical mole syndrome as this would result in unnecessary excisions.

Step 4: Compare and Monitor Multiple Moles

In people with atypical mole syndrome many nevi show some degree of dermoscopic irregular features. These people should be examined using the compare and monitor step. Compare refers to the observation that most lesions exhibit a similar (even if it is atypical) dermoscopic pattern while melanoma reveals different features.

However, in order no to miss a melanoma these people should also follow a monitoring with a first short term examination after 3 months being followed by an annual lifelong examination. Any lesions exhibiting changes in the follow up should be excised.

Step 5: Excise doubtful Nodular lesions

Missing a nodular melanoma is the worst nightmare for every physician. Many criteria are mentioned for the NM. Even with their addition, some NM may still be overlooked. Argenziano *at al* suggest that, when evaluating a nodular lesion, one should rather search for the presence of benign lesion criteria. When a safe diagnosis is not achieved the lesions should definitely being excised, while follow up is strongly discouraged.

Step 6: Combining clinical and dermoscopic criteria

Dermoscopy is a valuable tool for the physician but should never be used without being combined with patient's history and clinical examination. Even an innocent mole should be estimated if recently appeared in an old person. Generally, benign lesions have a harmony between history, examination, dermoscopic findings and histology.

Step 7: Combine clinical and histopathological criteria

Histopathology is the gold standard in the diagnosis of melanocytic lesions. Despite this fact, this method does not lack of limitations, technique failures, and subjective misinterpretation. Spitzoid tumors, lesions exhibiting a high degree of regression features as well as nevus associated melanoma, are some of the cases that may be difficult to interpret histopathologically. In cases that the histopathology lacks correlation with the clinical data, the lesion should be managed with caution.

Total Body Photographic Images and Short Term Surveillance

Total body photography (TBP) is used to sequentially document the stability of skin lesions, detect subtle changes in existing lesions, and recognize new lesions. Additionally, TBP has shown to help identify melanoma in its earlier stages and

promote continued surveillance of skin lesions via the patient performing SSE. It is still utilized in many practices today, mainly in patients with multiple atypical nevi, with benefits in reducing patient anxiety, earlier detection of melanomas, and fewer biopsies. Feit et al reported on patients who were undergoing TBP as part of their regular follow-up skin examinations, showing that 74% of the melanomas detected were a direct result of a noted subtle change on serial TBP.[3] The images taken can be electronically captured, archived, retrieved and compared.

Laser Based Enhanced Diagnosis

Confocal Scanning Laser Microscopy (CSLM)

CSLM is a non invasive technique that provides real time in vivo imaging of skin lesions at variable depths in horizontal planes equivalent to the resolution of conventional microscopes which allows imaging of nuclear, cellular and tissue architecture of the epidermis and underlying dermal structures without a biopsy. The confocal microscope uses a near infrared laser of low power so that no tissue damage occurs. In a study of 125 pigmented lesions (37 melanomas) CSLM had a sensitivity of 97.3% and specificity of 83%.[32]

Reflected Confocal Microscopy (RCM)

RCM allows noninvasive examination of native skin in real-time at a nearly histological resolution. The reflectance confocal microscope emits a near-infrared, coherent laser beam by which the human skin is illuminated. Some of the potential advantages are improvement of diagnostic accuracy, improved assessment of dermoscopic histological correlation, in vivo biopsy side selection, surgical margin assessment, and response control of conservative therapies in skin disease.[31]

RCM allows a higher resolution analysis of dermoscopic structures than CSLM but is more technically sensitive and expensive to use and is not as effective in analyzing deeper structures. The overall sensitivity and specificity of RCM has been found to be 90% and 86% respectively.[32]

Optical Coherence Tomography (OCT)

OCT is a technique that enables an examination of the skin to a depth of about 1mm. the light reflectivity of different tissue components (melanin and cell membranes) provides contrast in the images, and these findings correlate with pathology. Under OCT melanoma demonstrate increased architectural disarray, less defined dermoepidermal borders and vertically orientated icicle shaped structures not seen in nevi. Its utility for skin lesions has not been fully established because sensitivity and or specificity studies have not been reported. Furthermore, as histopathologic structures may be less clearly observed in hyperkeratotic or raised lesions, OCT may be better suited for flat and nonscaling lesions.[32]

Diagnostic Ultrasound

Ultrasound scanning is a safe noninvasive method that can be used to show subtle differences between nevi and melanoma. Transducers with higher frequency wavelengths are beneficial for diagnosing skin lesions because they allow better resolution of small lesions located near the skin surface. However, higher frequencies also lead to decreased depth of penetration by the ultrasound waves; thus the choice of the probe one depends on the diameter and site of the lesion.[69]

mRNA patterns

mRNA patterns that have been identified in melanomas can be tested in suspicious skin lesions with a non invasive method called tape stripping. An adhesive tape is applied on the pigmented skin lesion and the briskly rubbed in a circular motion. mRNA is then collected by the superficial cells being stripped off by removing the tape, enough for gene expression profiling by ribonuclease protection assay. This method allows differentiating melanoma from benign lesions with sensitivity and specificity of 68.7% and 74.5% respectively. Although still in early trials, tape stripping may eventually be most beneficial as a prescreen for patients with multiple suspicious lesions to identify which should be considered for biopsy confirmation.[32]

Cellular Electrical Resistence (Bioimpedance)

Bioimbedance is the electrical resistance whose levels depend on shape and structure, membranes and amount of water present in different cells. Counting on this the bioimpedance of cancer and benign cells is different and its measurement can help in the differential diagnosis between them. Lesional and reference skin are measured at 5 depth levels and data are analyzed in a computer in a process that takes approximately 7 minutes to complete. The method has a high sensitivity of almost 100% for in situ and thin melanomas and a specificity of about 65-75%. As electrical impedance properties of human skin vary significantly by location, age, gender and season more studies need in order to standardize these positive results.[32, 70]

Biopsy

The gold standard for a definitive diagnosis of cancer is a biopsy which may occur by removing part of the lesion (incisional biopsy) or the entire lesion (excisional biopsy). For a lesion clinically suspicious for cutaneous melanoma, one should ideally perform a narrow excisional biopsy that encompasses the entire breadth of the lesion with clinically negative margins to a depth sufficient to ensure that the lesion is not transected. It has been suggested that 1-3 mm margins are required to clear the subclinical component of most atypical melanocytic lesions. This can be accomplished in a number of ways including elliptical or punch excision with sutures, or shave removal to a depth below the anticipated plane of the lesion. The latter is commonly utilized when the suspicion of melanoma is low, the lesion lends itself to complete removal by this technique, or in the setting of a macular lesion suspicious for lentigo maligna where a broad biopsy may aid in histologic assessment.[71, 72]

Incisional biopsy of the clinically or dermoscopically most atypical portion of the lesion, is an acceptable option in certain circumstances, such as a facial or acral location, low clinical suspicion or uncertainty of diagnosis, or a very large lesion, although the selected area may not always correlate with the deepest Breslow

depth. If an incisional biopsy is inadequate to make a histologic diagnosis or accurately microstage the lesion for treatment planning, a repeat biopsy should be performed. When a biopsy of a suspicious nail lesion (melanonychia striata, diffuse pigmentation, or amelanotic changes such as ulceration) is performed, the nail matrix should be sampled.[71, 72]

Histology

When a biopsy is performed of a lesion clinically suspicious for primary CM, the following pertinent information should be provided to the pathologist:

- For identification purposes: the age and gender of the patient as well as the anatomic location of the lesion.
- Clinical information: type of surgical procedure performed (incision or excisional biopsy), size of the lesion. Optional, but desirable information: ABCDE criteria, dermoscopic features, photograph, presence or absence of macroscopic satellitosis.

The list of features used to diagnose malignant melanoma includes general architectural features (asymmetry, dimension greater than 6 mm, involvement of epithelial adnexal structures by atypical melanocytes), epidermal features (poor circumscription of the melanocytic proliferation, single melanocytes predominating over nests, suprabasal melanocytes, pleomorphic and confluent melanocytic nests), dermal features (band-like inflammatory infiltrate, lack of maturation of melanocytes with the progressive descent into the dermis), and cytological features (melanocytic atypia, mitotic figures, necrosis of melanocytes). These features are strongly associated with the various growth patterns of the most common subtypes of CM. However, such features do not appear to be exclusive to melanoma, but may also occur in benign melanocytic naevi. Therefore, the diagnostic process cannot just involve the strict use of a list, but should be a rigorous critical analysis of all the available clinical and histological features.[73, 74]

Immunohistochemistry has been the primary tool to distinguish melanomas from other tumors (epithelial, hematologic, mesenchymal, and neural tumors); it has also been studied for use as an adjunct to distinguish benign and malignant melanocytic tumors and to elucidate prognosis. Despite the proliferation of immunohistochemical markers, S-100 remains the most sensitive marker for melanocytic lesions, while markers such as HMB-45, MART-1/Melan-A, tyrosinase, and MITF demonstrate relatively good specificity but not as good sensitivity as S-100. No marker has proven useful in distinguishing spindle cell and desmoplastic melanomas from other tumors. Ki67 remains the most useful adjunct in distinguishing benign from malignant melanocytic tumors. None of the markers reviewed has been shown conclusively to have prognostic value for melanocytic neoplasms.[75]

As for the histology report three are the most important characteristics of the primary tumor to predict outcome and should be included:

1. Maximum tumor (Breslow) thickness as measured from the granular layer of the overlying epidermis or base of a superficial ulceration to the deepest malignant cells invading dermis to the nearest 0.1 mm. Microsatellitosis should not be included in this measurement, but commented on separately.
2. Presence or absence of microscopic ulceration, defined as tumor-induced full thickness loss of epidermis with subjacent dermal tumor and reactive dermal changes.
3. Mitotic rate, measured as the number of dermal mitoses per mm^2 (with 1 mm^2 approximately equal to 4.5 high-power [×40] microscopic fields, starting in the field with most mitoses).

An additional essential element of the pathology report is the status of the peripheral and deep margins (positive or negative) of the excision. The presence or absence of tumor at the surgical margin indicates whether the entire lesion was available for histologic evaluation and provides guidance for further management.

There is evidence that several other histologic features provide prognostic value, including the presence or absence of a vertical growth phase, tumor infiltrating lymphocytes, dermal regression and angiolymphatic invasion. While not essential, these should also be included as optional elements of the pathology report. The histology subtype of melanoma should also be mentioned even if the prognostic factor has not been established, with some notable exceptions – lentigo maligna pattern is associated with broader superficial extension; whereas purely desmoplastic subtype has lower risk of nodal and distant metastases. The presence or absence of neurotropism should also be excluded as provides valuable information that may alter future management.[71, 72]

Table 13. Strength of recommendations for the management of primary cutaneous melanoma (AAD, Guidelines of Care for the Management of Primary Cutaneous Melanoma)

	Strength of Recommendation	Level of Evidence
Biopsy	B	II
Pathology Report:		
Clinical information		I-II
Tumor (Breslow) thickness	A	I-II
Ulceration	A	I-II
Mitotic Rate	A	I-II
Level of Invasion (Clark)	B	II
Microsatellitosis	B	I-II
Angiolymphomatic Invasion	B	II
Histologic Subtype	B	II
Regression	B	II
Tumor Infiltrating lymphocytes	B	II
Staging Workup	B	II-III
Follow-up:		

Interval	B	II
Duration	B	II
Patient skin/self exam	B	II
Imaging and laboratory tests	B	II
Surgical management		
In situ	C	III
≤1.0mm thickness	A	I
1.01-2mm thickness	A	I
>2mm thickness	B	I-III
Non-surgical treatments		
Imiquimod	C	III
Radiotherapy	C	III
Cryosurgery	C	III
Sentinel lymph node biopsy	B	I-III

Molecular diagnosis

Molecular analysis of distant or regional metastasis or, if impossible of the primary tumour is required for patients with distant metastasis or non resectable regional metastasis, who are candidates for systemic medical treatment. Currently, the main test performed involves the BRAF V600 mutational status, in order to identify patients eligible for treatment with BRAF inhibitors and MEK inhibitors.

NRAS mutations are identified in around 15% of samples and as BRAF and NRAS mutations are mutually exclusive a positive NRAS mutation serves as to reassure that a BRAF mutation has not been missed. Presently, NRAS inhibitors are under clinical development.

CKIT mutations should additionally be analysed in patients with acral and mucosal melanomas, although the positivity rate is lower than previously expected in Europe.

In the near future, other genomic tests are expected to be identified as predictive markers for patients with stage IV melanoma.[1]

Staging approach

Physical exam

After the diagnosis of melanoma has been histologically confirmed, a thorough history and physical exam comprise the cornerstone of the initial workup with special attention on neurologic, respiratory, hepatic, gastrointenal, musculoskeletal, skin and lymphatic signs or symptoms. The examination should include a total body skin examination and palpation of both regional and distant lymph node basins. Any abnormal finding should direct the need for further studies to detect regional and distant metastases.[72]

Blood and imaging tests

The value of additional staging examination at first diagnosis in patients with primary melanomas is controversial. The American Academy of Dermatology supports that baseline blood tests and imaging studies are not recommended and should only be performed as clinically indicated for suspicious signs and symptoms. Screening blood tests, including serum lactade dehydrogonase (LDH) are insensitive for the detection of metastatic disease. The use of routine imaging studies (chest X-ray) is limited by a very low yield and the frequent occurence of false positive findings. Ultrasound, as well as PET (Positron Emission Tomography) have found to have low sensitivity for the detection of occult regional nodal metastases compared with SLNB (sentinel lymph node biopsy).[72]

However, it is widely agreed upon that high risk patients should perform staging examination; although definitions of low and high risk vary. Furthermore, as the efficacy of targeted therapies is clarified, then thresholds for screening may change. Useful staging examinations should include sonography of regional lymph nodes and

total body CT or PET-CT scans. LDH and serum protein S100 are routinely used as markers of relapse in some countries.[1]

Table 14. Recommendations for staging workup and follow-up (AAD, Guidelines of Care for the Management of Primary Cutaneous Melanoma)

Baseline laboratory tests and imaging studies are generally not recommended in asymptomatic patients with newly diagnosed primary melanoma of any thickness
No clear data regarding follow-up interval exists, but at least annual history and physical examination with attention to the skin and lymph nodes is recommended
Regular clinical follow-up and interval patient self exam of skin and regional lymph nodes are the most important means of detecting recurrent disease or new primary melanoma; findings from history and physical exam should direct the need for further studies to detect local, regional, and distant metastasis
Surveillance laboratory tests and imaging studies in asymptomatic patients with melanoma have a low yield for the detection of metastatic disease and are associated with relatively high false-positive rates

Sentinel Lymph Node Biopsy (SLNB)

SLNB is a minimal invasive staging procedure developed to identify patients with subclinical nodal metastases at higher risk of recurrence who could be candidates for complete lymph node dissection or adjuvant systemic therapy. SLNB is not recommended for patients with in situ melanoma (stage 0) or stage IA melanoma that is 1.0 mm or less with no adverse features. Discussion of SLNB should be considered for patients with stage IA thin melanomas (≤ 1.0 mm) with adverse prognostic features, such as thickness greater than 0.75mm, positive deep margins, lymphovascular invasion, or young age (although no threshold of young age alone is sufficient to recommend SLNB). Because the yield of a positive SLNB in patients with stage IA melanoma is low and the clinical significance of a positive SLN in these patients remains unclear, these factors should be discussed with patients considering the procedure. For patients with stage IB or II melanoma (≤1.0 mm thick with ulceration or mitotic rate ≥ 1 per mm^2; or > 1.0mm thick), SLNB should be discussed and offered. SLNB may also be considered for patients with resectable

solitary in-transit stage III disease. However, although SLNB is a useful staging tool, its impact on the overall survival of these patients remains unclear.[1, 71]

Treatment Options

The incidence of primary CM has been increasing dramatically for several decades. Melanoma accounts for the majority of skin cancer related deaths, but treatment is nearly always curative with early detection of disease. The therapeutic options, as described below should not be interpreted as setting a standard of care. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biological behavior of the disease.

Surgical therapy

Wide excision of the primary tumor

Surgery is the only potentially curative treatment for primary melanoma. The surgical standard requires the enbloc resection of the scar of the primary melanoma with the surrounding healthy skin and subcutaneous tissue down to the fascia. The muscle fascia is not removed, unless it has already been infiltrated, because its removal does not affect the local recurrence rate, while it has far worse cosmetic sequelae. The aim of this treatment is to achieve local disease control.[31]

The definitive surgical excision should be performed with safety margins preferentially within 4–6 weeks of initial diagnosis. The recommendations below are consistent with evidence that narrow excision margins are appropriate; the values given are in concordance with the American, UK and Australian recommendations.[1]

The recommended wide excision margins usually are 5mm for melanoma in situ, 10mm for melanoma ≤1mm to 2 mm, and 20mm for melanoma ≥2mm. In the case of lesions involving the face, the excision margins cannot always comply with the recommendations, given the need to reconcile oncological radicality with a satisfactory reconstruction.[1]

Lentigo maligna

Lentigo maligna requires narrower margins for safety when it is excised, and micrographic control of excision margins may be involved in order to conserve tissue particularly in the face. Surgical procedures should respect the anatomy of the face as well as aesthetic and functional aspects. Several retrospective analyses and phase II trials support a role for topical imiquimod as a potential alternative to surgery in selected cases. The complete response rate to imiquimod treatment is in the range of 75–88%. However, patients should be informed that imiquimod will not allow a histological evaluation of the tumour area (and clinically unsuspected invasive melanoma may therefore be missed) and the peripheral margins will require a thorough follow-up.[1, 72]

Acral and mucosal melanomas

Local recurrences are more frequent in these types of melanoma. Therefore, removal can be achieved with increased safety margins (at least 1 cm) or by narrow margins with micrographic control (e.g. Mohs' technique and variants).[1]

Lymph Node Dissection

For patients with negative SLN no further lymph node surgery is required.

In patients with micrometastases in SLN studies have not confirmed that radical lymph node dissection improves survival. Nonetheless, when SLND shows micrometastases, radical lymph node dissection is usually recommended as approximately 5-12% of patients will have involvement of non sentinel nodes. The prognostic classification of the presence of micrometastasis within the SLN may help to select patients for CLND in the near future.

Finally, if lymph node metastasis is diagnosed clinically or by imaging techniques, radical lymph node dissection is considered standard therapy.[1, 71]

Skin metastases

The treatment of choice for skin metastases is surgical, but systemic therapies should also be considered if numerous or extensive lesions are not amenable to surgery. Alternative options include cryotherapy, laser therapy and

intralesional/topical approaches such as IL-2, electrochemotherpay, miltefosine, interferon-α or imiquimod.[1, 71]

Distant metastases

For distant metastases, the therapy of choice is, if possible, complete operative removal. As for brain metastases, stereotactic radiation therapy is equally effective. The value of debulking procedures must be viewed critically, as there is no evidence that they improve survival.[1, 71]

Radiation therapy

CM was long considered a radio therapy resistant tumor. This idea was based on the fact that melanocytes are known to easily repair DNA damage induced by low dose radiation. However, clinical evidence suggests that certain types of melanoma, in particular mucosal melanomas of the head and neck region, should be treated with radiation to prevent recurrence. In addition, lentigo maligna melanoma relapses frequently when only surgical removal is employed. Unresectable lesions can also be treated with thermal neutron irradiation.[5] For transit metastases, too extensive for a surgical approach, may be controlled by radiation therapy alone.[1]

As for regional lymph nodes, adjuvant radiotherapy after lympadenectomy can be considered for patients at high risk to improve lymph node field control. When lymph node dissection is not complete or metastatic lymph nodes are inoperative, radiation therapy may be recommended, with absolute palliation of symptoms but unknown further value.[1]

Radiation therapy is also used for distant metastases. For bone metastases response rate is 67-85% with major indications pain, loss of structural stability and compression of the spinal canal. For melanoma metastases, with life expectancy of only 3-5 months, neurological deficits may be improved in 50-75% of cases with an overall improvement in health.[1]

Treatment of metastatic melanoma

Local treatment

Many treatments are available and the choice is based on the size, location, and number of tumor deposits, but evidence is limited and no consensus exists on the best approach.

Excision in clear margins is the mainstay for resectable tumors in small numbers. Moreover, several non surgical approaches are being used. Isolation limb perfusion or infusion is a method to administer high doses of chemotherapy to an affected extremity, with melphalan being the drug widely used in this method. A recent study showed a complete response rate of about 31%. However, a modified hyperthermic isolated perfusion rate was associated with a higher complete response of about 63%.

Other therapies include intralesional local injections with bacillus Calmette-Guerin (BCG) or interferon alpha, and topical imiquimod.[71]

Systemic therapy

Traditional chemotherapy

Common agents currently used in practice include decarbazine, temozolomide, high dose interelukin-2 and paclitaxel with or without cisplatin or carboplatin with decarbazine being the longest established monotherapy. These agents have shown modest response rates of less than 20% in first and second line settings.[40] The combination of cytostatic agents and cytokines produces an increase in the objective response rate, without significant improvement in the OS time. The tolerability of monochemotherapy is worsened when interferon-α or IL-2 is added. The combination of chemotherapeutic agents also achieves higher remission rates but once again does not improve OS.[1]

Novel therapies

The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents.

Ipilimumab, a monoclonal antibody directed to the immune checkpoint receptor termed cytotoxic T lymphocyte antigen-4 (CTLA-4), received FDA approval for treatment of metastatic melanoma in March 2011. Ipilimumab stimulates T cells and is associated with substantial risk of immune-related reactions. Patients with underlying autoimmune disorders may be especially susceptible to serious reactions.

Vemurfenib. Approximately 45% of patients with metastatic melanoma harbor an activating mutation of the intracellular signaling kinase, BRAF. Vemurafenib is a specific inhibitor of signaling by mutated BRAF. A randomized phase III trial associated vemurafenib with improved overall and progression-free survival. Skin complications were frequently associated with the agent: 18% of vemurafenib-treated patients developed cutaneous squamous cell carcinoma or keratoacanthoma that required simple excision, whereas 12% experienced grade 2 or 3 photosensitivity skin reactions. Arthralgia was the most common (21%) noncutaneous side effect. Based on the results of this randomized study, vemurafenib was approved by the FDA in August 2011 for the treatment of metastatic or unresectable melanoma with BRAF mutation.

Although approval of ipilimumab and vemurafenib has significantly altered the initial management of patients with stage IV melanoma, each agent has unique limitations. Ipilimumab is associated with the potential for serious autoimmune toxicity, clinical responses may take months to become apparent, and the overall response rate is less than 20%. However, when responses are seen, they can be durable. Vemurafenib, on the other hand, is associated with a 40% to 50% response rate in patients with a V600- mutated BRAF gene, and responses may be seen days to weeks after starting the drug. Unfortunately, the median duration of response is only 5 to 6 months.[71]

Biochemotherapy

Biochemotherapy is the combination of chemotherapy with biologic agents (interfeton alfa, interleukin-2). In several trials this combination produced better

response and complete response without any improvement in overall survival and with increased toxicity compared with chemotherapy alone.[71]

Follow up

In the absence of clear data, opinions vary widely on the appropriate follow up of patients with melanoma. Generally, the first 5 years following the surgery are the most important as 90% of all metastases occur during this period. Late recurrence (>10 years later) is however well documented, especially in patients with early staging melanoma. As the lifetime risk of developing a second primary melanoma is about 4-8% a recommendation for lifetime dermatologic surveillance for these patients is probably not useless. [1, 71]

Several reasons for a structured follow-up program include detection of a subsequent second primary melanoma, provision of ongoing psychosocial support, identification of familial kindreds, screening for second nonmelanoma primary malignancies, patient education, and documentation of treatment results.

The national comprehensive cancer network recommend skin self examination at least once a year for life for all patients with melanoma, including those with stage 0 in situ. All patients with IA to IV should be educated about monthly self examination of skin and lymph nodes. Moreover, comprehensive history and physical examination should take place every 3 to 12 months for 5 years and annually thereafter. Routine blood testing is not useful. CT, MRI and/or PET/CT every 6 to 12 months can be considered for patients with stage IIB-IV melanomas.

Education of skin cancer prevention, including sun protection should be promoted for patients with melanoma and their families, with increased evidence that regular use of sunscreen may diminish the incidence of subsequent melanoma.[71]

Future Perspectives

Despite the advances in recognizing and treating melanoma its mortality remains stable. Trying to overcome this situation, all health professionals associated should focus their efforts to three different directions. The first is to try finding a more

effective treatment for cutaneous melanoma. Novel therapies targeting on specific pathways are moving towards this direction. The second point is to modify patients' behavior. The World Day for Melanoma on 11 May (the day that the famous musician Bob Marley died from melanoma), the week against melanoma every May in Greece, as well as websites like www.myskincheck.gr are only some of the actions taken in order to sensitize people against melanoma. Last but not least is the parameter of what physicians could and should do. The first step towards the diagnosis is the full skin examination as it is proven that most patients with melanoma have at least one medical consultation but only 20% report a skin cancer examination. Dermatoscope is a valuable tool in the hands of dermatologists.

Abstract

Cutaneous melanoma is the rarest skin tumor but causes the 90% of skin cancer mortality. Its incidence increases steadily during the last decades being placed among the six most common malignancies among men and women. Compared with other forms of cancer CM remains one with relatively high 5 year survival, especially when diagnosed at an early stage.

Biopsy remains the gold standard for the diagnosis of cutaneous melanoma provided that the physician will suspect and excise the skin lesion. However, the challenge is to identify as early as possible lesions that have the possibility of being a melanoma. Dermoscope is an easy to use, hand held device, which enables the evaluation of skin lesions by observing lesion's color, patterns, vessels and structures. Nowadays, its use has gained profit and dermoscope is now considered as the dermatologist's stethoscope. With a magnification of 10 to 70 fold it represents a valuable tool between histopathology and naked eye examination.

Dermoscopy has been shown to increase diagnostic sensitivity for melanoma up to 35% compared to naked eye examination. Many algorithms are described for the evaluation of pigmented lesions and the early identification of melanoma. Beyond them, looking basically all person's lesions even only for 10 sec, undressing every patient, comparing and monitoring irregular moles, excising every doubtful nodular lesions and combining clinical, dermoscopical and histopathological criteria represents a more general approach in the direction of avoiding to missing melanoma.

Περίληψη

Το κακόηθες μελάνωμα αποτελεί τη σπανιότερη κακοήθεια του δέρματος αν και ευθύνεται για το 90% των θανάτων λόγω καρκίνων του δέρματος. Η σταθερή αύξηση της συχνότητας του τις τελευταίες δεκαετίες το έχει καταστήσει από μία σπάνια κακοήθεια στην έκτη πιο συχνή μεταξύ ανδρών και γυναικών. Παρ' όλα αυτά το μελάνωμα εξακολουθεί να είναι μία κακοήθεια με άριστη πρόγνωση αν διαγνωσθεί έγκαιρα.

Η βιοψία και η παθολογοανατομική εξέταση ήταν και παραμένουν ο θεμέλιος λίθος στη διάγνωση του μελανώματος. Το στοίχημα όμως για τον κάθε δερματολόγο είναι πλέον να εξασφαλίσει την έγκαιρη διάγνωση του εντοπίζοντας βλάβες σε πολύ αρχικό στάδιο που δεν μπορούν να διακριθούν με γυμνό οφθαλμό.

Στο σημείο αυτό αναδεικνύεται ο ρόλος και η αξία της δερματοσκόπησης, μίας αναίμακτης και γρήγορης μεθόδου που παρέχει πολύτιμες πληροφορίες αναδεικνύοντας δομές όπως το μελαγχρωματικό δίκτυο, τα αγγεία αλλά και άλλα στοιχεία κάθε βλάβης. Η χρήση του έχει αποδειχθεί ότι αυξάνει την ευαισθησία για τη διάγνωση του μελανώματος κατά 30%. Πολλοί κανόνες έχουν προταθεί για τη δερματοσκοπική ανάλυση μίας μελαγχρωματικής βλάβης, πέραν όλων αυτών όμως η υιοθέτηση βασικών αρχών δερματοσκοπικής εξέτασης είναι εις θέση να εξασφαλίσει την έγκαιρη διάγνωση αλλά και να αποτρέψει τον κίνδυνο μη διάγνωσης ενός μελανώματος.

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