Chapter 4

Current Management of Malignant Melanoma: State of the Art

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1. Introduction

The word "melanoma" was first used by *Rene Laennec*, inventor of the stethoscope, in his manuscript reporting a case of disseminated melanoma in 1812 [1]. Cutaneous malignant melanoma (CMM) arises from the malignant transformation of the pigment producing melanocytes, which are located and evenly distributed in the basal epidermal layer of human skin. These pigment-producing cells (melanocytes) are located predominantly in the skin, but also found in the eyes, ears, GI tract, leptomeninges, and oral and genital mucous membranes [2].

The incidence of cutaneous malignant melanoma has increased significantly among all Caucasian populations over the last several decades. The rate of incidence of cutaneous melanoma continues to rise almost inexorably in populations of European origin worldwide. Diagnosis of melanoma at an early stage is almost curable but there is currently no effective treatment for advanced melanoma. Probably a large proportion of melanomas can be ascribed to a single (modifiable) risk factor-sun exposure. It has not been established whether medical intervention of any kind influences the outcome in the case of melanoma. Major initiatives in recent years have concentrated on education about sun avoidance, the importance of skin awareness and skin examination, and the screening of populations at high risk for melanoma. However, it is unclear whether any of the latter measures have had any significant influence on mortality from melanoma. The annual increase in incidence rate varies between populations, but in general has been in the order of 3–7% per year for fair-skinned Caucasian populations. CMM represents a significant and growing public health burden because of the increase in incidence and the consequent mortality [3].

The cancer statistic in the United States was reported to be 6 cases per 100.000 inhabitants at the beginning of the 1970s and 18 cases per 100.000 and year at the beginning of 2000, thus demonstrating a threefold increase in incidence rates. Incidence rates in central Europe increased in the same time period, from 3 to 4 cases to 10 to 15 cases per 100.000 inhabitants and year, which is very similar to the increase in the United States. The highest incidence rates were reported in Australia and New Zealand, with 30 to 60 cases per 100.000 inhabitants and year [4]. Cutaneous melanoma ranks as the sixth most common cancer in American men and women, the second most common cancer in patients between the ages of 20 and 35, and the leading cause of cancer death in women ages 25 to 30 years [5]. Although melanoma accounts for 5% of all skin cancers in the United States, it is responsible for the most common skin cancer-related deaths (it accounts for 79 percent of all skin cancer deaths) because of its high mortality when identified at an advanced stage [6, 7]. The number of deaths due to CMM has also increased in most fair-skinned populations throughout the world in the past few decades. However, melanoma mortality rates have been rising at a rate of increase lower than that for melanoma incidence. Between 1955 and 1984, mortality from CMM had been rising both in young adults (20–44 years) and in middle-aged populations (45–64 years) in most European countries, North America, Australia and New Zealand, with a rate of increase of 2–4% annually. In Australia in 1985–1999 the mean age-standardized mortality rates were 4.8 and 2.5 per 100.000 in men and women, respectively. In 1990–1994 the rate rose by 3.7% in men to 5.0 per 100.000 and in women it fell by 5.2% to 2.4 per 100.000 [3]. Although mortality rates have increased, 5-year survival has steadily improved over recent decades, and is now greater than 85%, but melanoma causes disproportionate mortality in those of young and middle age, such that an average of 18.6 years of potential life are lost for each melanoma death in the USA, one of the highest rates for adult-onset cancers [8]. Predicted 1-year survival for stage IV disease ranges between 41% and 59% [5].

The etiology of melanoma is multifactorial that environmental, host, and genetic factors contribute to its development. The most important environmental risk factor is ultraviolet radiation (UVR) exposure [6]. Most melanomas are thought to be caused by periodic, intense sun exposure (particularly during the critical time period of childhood and adolescence), termed the *intermittent exposure* hypothesis, though exposure in adulthood certainly also plays a part. In older people, melanomas appear to be more related to chronic exposure. This is suggested by the body site distribution of melanomas in the elderly, with more melanomas on chronically exposed body sites [7, 9]. The most important host risk factor for CMM in fair-skinned people is the presence of both common acquired and atypical (dysplastic) melanocytic naevi. Patients with a family history of melanoma are at increased risk. Around 5–12% of patients with melanoma have a family history of CMM in one or more first-degree relatives. Some of these patients have an inherited mutation in highly penetrant susceptibility genes which are associated with a significantly increased risk of melanoma [3].

Cutaneous malignant melanoma is currently classified into four major clinical subtypes: Superficial spreading, nodular, acral lentiginous, and lentigo maligna, of which superficial spreading melanoma is by far the most common form (approximately 70%) of CMM [10]. CMM that is less invasive and locally defined at diagnosis has a five-year survival rate of more than

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95% after treatment by surgical excision alone. Fortunately, the vast majority of CMM (approximately 80%) are diagnosed at this early stage. If the cancer is more advanced, however, survival rates drop substantially to 30% to 60% after five years, depending on the tumor thickness in millimeters (*Breslow*'s depth). Metastatic disease has poor patient outcomes as treatment options are limited [10].

The prognosis for a patient with a newly diagnosed cutaneous melanoma depends mainly on two factors— the thickness of the primary tumour and the presence or absence of metastasis to regional lymph nodes. However, other prognostic factors are very important, including tumour ulceration, mitotic rate, and presence of regression, as well as sex and age of the patient, and tumour site [8].

For the primary prevention, physical protection from exposure to sunlight is generally accepted as the most important element of melanoma risk reduction. It seems particularly meaningful to prevent multiple erythemas during childhood, convincing parents and care takers not to let children stay too long under the sun. Sun-protective clothing and hats should be worn and peak hours of sun intensity should be avoided. For these purposes, mass media campaigns and widespread public education programmes would be most effective to make changes in attitude and behaviour towards sun protection [8,11]. The wavelength of light that is causal for melanoma is still not known and therefore sunscreens should be broad-spectrum types, providing protection across both UVB and UVA ranges. Advice should be to use sunscreens that are water proof, and sunscreens must be applied regularly and in sufficient quantities [12]. Regular screening of the total population for CMM does not seem useful and is not propagated in any country in the world. However, it seems likely that people with a familial risk of developing melanomas (those with familial or sporadic dysplastic naevus syndrome, xeroderma pigmentosum and large congenital naevi, representing approximately 10% of all melanoma patients) can benefit from regular check-ups. Screening in these populations, and regular checks (every 6–12 months) lead to earlier detection [11].

2. Etiopathogenesis

2.1. Risk factors

The etiology of melanoma is multifactorial, with environmental, host, and genetic factors contributing to its development. Ultraviolet radiation exposure is the most important environmental risk factor [6]. The precise type of sun exposure that is causal has been controversial but the data are now strong that the dominant cause is intermittent sun exposure [12]. Periodic and intense sun exposure rather than long, heavy sun exposure especially during childhood and adolescence is the feature of intermittent sun exposure. Also, sunburn history particularly blistering and peeling burns are important indicators for intermittent sun exposure [7].

In a meta-analysis by *Dennis* et al., an increased risk of melanoma was seen with an increasing number of sunburns for all time-periods, including childhood, adolescence, adulthood, and lifetime [13]. The relationship between melanoma and exposure to ultraviolet light is complex

that lower incidence of melanoma among people who work outdoors is seen compared with those working indoors. The possible explanation for this is that chronically tanned skin is less melanoma-prone than untanned skin exposed to bursts of high intensity sun, in particular sunburns [14].

The geographic distribution of melanoma supports the importance of UVR exposure in its pathogenesis. Living closer to the equator, where there is the greatest ambient solar radiation, is consistently associated with increased melanoma risk [6]. When the incidence and mortality rates of melanoma compared between Europe and Australia it was reported 5 to 10 times higher incidence rates in Australia [4]. Melanoma incidence and mortality among Caucasians correlate inversely with latitude of residence and dose of UV radiation, termed *latitude gradient.* In the United States, SEER (Surveillance Epidemiology and End Results) data from 1992 to 2001 demonstrate that the latitude gradient applies only to non-Hispanic whites; melanoma incidence was not associated with latitude and UV index in Afro-Americans, Hispanics, Asians and Native Americans [7]. Migration studies also provide evidence for the effect of ambient UVR exposure levels on melanoma risk [6]. Younger migrants to sunny areas have an increased risk for melanoma as compared with adult immigrants [7].

The anatomic distribution of melanoma also offers insight into the pathogenesis of the disease and the role of UVR. The most common sites for melanoma are the trunk in men and the lower legs in women which are areas of high levels of acute, intermittent sun exposure. In older people, there is a greater incidence of melanomas located on chronically sun exposed areas with maximal cumulative sun exposure that the face is the most common location [6,7].

Cust et al. reported that UV radiation exposure from sunbeds is a risk factor for early-onset melanoma, particularly melanoma diagnosed between ages 18 and 29 years [15]. Artificial lights (psoralen and ultraviolet A light (PUVA), UVB and tanning booths) have been associated with the development melanoma [7].

Weaker phenotypic risk factors are related to; the presence of skin that burns easily in the sun such as: skin phototype I-II, high density of freckles, fair complexion/sun sensitivity, an increased number of common or atypical/dysplastic nevi (moles), blue eye colour and red hair colour [12]. *Loria* et al. reported that the crude relative risk increased significantly for individuals with red hair, but hair color was no longer significant in multivariate analysis and light-colored eyes were an independent risk factor even after controlling for the number of nevi, skin type, and other relevant factors [16].

The strongest phenotypic risk factor for melanoma is the presence of increased numbers of melanocytic naevi [12]. With growing numbers of melanocytic nevi, the melanoma risk increases nearly linearly. In addition, the presence of atypical melanocytic nevi was found to be an independent risk factor [4]. Adults with more than 100 clinically typical-appearing nevi, children with more than 50 typical-appearing, and any patient with atypical nevi are at risk. Large congenital nevi are recognized potential precursors of melanoma, although the degree of risk varies depending on the size of the lesion [7]. Twin studies have provided strong evidence that naevus number is predominantly genetically determined with a smaller effect of environmental factors, particularly sun exposure. It is theorized, therefore, that the genes

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that determine naevus number are also common melanoma susceptibility genes [12]. Many of the oncogenic mutations initially identified in melanomas have also been detected in benign melanocytic proliferations [5].

Any family history increases the risk of melanoma. Familial melanoma comprises 10-15% of all patients with melanoma [7,12]. The presence of more than one case of melanoma in a family may occur by chance alone, or may be due to low penetrance alleles and/or sun exposure habits common to affected relatives. However, an estimated 25% of familial melanoma is associated with germline mutations of the CDKN2A gene on chromosome 9 (which codes for the cell cycle inhibitor protein, p16) and often presents with an autosomal dominant pattern of transmission [17].

2.2. Genetics

Melanoma develops as a result of accumulated abnormalities in genetic pathways within the melanocyte. These abnormalities promote cell proliferation and prevent normal pathways of apoptosis in response to DNA damage [8]. The driving force behind the initiation and progression of melanoma development is the acquisition of somatic mutations in key regulatory genes. The first gene found to be specifically altered in melanoma was *NRAS*, which harbors mutations in 15–25% of melanoma cell lines and primary tumors [14]. *NRAS* mutations tend to occur in melanomas arising from intermittently sun-exposed skin [5]. *NRAS* mutations are more common in patients with nodular melanomas and melanomas arising on chronically sun-damaged skin. Recent data have shown that *NRAS* mutations may be associated with thicker tumors (>1 mm) and higher mitotic rate (>1/mm2) compared with mutations in *BRAF*. In response to a variety of cellular stimuli, including ligand-mediated activation of receptor tyrosine kinases (RTKs), RAS assumes an activated, GTP-bound state, leading to recruitment of RAF to the plasma membrane and phosphorylation-driven activation of the RAF-MEK-ERK cascade [14]. RAS genes acquire their transforming activity following the acquisition of a single-point mutation that impairs their GTPase activity and leads to constitutive signaling through the mitogen-activated protein kinase (MAPK), PI3K/AKT, and Ral-GDS pathways [18]. *Omholt* et al. demonstrated that *NRAS* mutations are present in the radial growth phase (RGP) of primary melanoma lesions as well as in tumor-associated nevi and that they are preserved in corresponding vertical growth phase (VGP) and metastatic lesions [19].

BRAF is a serine/threonine kinase, which is a major player in the Ras-Raf-Mek-Erk mitogen-activated protein kinase (MAPK) signaling transduction pathway that regulates cell growth, proliferation, and differentiation in response to various stimuli [7]. Mutations in *BRAF* have been found in about 60% of melanoma samples and cell lines. *BRAF* mutations are common in benign and dysplastic nevi pointing to a potential initiating role of *BRAF* in melanocyte transformation [20]. *BRAF* mutations are more common in intermittently UV-exposed skin compared with chronically sun exposed skin or relatively unexposed skin (eg, acral sites, mucosal sites), which more frequently demonstrate *KIT* mutations. Acral and mucosal melanomas have infrequent *BRAF* mutations, and show greater numbers of chromosomal aberrations. There can also be frequent gains in *CCND1* and regions of chromosome 22, and losses from chromosome 4q. *Curtin* et al. demonstrated that melanomas arising on skin without

chronic sun-induced damage had frequent mutations in *BRAF* and frequent losses of chromosome 10, whereas melanomas on skin with chronic sun-induced damage had infrequent mutations in *BRAF* and frequent increases in the number of copies of the *CCND1* gene [21]. *Omholt* et al. demonstrated that *BRAF* mutations occur at an early stage during melanoma pathogenesis rather than being associated with metastasis initiation. Although the *BRAF* mutations do not seem to be important for metastasis initiation, the finding that they are preserved throughout tumor progression suggests that they may still influence tumor maintenance [19]. Although *BRAF* mutations are highly prevalent (59%) in melanomas occurring on skin without chronic sun damage, *BRAF* mutations are significantly less frequent in acral and mucosal melanomas. *BRAF* mutations are more commonly detected in superficial spreading melanomas and melanomas that arise on nonchronically sun-damaged skin [5].

The two recognized major melanoma susceptibility genes, *CDKN2A,* located on chromosome 9p21.3, and *CDK4* both, are involved in controlling cell division. *CDKN2A* mutations are found in approximately 20% of tested melanoma families, while *CDK4* mutations have been found to date in only a few families. *CDKN2A* encodes for two gene products, p^{14ARF} (alternative reading frame) and p16 (also known as INK4A, inhibitor of kinase 4a), which regulate cell cycle entry at the G1 checkpoint and stabilize p53 expression [18, 22, 23]. When defective, p16 is unable to inactivate CDK4 and CDK6, which phosphorylate Rb, releasing the transcription factor E2F and leading to cell cycle progression [8].

The *PTEN* gene, located on chromosome 10, encodes a tumor suppressor protein and has also gained considerable attention as the understanding of melanoma pathogenesis has increased [24]. The negative regulation of cell interactions with the extracellular matrix could be the way PTEN phosphatase acts as a tumor suppressor. PTEN gene plays an essential role in human development. Mutations in *PTEN* are found in 10%-20% of primary melanomas and have also been associated with thyroid, breast, and prostate cancer [5,25]. *PTEN* encodes a negative regulator of extracellular growth signals that are transmitted via the phosphatidylinositol-3-kinase (PI3K)-AKT pathway [14]. Inactivation of *PTEN* allows signaling through the AKT pathway, which contributes to aberrant cell growth and escape from apoptosis [5].

3. Epidemiology

Generally, an individual's risk for developing melanoma depends on two groups of factors; intrinsic and extrinsic that is environmental. "Intrinsic" factors are generally an individual's family history and inherited genotype, while the most relevant environmental factor is sun exposure. Epidemiologic studies suggest that exposure to ultraviolet radiation (UVA and UVB) is one of the major contributors to the development of melanoma. UV radiation causes damage to the DNA of cells, typically thymine dimerization, which when unrepaired can create mutations in the cell's genes. When the cell divides, these mutations are propagated to new generations of cells. If the mutations occur in protooncogenes or tumor suppressor genes, the rate of mitosis in the mutation-bearing cells can become uncontrolled, leading to the formation of a tumor [26].

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Cutaneous malignant melanoma is the most serious form of skin cancer. In general, cutaneous melanoma most commonly affects adult Caucasians and is rarely observed before puberty. Melanoma may occur at any age, although children younger than age 10 years rarely develop a de novo melanoma. It was reported that in 2002 there were 53.600 new cases, and 7.400 deaths from cutaneous malignant melanoma in the United States. The incidence rate of MM has increased 4% per year since 1973 [27]. This epidemic of MM is also evident in other parts of the industrialized world, including Australia and southern Europe. It is predicted that the incidence of MM will continue to increase as a result of the continuing decrease in the concentration of stratospheric ozone and increasing leisure time for sunlight-related recreation, including sunbathing, which increases exposure to solar UV radiation [28].

3.1. Environmental factors

Sunlight and most particularly the ultraviolet spectrum of sunlight is the only environmental factor that has been compellingly implicated as a cause of melanoma [29].

Possible significant elements in determining risk include the intensity and duration of sun exposure, the age at which sun exposure occurs, and the degree of skin pigmentation. Exposure during childhood is a more important risk factor than exposure in adulthood [30, 31].

Individuals with blistering or peeling sunburns (especially in the first twenty years of life) have a significantly greater risk for melanoma. This does not mean that sunburn is the cause of melanoma. Instead it is merely statistically correlated [32].

Fair and red-headed people, individuals with multiple atypical nevi or dysplastic nevi and people born with giant congenital melanocytic nevi are at increased risk [33]. Melanoma incidence is 10–20-fold higher among the fair-skinned than the dark-skinned people. Among fair-skinned people, melanoma incidence generally increases with proximity to the equator (some exceptions occur, particularly in continental Europe, where the association is confounded by pigmentation). Fair-skinned migrants from high- (e.g. the UK) to low-latitude countries (e.g. Australia) have lower melanoma rates than native-born residents, and vice versa [29].

History of melanoma in melanoma-prone families due to mutations in some genes were found to greatly increase the risk of a person. (e.g. CDKN2A and CDK4). Patients with a history of melanoma are at risk of developing a second primary tumor [34, 35].

Looking at the geographical distribution of the incidence of malignant melanoma in Europe has increased in Northern Europe, especially Scandinavian countries (20.7 per 100.000 person-year). Incidence rates were lowest in Southern and Eastern Europe for both males and females, with rates between 5-10 per 100.000 person-year. mortality rates in studies conducted in Europe (5.1 per 100 000 person-years ranging from 2.5) was found to be different in a lot less. Death rates lower in women than men had been established. In the 1990s compared the incidence and mortality rates in southern and eastern Europe, northern and western Europes have been identified as the highest and lowest [36].

Between the years 1970-2009, a study conducted among young adults in the United States the incidence of cutaneous melanoma is increasing rapidly, especially among women. This high-

risk population should be closely monitored constantly [37]. The incidence may be higher due to melanoma underreporting to cancer registries, particularly for tumors that are diagnosed and managed in the outpatient setting [38].

While melanoma accounts for roughly 4% of all skin cancers, it causes more than 75% of skin cancer deaths. Treatment of melanoma in its early stages provides the best opportunity for cure. In the United States, an estimated approximately 9.000 deaths will occur in 2012. Melanoma incidence has continued to increase worldwide, with the highest incidence in Australia and New Zealand. The most recent analysis of global cancer statistics for melanoma, from 2002, demonstrated a prevalence of 37.7 cases per 100.000 men and 29.4 cases per 100.000 women in Australia and New Zealand, compared with 6.4 cases per 100,000 men and 11.7 cases per 100.000 women in North America [39].

Differing melanoma incidence between males and females, and the tendency for females to develop excess melanin pigmentation during periods of hormonal stimulation such as pregnancy, has led to a number of studies investigating the role of pregnancy, oral contraceptives and hormone replacement therapy both as risk factors for melanoma and also as events that may affect prognosis. Cumulative data from publications on these topics provide no evidence that prior pregnancy is a risk factor for melanoma. Similarly, there is no evidence to indicate that oral contraceptive or hormone replacement use contributes to melanoma risk, nor that either factor alters the prognosis for those in whom melanoma has already been diagnosed [40, 41].

3.2. Occupation and melanoma

Airline crews, particularly pilots, have been recorded in a number of studies as having a higher-than-expected incidence of melanoma. It is suggested that this may be due to greater opportunities for recreational sun exposure during regulation breaks between flights in areas of the world with a high solar exposure [42].

A number of publications show conflicting results concerning the risk of melanoma developing after renal transplantation and the necessary immunosuppression. Studies from Sweden and the Netherlands show no increase in melanoma incidence over that expected in these countries [43], while studies from the USA and UK show a significantly increased risk, 3.6- and 8-fold higher for USA and UK patients, respectively. While some of these differences may relate to time frames of studies and changes in immunosuppressive regimes over time, further large long-term contemporary studies are required to determine the degree of increased cutaneous surveillance required for transplant patients [44].

3.3. Pesticide exposure

A case–control study comparing melanoma on the palms and soles in both the UK and Australia observed that melanoma patients reported greater exposure to pesticides than that reported by controls, and recently, an Italian case–control study has confirmed higher use of pesticides in a residential setting in melanoma patients compared with that in controls. Interpretation of these data is complex, as over the past decade there have been many regula-

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tory changes in *Europe* regarding the range of pesticides available for domestic use. However, data from these studies indicate that questions regarding the type and frequency of pesticide use should be added to future case–control studies [43, 44].

3.4. Genetic factors

Xeroderma pigmentosum (XPD) is a genetic disorder with a mutation of the XPD gene leading to nucleotide excision repair defects. Patients experience 1000-fold greater risk of melanoma as they are unable to repair UV-induced DNA damage. The relative ability to repair DNA modifies the risk in the presence of other host factors such as age, poor tanning ability and dysplastic naevi. Two polymorphisms of the XPD gene are associated with a decreased risk of melanoma among women with five or more severe sunburns or high cumulative sun exposure.

Mutations of the melanocortin-1 receptor gene variants are more common among fair-skinned and red-haired people. Polymorphism of this gene is associated with melanoma. The risky factors are the phenotype of pigmentation of the individual, the presence of atypical naevi, >50 melanocytic naevi, high recreational and occupational sun exposures [45]. People with a past history of other types of skin cancer (basal cell carcinomas and squamous cell carcinomas) caused by high doses of solar UV radiation have threefold higher risks of melanoma than the average population [46].

3.5. Artificial light

Several forms of artificial light have been associated with the development of melanoma in some studies: fluorescent lighting and suntan beds and parlors. Although exposure to fluorescent lighting was hypothesized to increase risk for developing melanoma, there have been no studies to support this idea. On the other hand, the use of tanning lamps and tanning parlors may increase risk for melanoma [47, 48].

3.6. Female sex hormones and melanoma

Differing melanoma incidence between males and females, and the tendency for females to develop excess melanin pigmentation during periods of hormonal stimulation like pregnancy, have led to a number of studies investigating the role of pregnancy, oral contraceptives and hormone replacement therapy both as risk factors for melanoma and also as events that may affect prognosis. Cumulative data from publications on these topics provide no evidence that prior pregnancy is a risk factor for melanoma. Similarly, there is no evidence to indicate that oral contraceptive or hormone replacement use contributes to melanoma risk, nor that either factor alters the prognosis for those in whom melanoma has already been diagnosed [41, 49, 50].

4. Clinical presentation

The most common sites that melanomas are found include the trunk (back) followed by the upper extremities, and head and neck for men; and the lower extremities followed by the back,

upper extremities, and head and neck for women. Amelanotic melanoma and those resembling keratoses are particularly difficult to diagnose without a high index of suspicion. Acral melanoma is the most frequent form of melanoma among Asians, Africans, and other ethnic groups of color. Subungual melanoma (SM) is a distinctive variant of acral melanoma that most often involves the nail bed of the great toe or thumb. Clinical types include;

4.1. Lentigo malign melanoma

Lentigo maligna melanoma is one of the 4 main subtypes of invasive melanoma and constitutes 10 to 15% of cutaneous melanomas. Generally, patients with lentigo maligna are older than 40 years, with a mean age of 65 years. The peak incidence occurs in the seventh to eighth decades of life [51]. The incidence of lentigo maligna subtypes (in situ and invasive) appears to be rising in the United States [52].

Sir *John Hutchinson* first described lentigo maligna in 1890; the disease continues to be called *Hutchinson* melanotic freckle on occasion. The lesion has subsequently been characterized as malignant lentigo of elderly people, junctional nevus, and melanoma in situ. Most authors currently refer to it as lentigo maligna when it is confined to the epidermis and lentigo maligna melanoma when it violates the dermis [39].

Lentigo maligna melanoma has evolved from a lentigo maligna.They are usually found on chronically sun damaged skin such as the face and the forearms of the elderly people. The risk increases as the number of years spent in sunny districts increases, as well as with increased hours of exposure to sunlight. The incidence of melanoma is highest in Australia, where lentigo maligna accounts for 10-15% of all melanomas. Approximately 10-30% of all cutaneous melanoma arise in head and neck regions. The other risk factors for lentigo malign melanoma are large or giant congenital naevi, fair skin and history of severe sunburn [53].

Many authors consider lentigo maligna to be a preinvasive lesion induced by long-term cumulative ultraviolet injury. Conceptually, the term melanoma is used when atypical melanocytes invade the rich vascular and lymphatic networks of the dermis, thereby establishing metastatic potential [12, 51, 53].

Most malignant melanomas arise as superficial tumors confined to the epidermis, which is often known as horizontal growth. At some point, a stepwise accumulation of genetic abnormalities leads to proliferation and progression to the vertical growth phase, which leads to dermal and deeper involvement and subsequently nodal metastases [54].

Initially the lentigo maligna is a flat, brown or black, irregularly shaped lesion. These lesions will grow very slowly, over months or years, and there may be central regression while the peripheral margin continues to extend. In time, a raised central nodule will develop, indicating transition to the vertical growth phase [12, 51, 53, 54].

Differantial diagnosis of lentigo malign melanom are solar lentigo, pigmented actinic keratosis, seborrheic keratosis, common acquired nevi and dysplastic nevi [12].

Lentigo maligna is basically in situ melanoma and is characterized by epidermal atrophy, extensive solar, lentiginous, and back-to-back proliferation of melanoma cells. Only 5% of

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patients with lentigo maligna progress to lentigo maligna melanoma, and it usually takes several years. Several methods of therapy can be used to treat lentigo maligna including cryotherapy, superficial radiation therapy, and surgical excision with mapping and modified *Mohs* surgery [55, 56].

Some imaging methods before proceeding to the treatment of lentigo maligna melanoma can be made. Especially, in patients with suspected metastatic disease, PET scan, CT scan and MR can be made to detect lymph node and internal organ metastases [57].

The treatment of the melanoma is as for other sites in that the margin of excision for tumours thinner than 2 mm is 1 cm minimum and for thicker tumours should be 2 to 3 cm. It is recognized, however, that on the face these margins may not be attainable without unacceptable cosmetic deficit. The surgery is also subject to the same constraints as described above for lentigo maligna, in that there is a high local recurrence rate of the in situ component [12, 58].

4.2. Superficial spreading melanoma

Superficial spreading melanoma is the most common type of cutaneous melanoma. It accounts for nearly 70% of cutaneous melanoma. The mean age at diagnosis is in the fifth decade. The commonest sites are the female leg and the male back (Figure 1), but every site may be affected [12].

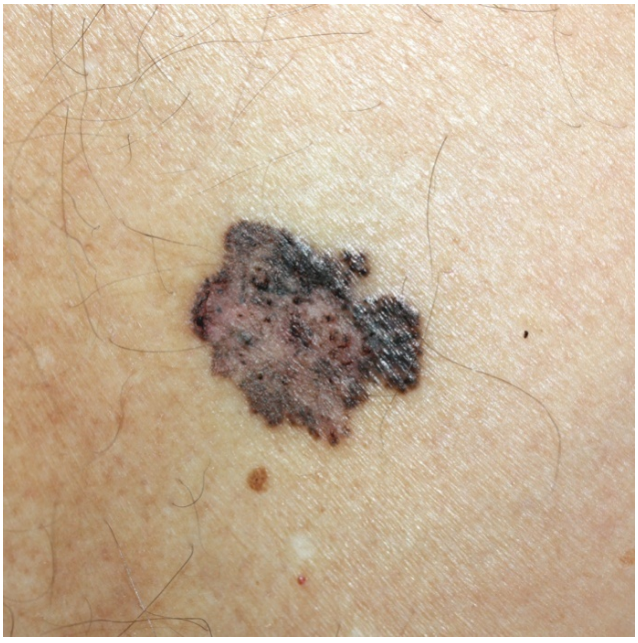

Figure 1. Superficial spreading melanoma with characteristic asymmetry, irregular borders.

Superficial spreading melanoma occurs in two phases: At first, superficial spreading melanoma grows horizontally on the skin surface (radial growth phase). The lesion constitutes as a slowly-enlarging flat area of discoloured skin. At second, superficial spreading melanoma becomes invasive, the melanoma cells cross the basal membrane of the epidermis. A rapidly-growing nodular melanoma can start to proliferate more deeply within the skin [59].

The main risk factors for superficial spreading melanoma are: age, previous invasive melanoma or melanoma in situ, nonmelanoma skin cancer, many melanocytic moles, multiple atypical naevi, family history of melanoma, fair skin and sun damage. Other risk factors include blue or green eyes and red or blond hair [60, 61].

Superficial spreading melanoma presents as a slowly growing or changing flat patch of discoloured skin. At first, it often resembles a mole or freckle. It becomes more distinctive in time, often growing over months to years or even decades before it is detected. Like other flat forms of cutaneous melanoma, it can be detected by the ABCDE rule: Asymmetry, border irregularity, colour variation, large diameter and evolving [51].

The characteristics of superficial spreading melanoma are larger size, irregular shape, variable pigmentation (colours may include light brown, dark brown, black, blue, grey) and irregular surface. It is generally greater than 6 mm in diameter. Irregular asymmetric borders are characteristic [12, 51, 59, 60].

Dermoscopy can be very helpful in distinguishing superficial spreading melanoma from other skin lesions, such as melanocytic naevi, solar lentigines, seborrhoeic keratoses and pigmented basal cell carcinoma (Figure 2) [62].

The initial treatment of a primary melanoma is to cut it out; the lesion should be completely excised with a 2-3 cm margin of normal tissue. Further treatment depends mainly on the *Breslow* thickness of the lesion. After initial excisional biopsy; the radial excision margins are measured clinically from the edge of the melanoma. Occasionally, the pathologist will report incomplete excision of the melanoma, despite wide margins. This means further surgery or radiotherapy will be recommended to ensure the tumour has been completely removed [12].

4.3. Acral lentiginous melanoma

Acral lentiginous melanoma (ALM) is a rare variant occuring exclusively on the sole, with the palm and subungual locations [7, 63]. Subungual melanomas often are mistaken for subungual hematomas (splinter hemorrhages). Subungual melanoma may show itself as a longitudinal pigmented band (melanonychia striata) within the nail plate. This variant of melanoma may also affect the oral and nasal mucosa and involve the anogenital area [64]. This is the least common subtype of melanoma in white people (2-8% of melanoma cases). It is the most common subtype of melanoma in dark skinned patients (ie, Afro-American, Asian, and Hispanic people), representing 29-72% of melanoma cases [65, 66]. Not all palmo-plantar melanomas are ALMs; a minority are superficial spreading or nodular melanomas [7]. ALM shows typically as an asymmetric, brown to black macule with variegations in colour and irregular borders [67]. They usually arise from the nail matrix or, less often, from the nail bed

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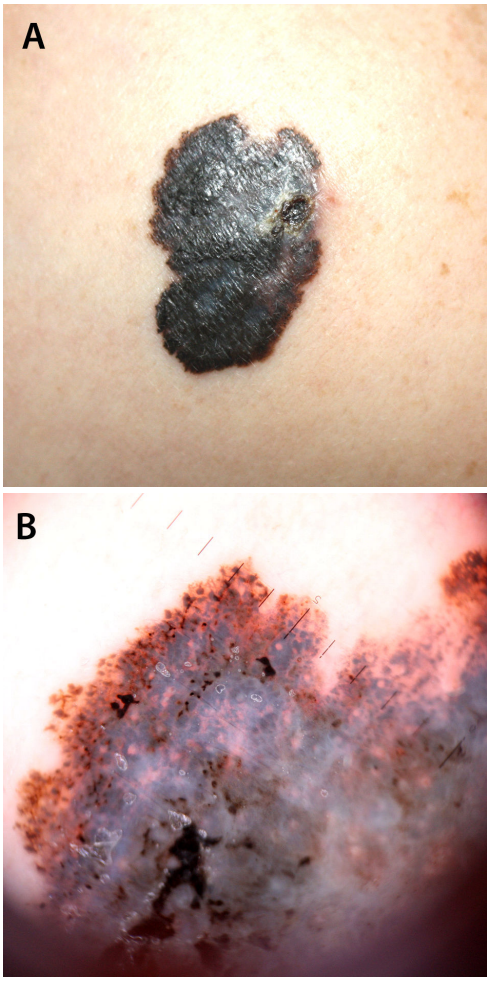

Figure 2. Macroscopic view of a superficial spreading melanoma (A), dermoscopic view characterized by blue-white veil (B).

or nail fold. ALM is similar to lentigo maligna melanoma in that an irregular pigmented macule is present for a long time [68].

Although the pathogenesis of ALM remains unknown, it has been theorized that the more intense and chronic trauma experienced in acral locations may be a predisposing factor [69].

ALM has key demographic and life-style differences to differentiate ALM from other melanoma subtypes: it occurs in an older patient population, and is associated with a lower number of common and atypical nevi, a lower incidence of familial melanoma, and a lower incidence of sunburn but a higher personal and family history of noncutaneous cancers [69].

There is often a delay in the diagnosis of ALM.The presence of invasion can be deceptive and may be present in entirely flat lesions [63]. The clinical differential diagnosis of ALM include a planter wart, which is common reason of delayed diagnosis, black heel (talon noir), lentigines, melanocytic nevi, tinea nigra, traumatic haemorrhage and tattoos such as by silver nitrate. Any growing, tender nodule, or an "ulcer" won't heal, on the sole of the foot, should give rise to concern that the lesion is a melanoma and biopsy should be considered [12, 70].

4.4. Subungual melanoma

Subungual melanoma, considered a variant of ALM, generally arises from the nail matrix. They are the most common on the thumb or great toe. It may manifest as diffuse nail discoloration, a longitidunal pigmented band (melanonychia striata) within the nail plate or growth in the nail bed. Furthermore, 20% of subungual malignant melanomas may present with amelanocytic lesions rather than melanonychia [7, 71].

Pigment spread to the proximal or lateral nail folds is termed the *Hutchinson* sign, which is a hallmark for subungual melanoma. Benign lesions that can mimic subungual melanoma include longitidunal melanonychia (Figure 3), subungual hematoma, pyogenic granuloma or even onychomycosis with pigmentation or hemorrhage [7]. Nonresponsiveness to antifungal drugs should prompt more thorough evaluation, including potential biopsy. Subungual melanomas are most commonly confused with traumatic hemorrhage. This process is persistent, often lasting for more than 1 year, but in contrast to melanoma the dark area moves forward with the nail plate, leaving a normal appearing proximal component. Moreover, melanoma usually shows distal tapering, with the proximal portion being wider. The possibility of melanoma should be considered for all pigmented nail bands in fair-skinned patients, especially if they are darkly pigmented and/or have a width >3mm [67]. If any pigmented lesion of the nail unit that is strongly suspected of being melanoma, an excisional or incisional biopsy of the affected area that includes nail matrix should be performed [70].

Overall 5 year survival is disproportionately poor (25-51%) compared to other histological subtypes [71].

4.5. Nodular melanoma

Nodular melanoma (NM) is the second most common subtype after superficial spreading melanoma and accounts for approximately 15% to 30% of all melanomas. It is diagnosed most frequently in patients in their sixth decade of life [63, 67]. NM tends to affect men more than women. The most common locations are head, neck, the trunk in men (Figure 4) and legs in women [70].

NM clinically lacks an apparent radial growth phase. It is more common for NM to begin de novo than to arise in a pre-existing nevus. Typically, it presents as a black or blue-black nodule, but 5 percent are amelanotic and often misdiagnosed clinically. Thus, any rapidly growing flesh-colored lesion that persists after 1 month or ulcerates or bleeds should prompt medical evaluation [7].

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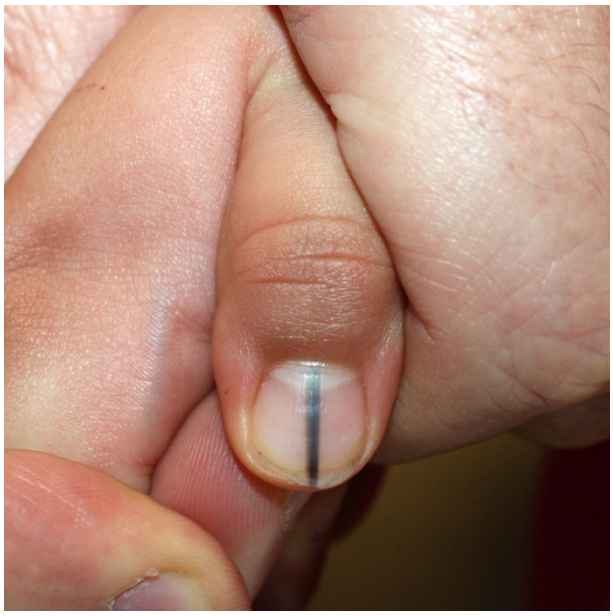

Figure 3. Longitidunal melanonychia: longitudinal pigmented band within the nail plate.

It tends to lack the typical ABCDE melanoma warning signs and thus, may elude early detection. Histologically, it is believed to lack a preceding radial or in situ growth phase. The prognosis of NM is generally worse than other forms of melanoma because there is involvement of the dermis and the lesion is in the "vertical growth phase" at the time of diagnosis.

The clinical differential diagnosis includes hemangioma, pyogenic granuloma, blue nevi, dermatofibroma, pigmented basal cell carcinoma, as well as other cutaneous neoplasms (Figure 5). As a general rule, a firm papule or nodule should never be subjected to any form of monitoring-biopsy if the diagnosis is in doubt [63, 70].

4.6. Mucosal melanoma

Mucosal melanoma is a rare cancer that is clearly distinct from its cutaneous counterpart in biology, clinical course, and prognosis. It accounts for 1.3%-1.4% of all melanomas; that they tend to occur near the mucocutaneous junctions of squamous and columnar epithelia. The most common sites are the head and neck region (conjuctival, intranasal, sinus and oral cavities), vulva, anorectal, or even urethral melanoma. Activating mutations in the c-KIT gene are detected in a significant number of patients with mucosal melanoma [72].

Sun exposure does not play a role in the pathogenesis of these lesions. Irritants and carcinogenic compounds in the air, such as tobacco smoke and formaldehyde, have been implicated in the devolepment of head and neck melanoma, the potential role of these compounds is not clear. The most common presenting trait of mucosal melanoma is the presence of extensive,

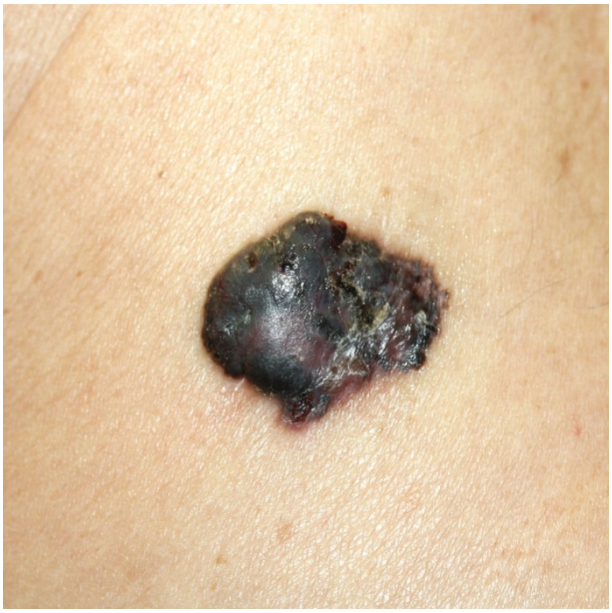

Figure 4. Nodular melanoma manifests as a dark brown-to-black dome-shaped nodule.

irreguler macular pigmentation. Most mucosal melanomas are lentiginous (mucosal lentiginous melanoma), followed in incidence by superficial spreading and nodular types.

Because of its hidden location and rich vascularization, mucosal melanoma usually presents at a more advanced stage and is therefore associated with a higher mortality rate than cutaneous melanoma [7, 12, 73].

4.7. Childhood melanomas

Childhood melanoma is very rare, particularly before puberty. Approximately 1% to 4% occur in patients younger than 20 years of age, and only 0.3 to 0.4% occur in pubertal children. After puberty the incidence of melanoma starts to rise slowly.

As in adults, childhood melanomas mainly affect the white population. Previous surveys have shown slight female predominance of melanoma in children. The most common primary tumor sites are the extremities, followed by trunk. Location in head and neck and trunk has been related to poor prognosis. The risk factors for melanoma in children are parallel those in adults. There are three known predispositions in childhood melanoma: congenital naevi, the atypical mole syndrome, familial melanoma and other family cancer syndromes such as xeroderma pigmentosum and retinoblastoma. Increasing age, UV exposure, and *Caucasian* background were also found to be important in pediatric melanoma.

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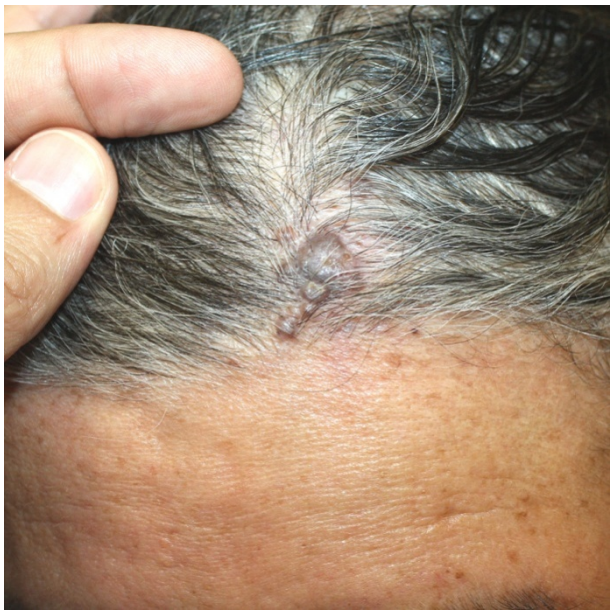

Figure 5. Nodular melanoma must be differentiated from pyogenic granuloma, blue nevi, and pigmented basal cell carcinoma.

Histologically, childhood melanomas may resemble those of adults, but small cell melanomas and melanomas with features of *Spitz* nevus are reported to be more common in this age group. The differentiation of melanoma from Spitz nevi with atypical features remains a major challenge for physicians.

Congenital melanoma is extremely rare; most melanomas in children are acquired after birth. In addition, a mother with visceral metastases can transfer tumor cells transplacentally, giving birth to a newborn with disseminated metastases.

Although, it seems that pediatric patients with melanoma may have a better prognosis than adults showing the same type of lesions, a number of children will still develop metastasis and die of their disease, especially when melanoma is diagnosed after puberty. Treatment follows the same rationale as in adults, with the aim of early detection and appropriate resection of the primary melanoma [12, 67, 68, 74, 75].

4.8. Unusual variants of melanoma

4.8.1. Desmoplastic-neurotropic melanoma

Desmoplastic melanoma (DM) is a rare sub-type melanoma that provokes a scar-like tissue reaction and is frequently associated with neurotropism. It makes up <1% of all melanomas. It is most commonly develops in older persons and has a male predominance 2:1. The head

and neck are the most frequently involved sites, although lesions may develop on the trunk and extremities, palate, gingiva, lip, vulva, anus, and conjunctiva. DMs usually arise on the skin that has been severely damaged by long-standing sun exposure, although they have been reported to develop on skin damaged by ionizing radiation and in burn scars [63, 70, 76-78].

Its clinical features are similar to nonmelanoma (keratinocytic) skin cancer. It may occur in association with macular, lentigo maligna-type pigmentation, or it may present de novo as a firm, amelanotic nodule or scar. Fifty percent of the time it is amelanotic and may be mistaken for something as innocent as a scar. In the other 50% of cases it is associated with an overlying lentigo maligna or superficial spreading melanoma [64, 78]. Lack of pigmentation and clinical features more suggestive of keratinocytic skin cancer may result in delay in detection and thicker tumors at diagnosis [39].

Histologically, the tumor is composed of collections of spindle cells diffusely infiltrating the dermis and often the subcutis, associated with abundant stromal collagen. Many DMs are deeply invasive at diagnosis and have a tendency to infiltrate perineurally, otherwise called neurotropic melanoma. Neurotropism is related to increase the frequency of local recurrences. Also, it seems that neurotropism is associated with a signifiant decrease in survival in patients with DM. Occasionally, there are some lesions with prominent perineural invasion and no evidence of an intraepidermal component. These lesions are designated neurotropic melanoma. This seen particularly in lesions on the head and neck area, and may cause severe, relentless pain. In the recent studies, the percentage of desmoplastic melanomas with neurotropism ranged from 16.7 to 77.8% [7, 79].

The clinical differential diagnosis is broad, because these lesions often do not have features that suggest melanoma. Some of the clinical diagnoses that may be rendered include, scar, basal cell carcinoma, squamous cell carcinoma, fibroma, recurrent nevus, and metastatic carcinoma. Deep tissue samples are necessary to establish the diagnosis. The use of immunochemistry (testing for S100 antigen) is suggested as a useful tool in establishing the diagnosis. This sub-type of melanoma usually lacks any valuable dermoscopic features [12, 76-78].

Local recurrence is common, in 22% to 70% of cases, largely because of the tendency of DM to exhibit neurotropism. Although deeply invasive, DM is associated with lower metastatic rates than other sub-types of melanoma when matched for depth of invasion. When they metastasize, these tumors, unlike most melanomas may by-pass regional lymph nodes and spread hematogenously [7, 64, 70].

4.8.2. Angiotropic melanoma

Angiotropic melanoma is defined by cuffing of (close apposition to) the external surfaces of either blood microvessels or lymphatic channels by melanoma cells in a pericytic location without evidence of intravasation in at least two or more foci. Angiotropic metastasis is not synonymous with vascular invasion. The mechanism of angiotropism of melanoma is not clear. There may be a special affinity between the tumor cells and the vascular wall. Angiotropism is seen with greater frequency in melanomas also showing desmoplasia and neurotropism.

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Angiotropism has been suggested to be a prognostic factor strongly predicting risk for metastasis of melanoma [77, 80].

4.8.3. Nevoid melanoma

Nevoid melanoma describes a heterogeneous grup of rare lesions that they may resemble a *Spitz* nevus or an acquired or congenital melanocytic nevus. Nevoid melanoma equally affects women and men and the mean age of diagnosis is 47 years. It occurs anywhere, but lower extremities and trunk are preferential sites. Clinically, this may correspond to a tan nodule typically greater than 1 cm in size, located on the trunk or proximal limbs of a young adult.

Histologically, the architectural pattern appears very similar to that of a compound or intradermal nevus with an overall symmetry, well-defined lateral margins, minimal or no intraepidermal pagetoid spread. Histological features mentioning melanoma include the absence of maturation of dermal tumor cells, slight cytological atypia with some mitoses in the dermal component [77, 78].

The differential diagnosis includes *Spitz* nevus, congenital melanocytic nevus, minimal-deviation melanoma, nodular melanoma and melanoma arising in a dermal nevus. Although only one study has reported a better biological behavior for this lesion, there is no evidence that nevoid melanoma has a better prognosis than ordinary melanoma [77, 78, 81].

4.8.4. Verrucous melanoma

Clinically, verrucous melanomas are usually small hyperkeratotic papules without areas of regression and mimic either a verruca, seborrheic keratosis, or a compound or congenital naevus. Some studies reported a greater frequency on the extremities of women, but this has not been confirmed. The back of men also frequently is involved. Histologically, the verrucous component is represented by marked epithelial hyperplasia. It has the same prognosis as conventional melanoma [68, 77, 82].

4.8.5. Small cell melanoma

Small cell melanoma describes a heterogeneous group of melanomas arising in different settings whose common denominator is a population of small cells. A first type, developing particularly in adults, is comprised of small cells with roundish, hyperchromatic nuclei, slight cytoplasm, and numerous mitoses resembling *Merkel*'s cells. A second variant of small cell melanoma has been described arising de novo in children and adolescent on the scalp or developing in a congenital nevus. A third type of small cell melanoma has been described in sun-damaged skin of old patients in the setting of solar melanocytic neoplasia or atypical lentiginous nevi.

A recent report suggested that a small-cell morphology in melanomas is significantly associated with positive sentinel lymph node involvement. Melanomas manifesting this morphology are invariably in vertical growth phase and have an aggressive course [77, 78, 83].

4.8.6. Spitzoid melanoma

Spitzoid melanoma is a rare sub-type of melanoma that resembles clinically and histologically a *Spitz* nevus. But it tends to be larger and have asymmetry and irregular coloration. It can occur in children but are more common in adults. Clinically, spitzoid melanomas are changing nodular lesions, often reaching 1 cm or more in diameter. The nodules are usually amelanotic. They can mimic hemangiomas, pyogenic granulomas, xanthogranulomas, or basal cell carcinomas. Less often, the lesions are pigmented and variegated in color. Nodular lesions can be crusted and ulcerated. The head and extremities are common sites.

Some spitzoid melanomas can evolve from a preexisting *Spitz* nevus, whereas other spitzoid melanomas can develop *de novo*. Differentiation between two of them is sometimes very difficult, especially in younger patients. The presence of mitoses, the nuclear and nucleolar pleomorphism of the cells, the asymmetric distribution of the pigment, and an inflammatory infiltrate with irregular disposition should prompt us to spitzoid melanoma.

The prognosis of spitzoid melanoma in adults is the same as that for other variants of melanoma of equal *Breslow* thickness [7, 77, 84].

4.8.7. Balloon cell melanoma

Balloon cell malignant melanoma (BCMM) is the rarest histological type of primary cutaneous melanoma and is composed of large, polyhedral, foamy cells with abundant cytoplasmic vacuoles. Clinically, lesions appear as soft, rubbery, or firm nodules with a polypoid or papillomatous contour whose cut surfaces are grayish white or brown. The differential diagnosis includes balloon cell change in benign nevi including blue nevi and common acquired nevi, with which balloon cell melanoma may coexist, as well as other malignant clear cell neoplasms. The presence of cytological atypia, nuclear pleomorphism, and mitoses are important for its distinction from the more common balloon-cell nevus. The expression of the usual immunohistochemical markers such as S-100 protein and HMB-54 helps to distinguish this lesion from other clear cell tumors of the skin. The prognosis is similar to that of other types of melanoma matched for depth of invasion [70, 77, 78, 85].

4.8.8. Clear cell sarcoma: Melanoma of soft parts

Clear-cell sarcoma (CCS) is a perplexing tumor considered by some authors as a soft tissue sarcoma derived from the neural crest and by others as an unusual variant or subtype of melanoma. CCS shows a predilection for the deep soft tissues of the lower extremities close to the tendon, fascia, or aponeuroses. The tumor presents as a slowly growing deep-seated mass in close relation with tendons and aponeuroses associated with tenderness and pain. It generally appears in young adults between the ages of 20 and 40 years.

Histologically, the tumor has a multilobulated apperance made by nests and fascicles of uniform plump spindle cells seperated by fine to coarse fibrous septa. CCS is an aggressive neoplasm with a poor prognosis similar to that of sarcomas, with a high rate of local recurrences and metastases to lymph nodes and lungs. Both survival and distant metastases seem to correlate with the tumor size more than the histological parameters [12, 67, 77, 86].

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5. Differential diagnosis

Melanoma must be distinguished from a variety of several cutaneous and mucosal lesions. The differential diagnosis change according to the subtype of melanoma.

5.1. Superficial spreading melanoma

This is the most common type of melanoma. It is usually seen on sun-exposed areas, mostly on the lower extremities of women, and the upper back of men. Superficial spreading melanoma can present as an irregular macule with variation in color and texture. A papule or nodule may arise from the macule as the tumor progresses from radial to vertical growth. Superficial spreading melanoma can present de novo or within a preexisting nevus. Atypical nevus, melanocytic nevus, lentigo, seborrheic keratosis, *Spitz* nevus and superficial basal cell carcinoma must be distinguished from superficial spreading melanoma [87-89].

There are several features that can aid in distinguishing the common melanocytic nevus from melanoma. The "ABCD" rule, which has been expanded to the "ABCDE" rule, provides a helpful aid in the diagnosis of pigmented lesions:

A = Asymmetry

B = Border irregularity

C = Color variegation

D = Diameter greater than 6 mm/Difference

E = Elevation/Evolving

Atypical nevus may be misdiagnosed as melanoma because of focal or minimal pagetoid spread, confluence of cellular aggregates along the dermal-epidermal junction, prominent variation in nesting pattern, significant cytologic atypia, entrapment of nests of dermal nevus cells in the papillary dermis, and dense mononuclear cell infiltrates. On occasion, the distinction of atypical nevus from melanoma is exceedingly difficult. The discrimination of melanoma from atypical nevus is usually possible because of the larger size, greater asymmetry, disorder, cellularity, and cytologic atypia encountered in melanoma. Usually atypical nevus will maintain an overall symmetry, a nevic appearance as exemplified by fairly organized junctional nesting, a basilar proliferation of melanocytes that is still concentrated along the epidermal rete and with greater density toward the lower poles of the rete [89-91]. Melanoma may mimic seborrheic keratoses but also may arise within the seborrheic keratosis. *Spitz* nevus is usually domeshaped but may be soft or hard, sessile or pedunculated. It is usually pink to red but may be brown. In contrast to melanoma, the patient can usually pinpoint the onset of the tumor. The nevus may persist but more commonly evolves into an intradermal melanocytic nevus. Histologically, the spindle and epithelioid nevi are characterized by a cellular uniformity, as opposed to the pleomorphism that characterizes malignancy. The development of an apparent spindle and epithelioid nevi after puberty should be regarded with concern. [7, 92, 93].

5.2. Nodular melanoma

Nodular melanoma is the second common subtype of melanoma. It is mostly seen on trunk. This type grows rapidly and enlarge. Instead of arising from the nevus, nodular melanoma begins de novo. Pigmented nodules may be mistaken with blue nevus, pigmented *Spitz* nevus, pigmented basal cell carcinoma, squamous cell carcinoma, metastatic melanoma, *Kaposi* sarcoma and angiosarcoma. Amelanotic nodules can be mistaken with basal cell carcinoma, hemangioma, pyogenic granuloma and *Merkel* cell carcinoma.

Metastatic melanoma is often fairly monomorphous with little stromal response while nodular melanoma are often polymorphous and exhibits greater stromal response.

The blue nevus is a dark blue or black, hairless, dome-shaped nodule, ranging in diameter from a few millimeters to several centimeters, but usually measuring about 5 mm. Its color results from the *Tyndall* light-scattering effect of light reflected from deeply placed dermal pigment through the colloidal medium of the dermis. It most commonly occurs on the head and neck, dorsum of the hands and feet, and buttocks [87, 94, 95].

The keratoacanthoma, in common with the spindle and epithelioid nevus of *Spitz*, may produce the sudden onset of a rapidly growing pigmented nodule, a presentation similar to that of nodular melanoma. Several vascular lesions, including pyogenic granuloma, thrombosed hemangioma, and capillary aneurysm may also produce similar findings.

Kaposi's sarcoma usually appears as multiple violaceous plaques or nodules on the lower extremity. Older tumors tend to assume a reddish brown hue, a pigmentation produced by extravasated red blood cells, and may regress as new ones appear. Ulceration and hemorrhage are frequently seen [96-98].

When there is a doubt in clinically; dermoscopic images and histopathological examination must be done and the exact decision must be made by that.

5.3. Lentigo maligna and lentigo maligna melanoma

Lentigo maligna (LM) has a long radial growth phase that may progress to invasive lentigo malign melanoma. Some authors consider LM as in situ melanoma. Both subtypes are seen in older population. The most common locations are cheeks, nose, neck and scalp. It is related to cumulative sun exposure. Most cases presenting as LM remain in situ lesions; these lesions commonly occur in cosmetically sensitive areas on the head and neck and can abut critical anatomic sites, such as the eyelids, ears, nose, and lips [7, 87, 88]. In dermoscopic examination; hyperpigmented follicular opening, annular-granular pattern, pigmented rhomboidal structures, obliterated hair follicles are seen. Classical dermoscopic features of extrafacial melanoma (atypical pigment network, irregularly distributed globules, dots, streaks and pseudopods) and vertical growth phase-associated dermoscopic criteria (ulceration, blue papular areas and black structureless areas) can also be seen. [99-101].

Lentigo malign melanoma is confused with solar lentigo, ephelids, pigmented actinic keratosis, solar melanocytic hyperplasia, flat seborrheic keratosis and superficial pigmented basal cell carcinoma. Solar lentigines and its amount in excess are predisposed to LMM [7, 99]. Ephelids

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appear early in childhood. They darken in the summer in response to UV irradiation and lighten in the winter. LM develops irregularities of color, margins, and surface characteristics and enlarges progressively, unlike a common ephelid. Benign lentigines are usually tan to brown, flat, and oval, measuring 5 to 10 mm in diameter. Lentigines, whether benign or lentigo maligna, do not fade when shielded from light. Histologically, they are characterized by an increased number of normal dendritic melanocytes along the dermo-epidermal junction. The solar lentigo appears on sun-exposed surfaces during middle to late life, in common with lentigo maligna, and may closely resemble lentigo maligna [87, 94, 102].

5.4. Acral lentiginous melanoma

The frequency of this subtype in various ethnic groups is different from each other. ALM represents the most common type in darker-pigmented individuals (in blacks 60-72 %, in Asians 29-46 %). ALM is diagnosed in fifth or sixth decades. The most common sites for ALM are the soles, palms and subungual locations. Subungual melanoma may be first evident as a split nail, a swelling of part of the nail bed, an ulceration with a bloody crust, or a longitudinal black or brown streak in the nail bed. The great toe and thumb are most often affected. ALM may be confused with plantar wart, hematoma, palmoplantar nevus and pyogenic granuloma. Subungual melanoma must be differentiated from glomus tumor, hemorrhage, infection, onychomycosis, *Kaposi*'s sarcoma, *Bowen*'s disease, tinea nigra, melanosis and keratoacanthoma [103-106].

Acral lentiginous melanoma, the most common clinicohistologic type of acral melanoma, shares some histologic features with LMM but differs from LMM in its younger age at onset, its anatomic site, the absence of chronic sun exposure, and the greater depth of penetration at diagnosis [71].

The differential diagnosis for acral melanoma primarily includes lentigines and lentiginous melanocytic nevi of acral skin. Lentigines of acral skin usually do not exhibit the frequency of melanocytic proliferation or cytologic atypia that is typical of acral melanoma [7, 97].

5.5. Mucosal melanoma

Mucosal melanomas can arise on the head, neck, vulva, anorectal region and even urethra. With the exception of conjunctiva, patients present with delayed diagnosis. Because of a radial growth phase manifesting as a macular pigmentation any suspicious area in these locations must be biopsied. It can be mistaken with melanotic macules, amalgam tattoo, venous lake, *Kaposi*'s sarcoma, genital lentiginosis and atypical intraepidermal melanocytic proliferation [107-109].

Melanoma of the vulva is really mistaken with vulvar melanosis. Lesions of vulvar melanosis manifest irregular pigmentation with skip areas up to several centimeters in size, but the borders are regular and sharp. Histologically, vulvar melanosis manifests prominent basal layer keratinocytic pigmentation with either a normal or slightly increased density of cytologically basal melanocytes having prominent elongated dendrites. Pigmented *Bowen*'s disease manifests hyperkeratosis and comprises nested neoplastic keratinocytes containing melanin

granules. Oral mucosal melanoma usually presents as an irregular brown patch or mass on the oral mucosa extending to the gingival margins. Esophageal and nasal mucosal melanomas are occult and present with obstruction or bleeding [108].

5.6. Desmoplastic melanoma

This subtype is rare and locally aggressive. Commonly it arise in the sixth or seventh decades. The sun-exposed head and neck regions are most effected parts. The lesions have typically have a firm, sclerotic, or indurated. One half of these melanomas are amelanotic. Desmoplastic melanoma is usually diagnosed at an advanced stage, because of the difficulty of its diagnosis.

Sclerosing blue nevus, desmoplastic *Spitz* nevus, dermatofibroma, leiomyosarcoma, malignant fibrous histiocytoma, atypical fibroxanthoma, spindle cell squamous cell carcinoma and, neurothekeoma should be thought in differential diagnosis. The desmoplastic *Spitz* nevus has an inverted wedge-shaped pattern, manifesting an admixture of spindle cells with delicate elongated nuclei and ganglion like cells. Early desmoplastic melanoma shows a infiltrative pattern of growth in which large atypical hyperchromatic spindle cells deform the dermal architecture and invade the dermis of hair follicles. The neurotropism and foci of chronic inflamation that exist in desmoplastic melanoma usually are absent in *Spitz* nevus [110-112].

5.7. Nevoid melanoma

Nevoid melanoma describes a heterogeneous group of rare lesions that histologically resembles benign nevus by their symmetry and apparent maturation with descent in the dermis. Histopathologic features include marked hyperchromasia of the nuclei of tumor cells, the presence of mitoses, and an expansile growth of the dermal cells with effacement of the adventitia in affected area. It may be seen as a papule or nodule that is more than 1 cm in diameter. Minimal deviation melanoma, nodular melanoma, and melanoma arising in dermal nevus must be considered in the differential diagnosis [51, 87].

5.8. Dermoscopy

Dermoscopy, dermatoscopy, epiluminescence microscopy, diascopy, surface microscopy and incident light microscopy are all synonym. Dermoscopy is a noninvasive technique in which a handheld device is used to examine a lesion through a film of liquid, mainly immersion oil, using nonpolarized light, or the lesion is examined under polarized light without a contact medium. Digital dermoscopy permits computerized digital dermoscopic images to be retrieved and examined at a later date so that comparisons could be made and changes detected over time. Confocal scanning laser microscopy and multispectral digital dermatoscopy are new imaging instruments used for early detection of cutaneous melanomas. Dermoscopy improves sensitivity up to 30% and specificity of melanoma diagnosis compared with clinical diagnosis. Morphologic features which are invisible to the naked eye, could be seen with the help of this technique.

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Various diagnostic dermoscopic algorithms such as the ABCD rule, the seven-point checklist, pattern analysis, *Menzies* method, and CASH (color, architechture, symmetry, and homogeneity) have been developed for cutaneous melanoma.

Melanomas are multicolored in brown colors and other colors such as black, blue, and pink.

Usually a multicomponent pattern of three or more distinctive features can be seen. Atypical pigment network (Figure 6), irregular dots and globules, irregular streaks (pseudopods, radial streaming), irregular blotches, blue-white veil, abrupt cut-off of the trabeculae (Figure 7), regression structures (peppering), and atypical vascular architecture are common in invasive melanomas.

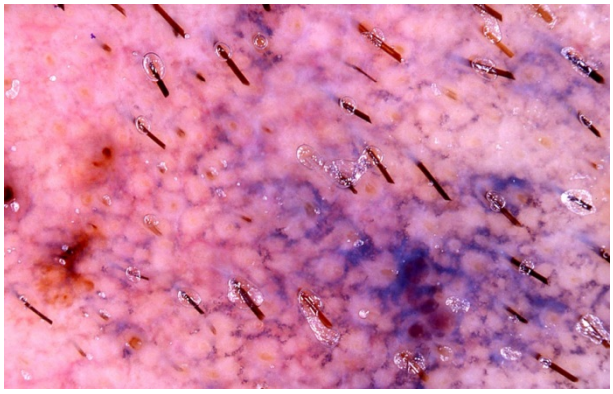

Figure 6. Irregular pigment network is seen (By the courtesy of Prof. Dr. Oya Oğuz).

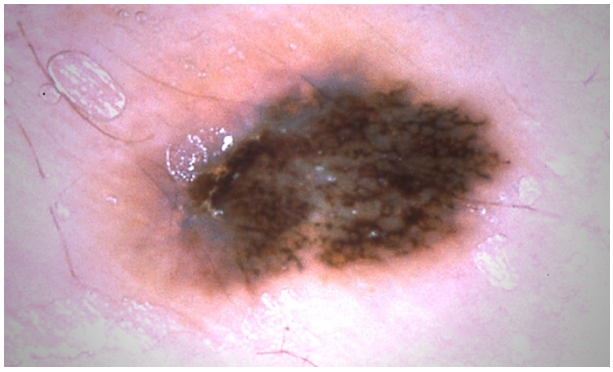

Figure 7. Notice the abrupt cut-off of the trabeculae (By the courtesy of Prof. Dr. Oya Oğuz).

Highly specific surface microscopic features of cutaneous malignant melanoma metastases are as follows: saccular pattern (red-blue, red-light brown, reddish-brownish-gray, blue-gray,

dark brown to black); gray streaks surrounding the lesion (melanoma cell infarcts); red-brown globules irregular in size and color; polymorphic angiectatic base pattern and/or aneurysms; areas of polymorphic ectatic vessels running parallel to the skin surface; peripheral erythema (red corona); microscopic ovoid blood lakes; and homogeneous pattern (brown or blue to black) [12, 51, 87].

6. Histopathological examination

Essentially all melanomas begin as a proliferation of melanocytes initially confined to the epidermis. Increasing cytologic atypia of melanocytes accompanies the aberrant architectural appearance of melanomas. After the period of intraepidermal proliferation, there is often invasion of the papillary dermis, primarily as single cells and small aggregates of cells. *Breslow* thickness (in mm) of melanoma is one of the most important factors determining prognosis and theraphy. Melanomas with prominent invasive components may display polypoid morphologies.

6.1. Lentigomaligna/ Lentigomaligna Melanoma (LM/LMM)

Lentigomaligna (known as *Hutchinson*'s melanotic freckle) which is the precursor lesion of LMM is characterized by reproduction of atypical melanocytes mainly present in the basal layer of the epidermis. Tumor cells contain polygonal-shaped, pleomorphic irregularly hyperchromatic, angulated nuclei (Figure 8). In approximately 85% of cases of LM, multi-nucleated melanocytes are seen in the basal layer. These cells are named as "starburst giant cell". The presence of atypical melanocytes in the hair follicles and sweat duct epithelium is a characteristic feature but sometimes it may lead to difficulties in evaluation of tumor thickness [109, 113, 114]. Also there is effacement of rete ridges [115]. Due to chronically actinic damage, epidermis is usually atrophic and solar elastosis is seen in the dermal layer [116]. The upper part of the dermis usually contains melanophages and lymphocytes to a lesser extent [114]. If the lesion progresses, pagetoid spread may be observed within the epidermis [109]. When invasion occurs into the dermis, spindled cells and tumor cell pigmentation can be seen [117].

6.2. Superficial spreading melanoma

Superficial spreading melanoma is also known as pagetoid melanoma which characterized by a proliferation of atypical melanocytes singly and in nests in all layers of the epidermis [114]. Atypical melanocytes sometimes show "buckshot scatter" within the epidermis (Figure 9) [113]. The large tumor cells contain dark, atypical nuclei and abundant, pale cytoplasm [118]. The epidermis may have normal or hyperplastic appearance [119]. There is a continuous spread of tumor growth from one rete ridge to another [114]. If the tumor progresses to vertical growth phase, microinvasive tumor which contains nested and dispersed cells is seen within the dermis [109].

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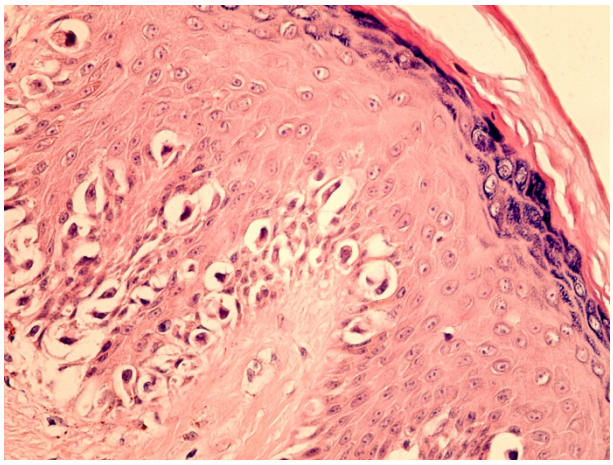

Figure 8. Lentigo maligna: in this in situ lesion, tumor cells are hyperchromatic and distributed in a lentiginous pattern (By the courtesy of Dr. Ahmet Cemil Kaur).

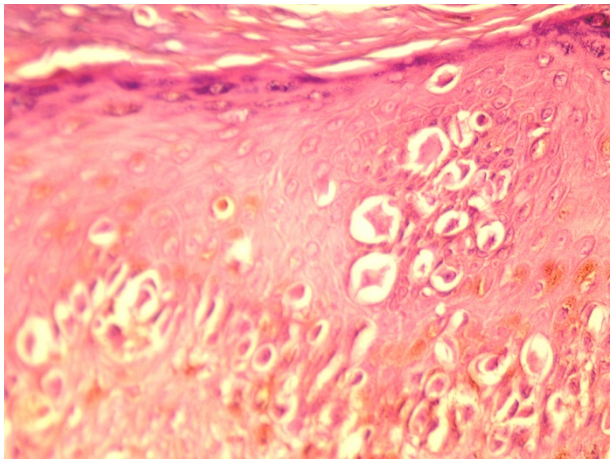

Figure 9. Superficial spreading melanoma: atypical melanocytes are scattered throughout the epidermis. Tumor cells compose cell groups at basal layer, The melanocytes have abundant eosinophilic cytoplasm and pleomorphic vesicular nuclei. Nucleoli are prominent (By the courtesy of Dr. Ahmet Cemil Kaur).

6.3. Nodular melanoma

Nodular melanoma has no concomitant or preexisting radial growth phase [109]. It grows vertically from the beginning and thus may invade the epidermis [113, 114]. Cellular features include a large nucleoli and frequent mitosis [118]. Epidermal melanocytic proliferation is so minimal which typically extending less than three epidermal ridges on both sides of tumor

[120]. The tumor mass contains small nests and aggregates of atypical melanocytes (Figure 10, 11, 12) [117].

6.4. Acral lentiginous melanoma

Histological changes are not fully clear in the early stages which may be seen irregular epidermal hyperplasia and dispersed, localized to the basal layer, atypical melanocytes [114]. Atypical cells proliferate as diffuse along to dermoepidermal junction in the radial growth phase. These cells create a lentiginous pattern by scattered severally [121]. Atypical melanocytes have marked nuclear atypia and also seen around the adnexal structures [109]. In contrast to acral nevi, pigment is seen throughout the stratum corneum [105]. Other changes in the epidermis include acanthosis and elongation of the rete ridges.Tumor infiltration of lymphocytes and tumor regression are common findings in ALM. Kim et al. observed that the frequencies of these findings are 75% and 25% of ALM cases, respectively [122]. The dermal invasive component is predominantly spindle cell type, but epitheloid or nevoid cells may be seen. The presence of small nevus cells may indicate a worse prognosis. Additionally lack of elastosis in dermis is prominent [105, 113, 123].

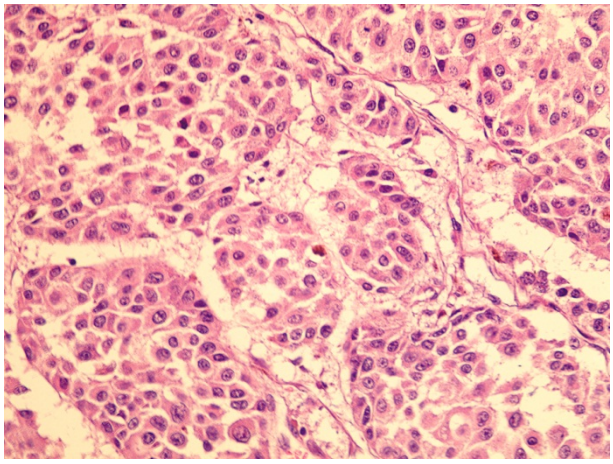

Figure 10. Nodular melanoma: characteristic melanoma morphology, the tumor is composed of cell groups (By the courtesy of Dr. Ahmet Cemil Kaur).

6.5. Desmoplastic melanoma

Desmoplastic melanoma is characterized by intensive atypical spindle-shape melanocytes within dense collagen bundles [124]. Tumor cells have hyperchromatic, elongated nuclei but usually no contain pigment in their cytoplasm [125, 126]. There are often nodular lymphocytic aggregates that are helpful in diagnosis [114, 127]. Perineural invasion has been reported in some studies. In a study by Lens et al., the percentage of desmoplastic melanoma with

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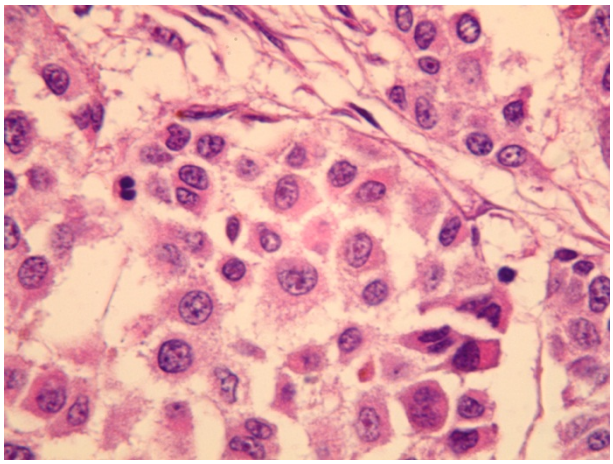

Figure 11. Nodular melanoma: close view, the tumor cells are pleomorphic with abundant cytoplasm, large vesicular nuclei and prominent nucleoli (By the courtesy of Dr. Ahmet Cemil Kaur).

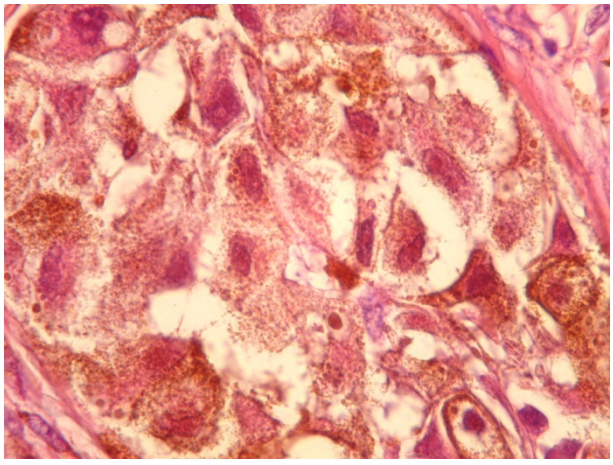

Figure 12. Nodular melanoma: in this example there is heavy melanin pigmentation (By the courtesy of Dr. Ahmet Cemil Kaur).

nuerotropism ranged from 16.7% to 77.8% [76]. *Kay* et al. reported that perineural invasion was 82% [128]. There are two subtypes of desmoplastic melanoma histologically; i) pure desmoplastic melanoma that characterized by desmoplasia through out the tumor, ii) and mixed desmoplastic melanoma that characterized by desmoplasia associated with non-desmoplastic invasive melanoma [129].

6.6. Minimal deviation melanoma

Minimal deviation melanoma is a variant of invasive melanoma that characterized by a nodule with minimal histologic deviation compared to ordinary nevus. It may be confined into the papillary dermis or may invade into the reticular dermis or beyond. This melanoma variant is divided into 6 subtypes according to cytological features (Spitz, halo-nevus like, pigmented spindle cell, desmoplastic, small cell and dermal variant). The average thickness is 3, 40 mm. The infiltration into the subcutaneous fat tissue is not often seen. Necrosis is absent while perineural invasion, mitoses and inflammation with desmoplasia can be seen. Mitotic activity is usually quite low [78, 114, 130, 131].

6.7. Special variants

6.7.1. Follicular melanoma

This rare variant is characterized by a deep-seated follicular structure in which atypical melanocytic cells extend downward along the follicular epithelium and mainly involves follicular unit as well as adjacent dermal layer [113, 132, 133].

6.7.2. Myxoid melanoma

Myxoid variant is characterized by spindle and stellate-shaped cells embedded within myxoid stroma. There is no cytoplasmic mucin in tumor cells. The stroma stains with *Alcian* blue. HMB-45 is showed less often while tumor cells strongly express S-100 protein [109, 113].

6.7.3. Balloon cell melanoma

The tumor is composed of large cells that exhibit an abundant quantity of clear or finely vacuolated cytoplasm. The other histopathological features include nuclear pleomorphism, mitotic activity, cytological atypia and necrosis [78, 113].

6.8. Histopathologic prognostic factors in melanoma

6.8.1. Tumor thickness

Primary tumor thickness is the most powerful predictor of melanoma survival. The *Breslow* thickness that is measured from the most superficial aspect of the granular cell layer to the deepest point of invasion of the tumor is the better prognostic indicator. If the tumor is ulcerated, the measurement should be from the base of the ulcer to the deepest dermal melanoma cell. In AJCC staging system (2001), the thickness thresholds have been revised as ≤1.0 mm, >1.0-2.0 mm, 2.1-4.0 mm and >4 mm. The *Breslow* thickness increases with increasing rate of sentinel lymph node involvement: 4% in melanoma smaller than 1.00 mm, 12% in melanoma 1.01 to 2.00 mm, 28% in melanoma 2.01 to 4.00 mm, and 44% in melanoma exceeding 4.00 mm.

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Clark's level which is other tumor thickness indicator is described by *Clark* as anatomic levels in melanoma invasion (Table 1):

Level I	Melanomas confined to the
Level II	Penetration by melanomas into the papillary dermis
Level III	Tumor cells fill and expand the papillary dermis
Level IV	Spreading into the reticular dermis
Level V	Penetration into the subcutaneous fat

Table 1. *Clark* level of invasion

If Clark's level increases, the mean life span is decreased [119, 134-137].

6.8.2. Ulceration

Ulceration is defined as disappearance of the all layers of epidermis (including basement membrane), evidence of host response, and thinning, effacement or reactive hyperplasia of adjacent epidermis. The presence of ulceration shows that the lesion has aggressive feature. Ulceration due to trauma should be excluded. The presence of ulceration is associated with a higher risk of metastases. According to the presence or absence of ulceration, each T category is divided into two as "a" and "b" in the AJCC cutaneous melanoma classification 2009 (Table 2). This system classifies melanomas on the basis of their local, regional, and distant characteristics, as follows: [39, 51, 135, 138]

- Stage I and II - Localized primary melanoma
- Stage III - Metastasis to single regional lymph node basin (with or without in-transit metastases)
- Stage IV – Distant metastatic disease.

6.8.3. Mitotic rate

The mitotic rate is important prognostic indicator that is determined by the number of mitotic figures/1 mm^2 of tumor in the most mitotically active area. The increased mitotic activity is associated with poor prognosis [51, 114].

6.8.4. Satellite deposites

Microsatellites are defined as discrete tumor aggregates separated from the main body of the tumor mass. These deposites settled to 0,05 mm or more away from the main tumor mass are

associated with an increased risk of local recurrence, regional lymph node metastases and diminished survival [114, 134].

Stage	T	N	M	Clinical-Histopathological Features
0	Tis	N0	M0	In situ melanoma (ıntraepithelial)
IA	T1a	N0	M0	≤1 mm without ulceration
IB	T1b	N0	M0	≤1 mm with ulceration
	T2a	N0	M0	1.01-2 mm without ulceration
IIA	T2b	N0	M0	1.01-2 mm with ulceration
	T3a	N0	M0	2.01-4 mm without ulceration
IIB	T3b	N0	M0	2.01-4 mm with ulceration
	T4a	N0	M0	4 mm without ulceration
IIC	T4b	N0	M0	"/>4 mm with ulceration
IIIA	T1-4a	N1a	M0	Single regional nodal micrometastasis, without ulceration
	T1-4a	N2a	M0	2-3 microscopic positive regional nodes, without ulceration
IIIB	T1-4b	N1a	M0	Single regional nodal micrometastasis, with ulceration
	T1-4b	N2a	M0	2-3 microscopic positive regional nodes, with ulceration
	T1-4a	N1b	M0	Single regional nodal macrometastasis, without ulceration
	T1-4a	N2b	M0	2-3 macroscopic regional nodes, without ulceration
	T1-4a/b	N2c	M0	In-transit met(s)/ satellite lesion(s) without metastatic lymph nodes
IIIC	T1-4b	N1b	M0	Single regional nodal macrometastasis, with ulceration
	T1-4b	N2b	M0	2-3 macroscopic regional nodes, with ulceration
	Any T	N3	M0	4 or more metastatic nodes, matted nodes, or in-transit met(s)/satellite lesion(s) with metastatic nodes
IV	Any T	Any N	Any M1	M1a: Distant skin, subcutaneous, or nodal mets with normal LDH levels M1b: Lung metastases with normal LDH M1c: All other visceral metastases with normal LDH or any distant metastasis with elevated LDH

T=tumor size; N=node status; M=metastasis; Ta=without ulceration; Tb=with ulceration;

Table 2. Cutaneous Melanoma Staging

6.8.5. Lymphocytic infiltration

Tumor-infiltrating lymphocytes are an important indicator of host immune response against melanoma. This response is divided into 3 categories and should be reported as brisk, non-brisk and absent. Although the presence of host inflammatory response is generally associated

with a better prognosis in melanoma, there are also studies reporting that no significant correlation between lymphocytic infiltration and prognosis [119].

6.8.6. Histological subtype

There is no survival difference among three histological subtypes (superficial spreading, nodular and acral lentiginous) when these are corrected for thickness. But lentigo malign melanoma, particularly in woman, has been reported to have a better prognosis, independent of thickness [51].

6.8.7. Regression

Regression is caused by the interaction between melanoma cells and host immune system. Tumor tissue replaced with degenerative melanoma cells, melanophages, lymphocytic proliferation, haphazard fibrosis and telangiectasias. Complete regression is characterized by total absence of malignant melanoma cells in both dermis and epidermis. The correlation between regression and prognosis is still controversial [119, 134].

6.8.8. Vascular invasion

Tumor cells may invade the vessel lumen. It correlates with the development of in-transit metastases, when the presence of blood vessel and lymphatic invasion should be reported. Vascular invasion is associated with poor prognosis and decreased survival in thick cutaneous malignant melanomas [109, 119]. Angiogenesis is a distinct histological prognostic indicator that is defined as the increasing development of new blood vessels at the base of the tumor mass. Increasing angiogenesis is associated with thick tumors, surface ulceration, relapse and tumor related death [114].

6.9. Immunohistochemistry of melanoma

Immunohistochemical staining is often used for differentiate melanomas from tumors that they mimic in conventionally stained sections [139].

S-100 is a commonly used sensitive marker for melanoma. But its positivity appears some tumors such as nerve sheath and granular cell tumors and myoepitheliomas. Although its sensitivity is 97-100%, its specificity for melanocytic lesions is limited. The specificity of S-100 is ranged from 75% to 87%. S-100 A6 is one of the subtypes of S-100 protein, expressed in both benign and malignant melanocytic lesions. S-100 A6 has been reported that it is expressed in approximately 62-100% of metastatic and primary melanomas [140, 141].

HMB-45 is an antibody formed against the cytoplasmic premelanosomal glycoprotein gp100 while its sensitivity is lower than S-100, its specificity is greater. HMB-45 expression is maximal (77-100%) in primary melanomas. This rate is lower (58-83%) in patients with metastatic lesions [139].

Melan-A, also known as melanoma antigen recognized by T cells-1 (MART-1), is an important melanocytic marker. Sensitivity and specificity of Melan-A are similar to HMB-45 that ranged

from 75-92% and 95-100%, respectively. It is less positive in lesions with metastatic melanomas than primary melanoma [139].

MIB-1, also known as Ki-67, is a proliferation marker that is expressed by proliferating cells. It provides guidance about presence or absence of "maturation". MIB-1 has an important role in distinguishing between melanocytic nevi and melanoma. While less than 5% of nuclei is positive in melanocytic nevi, this ratio is greater (25% or more) in melanoma [114, 141].

Tyrosinase is an enzyme that plays a role in hydroxylation of tyrosine in the synthesis of melanin. Its sensitivity for melanoma is slightly better than HMB-45 at 84-94%. The sensitivity is reduced in advanced diseases and metastatic lesions (79-93%). The specificity is very high for melanoma (97-100%) [139].

Microphthalmic transcription factor (MITF) is expressed in most benign melanocytic nevi and melanomas. Nuclear staining occurs with MITF unlike cytoplasmic markers. MITF expression has been reported in 81-100% of melanomas [51, 113].

There are also numerous immunohistochemical markers such as epithelial markers (keratin, EMA, CEA), histiocytic markers (eg. CD68, Mac 378, alpha-1 antitrypsin), Bcl-2, Cyclin D1, p16, CD40, CD44, melanoma cell adhesion molecule (Mel-CAM) [114].

7. Treatment

7.1. Staging workup

Any lesion that is clinically suspicious for melanoma should ideally undergo an complete elliptical excisional biopsy with narrow margins (such as 2 mm) [12]. Wide excisions should be avoided for obtaining an accurate result of the subsequent sentinel lymph node biopsy, if necessary. Examination of the entire pigmented lesion allows for the greatest chance of accurate diagnosis and also for the measurement of *Breslow* thickness and the assessment of other prognostic factors [142]. Although there is evidence that an incisional biopsy does not adversely affect survival, this approach should be an exception and reserved for cases in which the tumor is too large to be excised, or when it is not practical to perform an excision. If the lesion is large or located on certain anatomical sites such as palm/sole, digit, face or ear, a full-thickness incisional biopsy can be performed, reaching to the adipose tissue. This biopsy should be obtained from the most elevated or darkest area of the lesion, although there is not always a correlation between clinical appearance and the thickest part of the lesion. If initial biospy confirms melanoma with subtotal excision and if there is significant amount of residual lesion, a narrow margined re-excision should be immediately made, to evaluate if the patient is a candidate for sentinel lymph node biopsy.

Although cutaneous melanoma is rare in children and young adults, the incidence is rising annually in this population. Staging work up is almost similar, in children and adults [143].

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7.2. Evaluation for regional metastasis

7.2.1. Macroscopic metastases

First step should always be history taking and physical examination. A careful lymph node examination of the whole body should be made, particulary the regions close to the site of the primary lesion. Also because of the aberrant lymphatic drainage pathways to unexpected nodal basins and to interval nodes between the primary site and expected regional nodal basin, a search for clinically detectable nodal disease in unexpected locations is crucial. If there is a palpable lymph node during physical examination, first a fine needle aspiration biopsy should be performed to make a histological confirmation. If the result of the fine needle aspiration is inconclusive, an excisional biospy can be made. For the detection small nodal metastases, best noninvasive methods seem to be ultrasound imaging and positron emission tomography, with sensitivity and specificity being lower than tissue diagnosis [144].

7.2.2. Microscopic metastases

Sentinel lymph node biopsy (SLNB) as elective lymph node dissection (ELND) does not offer a survival advantage to melanoma patients, a new approach, SLNB has become the choice of biopsy type. *Morton* developed sentinel node biopsy as a means of ensuring that the node biopsied was the one most likely to be the first draining lymph node. This technique was widely adopted although the first randomized clinical trial to evaluate it was only published in 2006. In SLNB, lymphoscintigraphy is used to identify the lymphatic drainage pattern from the site of the primary melanoma, by injecting radiolabelled colloid and/or blue dye at the site of the primary melanoma [145]. The tracer/dye is concentrated in the sentinel node and is detected using a hand-held gamma probe (neoprobe) and examination by naked eye for the blue stained node. Sometimes there is more than one sentinel node and sometimes these sentinel nodes are in different lymph node basins. The node is removed and subjected to pathological examination using immunohistochemistry (S100 and HMB-45) The surgical technique must be learnt and false-negative results are more common in trainees, so an experienced medical team is vital. The pathological examination of the nodes is also a skilled procedure; naevus cells may be seen, for example, in the subcapsular area of the node and must be distinguished from melanoma cells. The likelihood of a positive SLNB result is correlated with *Breslow* thickness. Use of SLNB to stage patients for trials of adjuvant therapies would appear reasonable but the patient should be aware that the risk of positivity is low. In patients with melanoma of *Breslow* thickness from 1.5 to 4.0 mm, the risk of positive SLNBs is significantly higher at 23% [146]. The value of SLNB in patients with tumours of *Breslow* thickness 4 mm or thicker is questionable (if the intent is therapeutic as well as being a staging tool) because the risk of haematogenous spread is so high. At present SLNB is of proven staging value but of no established therapeutic value. Its use in identifying patients for adjuvant therapies means that it will continue to be used, but its role must be evaluated in the long term.

7.3. Evaluation for distant metastasis

For the evaluation of distant metastases, a thorough examination of the neurologic, psychiatric, musculoskeletal, skin, lymphatic, endocrine, cardiovascular, and respiratory systems is necessary. Patients with newly diagnosed melanoma require a complete cutaneous and physical examination with particular attention to lymphadenopathy and hepatomegaly, and a baseline chest radiograph. If the latter examinations fail to detect any evidence of metastatic disease and the patient has no other symptoms or signs, no further laboratory evaluation is indicated. Current imaging technics like computed tomography, magnetic resonance imaging, PET, chest X-ray and laboratory tests like LDH are not routinely indicated as their sensitivity ans specificity are low. According to current guidelines, no additional work up is necessary in stage 0 and 1A, optional chest X-ray may be performed in stage 1B and 2, optional chest X-ray and LDH for stage 3 and chest X-ray and/or chest CT and LDH for stage 4 can be done [146].

7.4. Treatment of primary melanoma

The Standard treatment for primary cutaneous melanoma is wide local excision. The aim of wide excision is to reach histopathologically confirmed tumor-free margins, as well as preventing local recurrence. Recommended clinical margins around the residual lesion or biopsy scar for melanoma in situ, non lentigo maligna pattern, is 0.5 to 1 cm; for melanoma <1 mm *Breslow* depth a 1-cm margin; for melanoma 1 to 2 mm a 1- to 2-cm margin as anatomically possible; for melanoma ≥ 2 mm a 2-cm margin. lesion excision at special sites, such as the digits, soles, ears, vagina or anus, also requires individual surgical and functional consideration. For subungal melanoma, partial or complete amputation of the digit is the choice of treatment.

Lentigo maligna and lentigo maligna melanoma have high potential for sub-clinical peripheral extension, as their clinical margins are usually poorly defined and obscured by background photo-damage. For lentigo maligna melanoma, the probability of a macular invasive desmoplastic component is increased. Thus, standard surgical safety margins recommended, are often insufficient for these two subtypes [12, 51].

7.5. Treatment of regional metastasis

7.5.1. Macrometastatic nodal disease

One of the main causes of melanoma-related morbidity with an important negative effect on quality of life is the poor control of the nodal disease. Therefore, current standard of therapy for microscopic or macroscopic melanoma in lymph nodes is complete dissection of the node in the involved regional basin. According to the current guidelines, adequate lymphadenectomy is described as at least 10 nodes in the groin region, 15 lymph nodes in the axillary region and 15 lymph nodes in the neck area. There are also some complications, leading to significant morbidity, of the lymph node dissection, like wound infection, delayed wound healing, seroma, lymphedema and nerve damage. In the case of regional metastatic melanoma, complete lymph node dissection is associated with long-term survival rates [87].

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7.5.2. Micrometastatic nodal disease

For micrometastatic disease, elective lymph node dissection was the procedure of choice, historically. It is the dissection of regional lypmh nodes draining the site of a primary cutaneous melanoma, with no clinically palpable lymph nodes or overt metastatic disease. With today's knowledge, according to multiple prospective randomized-controlled trials, survival rates of the patients undergoing elective lymph node dissection were found to be no higher than other patients. Thus there is no role for elective lypmh node dissection today, especially considering its significant morbidity and the availability of sentinel lypmh node biopsy [144]. For the identification of micrometastatic nodal disease, sentinel node biopsy is the tool of choice. The only handicap of sentinel node biopsy is that, it can not be classified as therapeutic yet. If the result of the sentinel lymph node biopsy returns as positive, always a complete lymph node dissection should be performed. According to current trials of investigations, immediate complete lymph node dissection has a higher survival rate than delayed dissection.

7.5.3. Adjuvant therapy

Adjuvant therapy is usually given after surgical resection of the primary lesion. It is preferred in patients with increased relapse risk. When thickness of the primary lesion is higher than 4 mm or when there is nodal involvement, adjuvant therapy is necessary. Up to now, interferon-α2b (IFN- α2b) is the only form of adjuvant therapy, which is approved by U.S. Food and Drug Administration. It has been shown that interferon-α2b improves disease-free survival for stage 2B and 3 melanoma, and it also improves overall survival. Interferon-α2b is used in high doses. There are two phases of treatment with interferon, first phase is induction phase. During induction, 20 million units per square meter of body surface area per day, are given intravenously, 5 days a week, for 4 weeks. After this high dose period, during the maintenance period, 10 million units per square meter per day, given subcutaneously three times a week for 48 weeks. During or after interferon treatment, autoantibodies like antithyroid, anti-nuclear, anti-DNA, anticardiolipin autoantibodies may appear in blood tests of the patients and some autoimmune diseases may develop. Both autoantibody positivity and development of autoimmune diseases are associated with increased survival in those patients. High dose interferon treatment may cause flu-like symptoms, fatigue, malaise, fever, nausea and headache, depression, elevated levels of transaminases and myelosupression [147].

Melanoma vaccines: Vaccines stimulate specific immune response against melanoma-associated antigens. They can be of autologous, allogenic or peptide type and also immunologic adjuvants like bacille Calmette-Guérin or DETOX are added. Target of the vacines can be autologous tumor cells, allogenic melanoma cells, or more specifically heat shock proteins and T cell defined antigens glycoprotein 100, tyrosinase, MART-1. Up to now, none of the trials showed increased survival for the patients using these vaccines but more research on this area should be done.

7.5.4. Satellite metastases

For localized disease, limited to one extremity only, first choice of treatment should ideally be surgical excision with clear margins if possible. But in case of multiple lesions, chance of performing an ideal excision may be low, so in that case, isolated limb perfusion can be considered. It is a simple and less invasive, yet more effective treatment. Main idea about isolated limb perfusion is giving high doses of chemotherapeutic agents locally, to avoid systemic toxicity, and obtain more therapeutic effect. The technique of this method involves perfusing an isolated arm or leg, in a hyperthermic environment, with cytotoxic agents. Conventinally chemotherapeutic agent used in this procedure is melphalan. Approximately in half of the patients, complete disappearance of the lesion is observed. Although systemic side effects of this method is fairly less, when compared to conventinal chemotherapy, local side effects can be serious. Significant tissue damage due to high concentrations of cytotoxic agent can be seen. Compartment syndrome is one of the most severe morbidities. Advanced age and patients with serious co-morbidities are usually not preferred for this type of treatment. A new approach is isolated limb infusion, which is a less invasive method, for appliance on patients with older age or worse general health conditions. Isolated limb infusion can be done with melphalan and actinomycin D [51, 67].

7.6. Treatment of distant or disseminated metastasis

In case of stage 4 melanoma, with distant metastasis, mean survival is 6 to 8 months and there is currently no effective systemic treatment, to increase survival rate. For this reason, main treatment goal is the palliation of symptoms. For the patients with increased age and serious comorbidities, observation and conservative treatment may also be the option of choice [146]. If there are symptomatic visceral metastasis, surgical excision to perform metastasectomy can be tried. Also excision of skin metastasis or lymph node metastasis may improve the locoregional control of the disease and may help to decrease morbidity.

In one case report [148], a 44-year-old *Caucasian* woman who underwent extensive surgical resection of a melanoma on the right side of her scalp, came with a new metastasis, a large nodule in her right cheek. The patient underwent two sessions of electrochemotherapy with intravenous injections of bleomycin, as neoadjuvant treatment permitting conservative surgery three months later. In this case, electrochemotherapy offers the option of more conservative surgery and an improved cosmetic effect with complete local tumor control.

Although melanoma is known to be radiotherapy resistant, for brain metastasis, spinal cord compression and painful bone metastasis, local radiation can be used.

7.7. Radiation therapy

Radiation therapy plays a role in the management of primary cutaneous melanoma in definitive, adjuvant, and palliative settings. The role for radiation therapy in early stage primary melanom is limited as the treatment is adequate excision. However desmoplastic melanoma and those with neurotropism invasion are exceptions, due to frequent local recurrence [149]. The greatest controversy regarding radiotherapy lies with its use in stage III

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disease, particularly as postoperative treatment after lymph node dissection. A recently completed randomized trial confirmed the benefit of adjuvant radiotherapy in improvement in nodal field control after nodal dissection for patients who are at moderate to high risk for regional relapse [150].

For primary melanoma, adequate surgery is usually the best option for local control and cure. Factors often considered indicative of the need for adjuvant radiation therapy include primary site in the head and neck region, close or positive margins not amenable to further excision, lymphatic space invasion, multiple recurrences, and desmoplastic neurotropic growth [149]. Apart from its use in an adjuvant setting, radiation therapy has been used as the definitive treatment of primary melanomas, locally advanced acral lentiginous melanoma, and as a substitute for wide excision after limited excision.

Radiation therapy has a well-established role in patients with metastatic melanoma. Symptoms of pressure, mass effect, and bleeding from metastases in a variety of locations may benefit from palliative radiation. The development of stereotactic techniques has improved the efficacy of radiation for brain metastases. Expansion of this methodology to stereotactic body radiation metastases has the potential to improve further palliation of unresectable metastases.

7.8. Systemic therapies

7.8.1. Chemotherapy

For systemic chemotherapy, first line chemotherapeutic agent is dacarbazine, an alkylating agent. It is an U.S. Food and Drug Administration (FDA) approved chemotherapy drug for metastatic melanoma. It is thought to be the most effective single agent therapy. Approximately 10 to 20% of the patients response to treatment and the mean duration of response is 4 to 6 months. Dose of the treatment does not affect the response rate. Major side effects of dacarbazine are nausea and vomiting. Temozolomide is also an alkylating agent. This chemotherapeutic agent can also be used orally. Another advantage is that, temozolomide can cross the blood-brain barrier. Thus for patients with central nervous system involvement, temozolomide can be preferred. According to a randomized phase 3 study, its efficacy is equal to dacarbazine. For metastatic melanoma to brain, a combination of temozolomide and thalidomide, along with radiation, can be benefical. For dacarbazine, increased response rates are reported, when combined with other cytotoxic agents like cisplatin, vinblastine, carmustine or tamoxifen [144].

7.8.2. Immunotherapy

Among immunotherapeutic agents, interleukin 2 (IL-2) is the only agent, which has an approval form FDA. Overall response rate of this agent is 16%, but a durable response rate is 5 to 8%. Approximately the time for the duration of response is 9 months. Of the 28% of the patients with metastatic melanoma who responded to IL-2 treatment, no progression was observed at a follow-up period of 62 months. Also patients who responded longer than 30 months, did not show any sign of relapse afterwards. On the other hand, there are some

important side effects of IL-2 treatment. Most common side effect of IL-2 is hypotension. It can also cause capillary leak syndrome, supraventricular tachycardia, transient renal insufficiency, respiratory distress, increased susceptibility to infections. There are also newer investigations about combining IL-2 with tumor-infiltrating lymphocytes and lymphokine activated killer cells. These immunologically active cells are considered to be helpful in transferring and adoptive immune force, to generate an antitumor effect.

In a case study [151], patient with cutaneous metastasis with significant comorbidities, including advanced age, anticoagulation for a metallic valve, chronic anemia, macular degeneration, and history of hematopoietic malignancy (high-grade lymphoma, *Waldenstrom* macroglobulinemia) was treated with a novel method. 1% gentian violet was applied to the wounds, and the patient was instructed to apply gentian violet and imiquimod to the base of the lesions daily. This was accompanied by a brisk inflammatory response. At the time of reexamination, 4 months after the procedure, no clinical recurrence was noted. This method can be useful when surgery is not an option.

In another case [152], 82-year-old man who presented with rapidly progressing cutaneous melanoma metastases, together with inguinal lymph nodes and bilateral pulmonary involvement, treated with topical immunotherapy with diphencyclopropenone (DPCP) in aqueous cream weekly to elicit moderate contact hypersensitivity. Larger lesions were also treated with intralesional 5-fluorouracil (50 mg/mL). One month later, cutaneous metastases began to regress, and during the following 4 months his inguinal lymphadenopathy and pulmonary lesions disappeared. He remains clinically disease free 18 months after his metastases began to regress. This can show the potential for some patients to overcome even widespread and extensive disease, presumably via immune-mediated regression, and raises the possibility that topical immunotherapy may play a role even in patients with bulky disease.

7.8.3. Biochemotherapy

Biochemotherapy alone has not shown any increase in overall survival rate, but when compared to other systemic chemotherapeutic agents like dacarbazine, or interferon, vaccines, IL-2, it can show better results.

7.8.4. Novel therapies

About the etiopathology of intrinsic resistance of malignant melanoma to chemotherapy, the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) is found to play an important role. A new antisense Bcl-2 oligonucleotide, Oblimersen, is targeting Bcl-2 messenger RNA selectively and this leads to the degradation of the Bcl-1, thus decreasing the levels of Bcl-2 in the body. Oblimersen can also be used in combination with conventional systemic chemotherapeutic agents, like dacarbazine.

Also in two-thirds of melanomas, there is a mutation in B-raf gene. A RAF inhibitor, Sorafenib, inhibits both B-raf and C-raf, and also used orally. Since the evaluation of sorafenib, a new generation of BRAF inhibitors has been developed. These drugs show higher potency against mutated BRAF and have fewer off-target effects; the list of those currently under preclinical

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investigation includes SB590885, dabrafenib (GSK2118436), AZ628, XL281, GDC-0879, and vemurafenib (RG704, PLX4032/4720) [153]. PLX4032 (and its analogue PLX4720) are adenosine triphosphate (ATP)-competitive RAF inhibitors (wild-type BRAF 50% inhibitory concentration [IC50]-100 nmol/L, mutated BRAF IC50-31 nmol/L) that selectively inhibit growth in melanoma cell lines harboring the BRAF V600E mutation in both in vitro and in vivo mouse xenograft models [154].

Much of the foundation for the development of these treatments is the realisation that melanoma growth and progression is driven by somatic activating mutations in signalling molecules such as BRAF, KIT, NRAS and GNAQ/GNA11 [147]. Active drugs targeting BRAF and KIT are available and and the anti-CTLA4 antibody ipilimumab has shown an overall survival benefit and the possibility of prolonged disease control in the metastatic setting.

Although there are many phase III trials in progress, about treatment of metastatic melanoma, up to now, no curative adjuvant or systemic therapies have been approved for stage 4 metastatic melanoma. Among these treatments some may have serious side effects. According to one study [7], patients with metastatic melanoma are treated with the selective BRAF inhibitor, dabrafenib. Keratinocyte proliferation is characteristic of BRAF inhibitor induced cutaneous toxicities, and the spectrum of lesions ranges from benign seborrhoreic keratoses, *Grover*'s disease and plantar hyperkeratosis through to verrucal keratoses of undetermined prognosis and malignant well differentiated SCCs.

In the future of metastatic melanoma treatment, molecular profiling of patient tumors will play an important role in the part of therapy selection for medical oncologists. Recent preclinical studies shows that inhibitors of BRAF paradoxically activate MAPK signaling in tumors that lack activating BRAF mutations [153]. Reports from six independent groups have shown that BRAF inhibition activates MAPK in cell lines with NRAS and KRAS mutations, as well as those cell lines where the MAPK pathway is activated through other oncogenes such as HER2. Studies showed that although vemurafenib and other BRAF inhibitors were able to profoundly inhibit the activity of BRAF V600E-containing complexes in melanoma cells, they instead promoted the activity of CRAF-CRAF dimers in cells with RAS mutations, leading in turn to MEK activation. There is also evidence that PLX4032 increases the invasive potential of NRAS-mutated melanoma cells through the activation of ERK and FAK signaling. Additional studies demonstrated that BRAF inhibitors may even contribute to the progression of NRAS-mutated melanomas in part by suppressing apoptosis through the modulation of Mcl-1 expression.

According to one study [155], data of 97 patients with melanoma show substantial clinical activity of trametinib, MEK inhibitor. Differences in response rates during this treatment, according to mutations indicate the importance of mutational analyses.

These studies are extremely important for approaching the development of new cancer therapies as they indicate that simple empiric evaluation of novel cancer therapeutics in patients could be associated with adverse outcomes. Instead they affirm the approach of rationally developing therapies in cancer patients based on strong preclinical data and individual patient molecular profiling.

7.9. Vaccines

Melanoma is considered as a rather "immunogenic" tumor. One can understand it by the spontaneous immune-mediated regression of primary tumors, association between infiltrating T lymphocytes and improved survival, response to nonspecific immunotherapy agents, including interferon-alpha, IL-2, and ipilimumab and identification of tumor-associated melanoma antigens and human leukocyte antigen (HLA)-restricted epitopes within these anti- gens [156].

A variety of strategies, including peptide and protein vaccines, recombinant DNA and viral vectors, and the use of autologous and allogeneic whole cell vaccines, have been tested in patients. Although many studies have not had significant clinical benefit, there are some important data that have emerged from these clinical trials. There also have been at least two randomized phase III vaccine trials that have shown a clinical benefit in melanoma [157].

There has been considerable interest in the identification of patient-specific and tumor-specific biomarkers that may predict therapeutic response and clinical outcomes. These studies would help select patients more likely to respond to a particular vaccine approach and might identify new strategies for improving the potency of individual vaccines so that more patients might benefit from immunotherapy.

8. Prognosis

Malignant melanoma is the most fatal type of the skin cancers. The best survival rates of melanoma arise if it is detected at the early stages, this is generally when the size of the tumours is small and treatable. After detection the prognosis of the melanoma can be determined by assessing a number of histopathological (morphological) factors such as the thickness of lesions, levels of invasion, presence of ulceration and the number of metastatic lymph nodes involved. Clinical prognostic factors such as age, sex, anatomical location of the tumour can also be used to determine the possible progression of the cancer and the likely survival rates of the patient. The thickness of the tumor is the dominant prognostic factor in determining risk of metastasis and prognosis for cutaneous melanoma [158, 159]. The American Joint Committee on Cancer (AJCC) tumor node metastasis committee has approved a new melanoma staging system, which was implemented in 2009 [160]. The prognostic factors included in AJCC staging system are tumor thickness, ulceration, level of invasion (*Clark*'s level) and mitotic rate [160, 161].

In the AJCC staging system, tumor thickness is the most powerful independent prognostic factor for patients with cutaneous melanoma. Melanoma thickness is measured from the granular layer of the epidermis to the greatest depth of tumor invasion, this was originally described by *Breslow* in 1970. Now it is correlated with a thickness of ≤1 mm (T1), 1.01 to 2 mm (T2), 2.01 to 4 mm (T3), or ≥4 mm (T4) [159]. In it, invasive tumor thickness is used to predict

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5-year survival. In general, the higher the *Breslow* thickness, the worse the prognosis (Table 3) [161,162].

Breslow thickness	5-year survival
≤1 mm (T1)	95% to 100%
1.01 to 2 mm (T2)	80% to 96%
2.01 to 4 mm (T3)	60% to 75%
>4 mm (T4)	37% to 50%

Table 3. The relation of *Breslow* thickness and prognosis

The depth of the tumor is most accurately measured by evaluating the entire tumor via an excisional biopsy. Determination from specimens obtained using other biopsy techniques, such as a wedge or punch biopsy, is less accurate. Tumor depth cannot be calculated from a shave biopsy that only contains a portion of the tumor because it leads to an underestimation of its thickness. Excisional biopsy should extend down to the subcutaneous fat tissue [163].

Clark level of invasion is a method for determining the prognosis (outlook) with melanoma. This method was devised by the pathologist *Wallace Clark* and measured the depth of penetration of a melanoma into the skin according to anatomic layer. There are five *Clark* levels of invasion (Table 1).

The *Clark* levels provide a system to relate the degree of penetration of melanoma into the skin to the 5-year survival rate after surgical removal of the melanoma [158, 161, 164].

Ulceration is the second most powerful factor for poor prognosis. The presence of ulcerations on the surface of the tumour causes a reduction in the survival rate. Ulcerations appear when an intact epidermis is not present around the tumour and is usually a result of an aggressive tumour. The presence of ulceration in tumours less than 1mm, causes a reduction in survival rate by 4% compared to non-ulcerated tumour. Survival rates can be reduced by up to 22% if the tumour thickness is greater than 4mm.This therefore, indicates that tumour thickness and ulceration have strong relationship with survival rates and so the prognosis of thin non-ulcerated melanoma is excellent [51].

Current studies have shown that tumor mitotic rate is a powerful independent prognostic factor. But the prognostic importance of mitotic rate in melanoma recurrences is not known. A high mitotic rate also correlates with a greater likelihood of having a positive sentinel lymph node biopsy. The mitotic rate is measured by simply examining the excised tumor with a microscope and manually counting the number of cells exhibiting mitosis, an easily identifiable characteristic of dividing cells. Most often, the mitotic rate is reported as one of three categories :

- less than 1 per square millimeter
- 1 to 4 per square millimeter

- greater than 4 per square millimeter

The higher the mitotic count, the more likely the tumor is to have metastasized. The logic is that the more cells are dividing, the more likely they will invade the blood or lymphatic systems and thus spread around the body. Research has shown that the odds of survival for patients with stage I melanoma and a mitotic rate of 0 per square millimeter is twelve times better than that of patients with a mitotic rate of greater than 6 per square millimeter. Also, only 4% of lesions with low mitotic rate recur compared to 24% of those with a high mitotic rate. Mitotic rate can also help to predict that your sentinel lymph node biopsy will be positive or not. Although mitotic rate has no role in the current staging system for melanoma, research has demonstrated that it is a more important prognostic factor than ulceration, which does have an important role in staging. The American Academy of Dermatology argues that mitotic rate should be optional in biopsy reports or not. On the other hand, the National Comprehensive Cancer Center recommends that mitotic rate should be reported for all lesions in stage I to II patients. Still other experts argue that measuring the mitotic rate should only be done in large academic medical centers for future research purposes. Increasing mitotic rate is related with a decreasing survival [165, 166].

Tumor-infiltrating lymphocytes (TILs) describe the patient's immune response to the melanoma. One marker used to determine immune activity in melanoma is the presence in sentinel lymph node biopsy samples, which has been variably associated with a favorable prognosis. Some investigators assessed whether the presence of tumor-infiltrating lymphocytes was an independent predictor of sentinel lymph node biopsy status and survival or not [167, 168].

Microscopic satellites are defined as dermal or subcutaneous nodules. Microscopic satellites in primary melanomas are considered to be localized micrometastases developing in close proximity to the main tumoral portion of melanomas and show bad prognosis. In particular, the presence of angiotropism predicts the detection of microscopic satellites, and microscopic satellites probably develop as a result of extravascular migration. Consequently the linkage between microscopic satellites and angiotropism provides additional support for extravascular migratory metastasis as a mechanism of melanoma metastasis. Finally, ongoing investigations to develop a more specific biomarker for angiotropism and extravascular migratory metastasis are essential for the more precise recognition of extravascular migratory metastases and the explaining of its biological and prognostic significance. This pericytic angiotropism of melanoma cells, without any sign of intravasation, suggests that melanoma cells may migrate along the external surface of vessels, a mechanism we have termed extravascular migratory metastasis (EVMM), as distinct from intravascular dissemination [51, 169].

Common cell types are epithelioid and spindle cells, although mixed cells may also be seen. Generally, spindle cells are associated with better prognosis than other cell types.

The incidence of malignant melanoma appears to be increasing at an alarming rate throughout the world over the past 35-40 years and continues to increase in the USA, Canada, Asia, Australia, and Europe. The behavior of head and neck melanoma is aggressive, and it has an overall poorer prognosis than that of other skin sites. Correlations between different factors were found, e.g. tumour localisation predominating on the back in males and on the legs in

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female. In one study, 11.734 patients were analyzed, 49.3% were male. Between 1978 and 1992, most of the newly registered melanoma patients were female, but after 1992 there was a higher incidence of male patients. Men exhibited a disadvantaged distribution for almost all prognostic indicators being significantly older at diagnosis, having thicker melanomas, and having more melanomas localized on the trunk or head and neck. In analyses of histological subtypes, females had significantly more lentigo maligna melanomas and acral lentiginous melanomas, but the incidence of superficial spreading melanoma and nodular melanoma did not differ across gender. Males more often presented with lymph node metastases or distant metastases at the time of diagnosis than did females (5.2 vs. 3.0% and 1.7 vs. 1.1%, respectively). Whereas overall disease progression, lymph node metastasis, and distant metastasis occurred significantly more often in males than in females, local recurrence and in-transit/satellite metastases were equally common [170-172].

If we summarize, prognostic factors include tumor thickness (mm), levels of invasion, presence of ulceration, increased mitotic rate. Prognosis is better if there happens to be tumor-infiltrating lymphocytes around the lesion. There is stil controversy going on about regression. Some studies have shown an adverse outcome while others no effect, or a favorable outcome. Presence of microscopic satellites shows bad prognosis and also angiotropism is a bad prognostic marker. Vascular/lymphatic invasion, although seen very rarely, indicates unfavorable prognosis. Tumor cell type also has an effect on prognosis. Better prognosis with spindle cells versus other cell types. Prognosis worsens with increasing age and women have better prognosis than men. Extremity lesions have better prognosis than axial lesions (trunk, head and neck, palms and soles) [12, 173].

9. Patient education

Melanoma is the most dangerous form of skin cancer [174]. The incidence of melanoma is increasing worldwide, more than other cancers. The clinicians has the greatest impact on reducing these cases. They educate patients about early detection, treatment and prevention methods [175]. UV light is the most important risk factor for melanoma development. The risk of developing melanom may be reduced by protecting from UV light exposure. We must educate others as to the importance of sun protection [174]. Patients should be educated to avoid intense intermittent sun exposure and minimize cumulative sun exposure [176]. Avoiding overexposure to direct sunlight during the peak daylight hours, wearing protective clothing, and applying sunscreen are the ways to protect the skin [177].

Clinicians must educate patients as to the importance of using sunscreens that protects against both UVA and UVB light and with an SPF 30 or greater [174, 175]. It is important to emphasize the correct application of the recommended amount of sunscreen and the need for reapplication of sunscreen [176]. Sunscreen should be applied to exposed dry skin 15 to 30 minutes before sun exposure. The standard amount of sunscreen used in SPF testing is 2 mg/cm^2. Sunscreen should be reapplied every 2 hours or after swimming or heavy perspiration; many water-resistant sunscreens lose effectiveness after 40 minutes in the water [177]. Clinicians

recommend patients sun protective clothing such as sunglasses, hats or long sleeve clothing. Patients should be avoided direct exposure to the sunlight between 9 AM - 3 PM and tanning beds [174]. There is great concern in regard to the total amount of sun exposure during infancy and early childhood [175]. The importance of sun protection in childhood should be emphasized [176].

Self-examination of skin by informed patients in terms of suspicious nevi is an important contributory factor in the early diagnosis of melanoma [178].

Skin self examination has the potential to significantly reduce melanoma mortality. One retrospective study concluded that skin self examination has the potential to reduce melanoma mortality by 63% [179]. One study found that 44% of diagnosed recurrent melanoma was initially detected by patients based on symptoms that raised suspicion of metastasis [180]. For this reason, patients shoul be educated about the skin self examination. Patient education in skin self examination includes information on the warning signs of melanoma. Also it includes directions on how to perform a thorough whole-body skin examination [176]. Patients at higher risk should carefully examine their own skin monthly and also be frequently examined by dermatologists professionally [174].

Older individuals are both more likely to acquire and to die from cutaneous melanoma; thus, elderly people should be a primary target for secondary melanoma prevention. We must be careful for the early detection and patient routine screening. Also secondary melanoma prevention should be focused on targeted education to older men and their spouses for early detection and reduction of mortality in this extremely high-risk group [181].

Following the diagnosis of cutaneous melanoma, all patients should be educated on the risks of developing a second primary melanoma. In addition, counselling on the common clinical characteristics of cutaneous melanomas and instruction on how to perform a skin self examination should be provided. In the event of the development of new pigmented lesions or changes in preexisting pigmented lesions, patients should be advised to seek medical attention. In addition, appropriate lifelong follow-up surveillance is critical for the detection of thinner, more curable melanomas [182].

Most of the studies suggested that many cancer patients want to get detailed information about their disease, treatment options and prognosis of the disease. The most common complaint of these patients is not to told what is wrong with them, during the treatment. Cancer care professionals are beginning to recognize that patients' information needs and preferences [183].

With growing evidence that well-informed patients are more satisfied with their care and do better clinically. Efforts are needed to improve the information provision to melanoma patients. Exploration of the patients' personal information needs must lead to a more patient-tailored approach of informing melanoma patients. A good opportunity would be the implementation of a survivorship care plan, which aims at providing a cancer survivor with a summary of their course of treatment, management of late effects, and strategies for health promotion [184].

The importance of malignant melanoma as a potentially fatal skin cancer among Caucasian populations worldwide has received critical attention in recent years. As compared to other life-threatening malignancies such as breast or prostate carcinoma, melanoma may be diagnosed by simple inspection of the skin surface with 80 to 90% accuracy. Sun avoidance, regular self-examination are important measures that can easily be applied. Future investigations is needed to establish whether education and modification of behavior such as reduced sun exposure and various methodologies of skin examination have a significant impact in reducing mortality from melanoma.

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