# A REVIEW OF FREQUENT CUTANEOUS MALIGNANCIES – PART II: MALIGNANT MELANOMA

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**Open Access Article**

## Abstract

Malignant melanoma has a lower incidence than basal or squamous cell carcinomas, but is the most dangerous type of skin cancer due to the high capacity of metastasising. The main risk factor is sun exposure, although genetic predisposition is also involved. Early diagnosis realised through an excisional biopsy is very important because the cure rate depends on the stage of the disease. Proper surgical and adjuvant treatment lower the incidence of metastases and raise patient's survival rate. The article reviews the important aspects of malign melanoma from etiology to diagnosis, treatment and follow-up.

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**Keywords:**

malignant melanoma,
skin tumors,
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## Introduction

This article is a continuation of the previous article that reviewed non-melanoma cutaneous malignancies, regarding epidemiology, etiology, diagnosis, clinical types and treatments (1). Even though it has a lower incidence than basal cell carcinoma and squamous cell carcinoma, malignant melanoma is one of the most aggressive skin cancers due to the high capacity of metastasizing, being responsible for 75% of the skin cancer related deaths (1).

## Epidemiology

Presently, the general population risk for melanoma is 2,5% in white persons, 0,5% for Hispanics and 0,1% for Blacks (2, 3). Studies have shown that in U.S. the number of melanoma cases have doubled in the past 35 years (4) with a lifetime risk of 1 in 49 men and 1 in 72 women (5), with a median age of 63 years old at diagnosis.

Even though the risk of melanoma increases with age, melanoma is common seen also in people less than 30 years old, being the second

most common cancer in women between 20 and 29 years old after leukaemia (6). Australia and New Zealand (extreme southern latitudes) (3) present the highest rates (45/100.000) (7), while China and Japan present the lowest rates (<1/100.000) of malignant melanoma (5).

## Etiology and pathophysiology

Melanoma is the consequence of malignant transformation of melanocytes, pigment producing dendritic cells situated in the skin's basal layer (7). This event may occur not only on skin but wherever there are melanocytes, including the eye and mucous membranes of the sinuses, upper digestive tract, anus and vagina (7) or even in lymph node capsules (8).

Besides the topographical risk factor, the high incidence of melanoma is also associated with certain individual factors like fair skin, light hair and eye colour (Fitzpatrick I and II), immunosuppression and more than 50 common nevi (9). The most prominent risk factor remains the exposure to UV in the form of severe blistering sunburns, freckling and allergies after sun exposure, high amount of sun exposure over a lifetime, as well as the use of sunlamps and tanning booths especially before 30 years old (3, 4, 7, 9).

Furthermore, the genetic predisposition for melanoma is an important factor to consider (9) as it affects 10% of patients. The family history of the disease increases the risk of melanoma for up to eight times, appearing at a younger age than in the general population (3). The hereditary susceptibility is associated with mutations of p16 gene and CDK4 gene (7).

Among the predisposing conditions of melanoma, we mention the dysplastic nevus (6-10% lifetime risk), congenital nevus (6% lifetime risk), xeroderma pigmentosum (3, 9), lentigo malign (senile freckle) and the atypical mole syndrome (familial atypical multiple mole melanoma) (3). The atypical mole syndrome is characterized by a 10% lifetime risk of melanoma, with nevi present at birth and rising in number during puberty, resulting in more than 100 melanocytic nevi with a diameter from 6 to 15 mm (3).

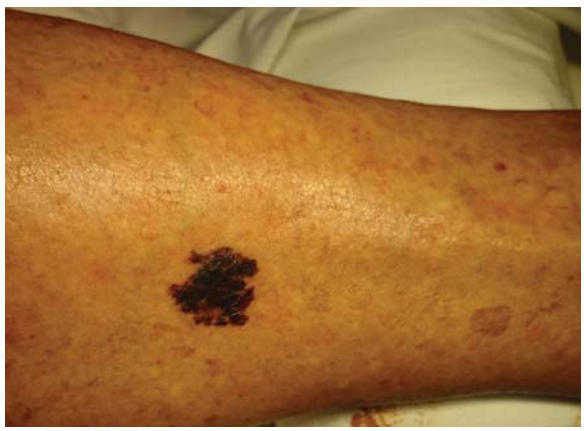

**Figure 1.** Malignant melanoma on the calf

## Diagnosis

The suspicion of melanoma arises when we are confronted with a pigmented, asymmetrical lesion with border irregularities, colour variations and more than 6 mm diameter (ABCDs of malignant melanoma) (3, 10). Also, an ulcerating or rapidly growing lesion increases the suspicion of melanoma (4) (Fig. 1).

## Differential diagnosis

A number of pigmented lesions can be mistaken for malignant melanoma: junction nevi (uniform coloured nevi that appear during childhood on mucosa, genitalia, palms and soles), compound nevi (dark coloured nevi that appear during puberty), intradermal nevi (pale nevi that appear more frequently during young adulthood on face and neck), blue nevi (nevi less than 5 mm in diameter located on hands, feet, head, neck or buttocks), spitz nevus (children and young adults melanoma usually less than 6 mm in diameter with a recent change in size or colour), lentigo (pigmented nevus with reticular pattern which usually appears in older patients), seborrheic keratosis (verrucous raised nevus usually occurring on the trunk that can resemble melanoma), pyogenic granulomas (nevus that develops with adjacent inflammation in a matter of days or weeks after a minor trauma) and pigmented basal cell carcinoma (11).

## Biopsy

Suspicious lesions can be biopsied by complete elliptical excision with a 1-3 mm margin including the subcutaneous fat (excisional biopsy), that permits to assess the lesion invasion depth (9). In lesions greater than 1.5 cm or located on aesthetically important areas, when a diagnosis is needed before performing the excision, a incisional biopsy can be realised, from the most relevant aspects of the tumour, but is important to know that this may affect the tumour staging even though it has been shown that in the end it does not affect the survival or recurrence (13). In subungual lesions, the biopsy involves removal of the nail with an excisional biopsy down to the periosteum, without including it (4).

## Classification

Melanoma can be presented in distinct subtypes: superficial spreading melanoma, nodular melanoma, acrallentiginous melanoma or lentigo malign melanoma.

- *Superficial spreading melanoma* is the most frequent subtype (70-75%) and it usually de-

velops from pre-existing nevus (3). It has a radial growth phase, typically with an ABCD (4) appearance of flat, asymmetrical nevus with colour variations and an average size of 2 cm (3).

- *Nodular melanoma* (15%) is an aggressive form of melanoma that does not develop from pre-existing nevus and lacks a horizontal growth phase which leads to delayed diagnosis (4). It is more frequent in men (2:1) and appears on the trunk, head and neck as a 1-2 cm wide, dome shaped tumour of homogeneous colour with smooth and shiny surface, that may simulate a blood blister (3, 4). Also, 5% of nodular melanoma can be amelanotic (3).
- *Lentigo malign melanoma* (4%) is the least aggressive form of melanoma, more common in women, appearing on chronically exposed regions as a large lesion of highly irregular bordersand multiple shades of dark brown (3, 4).
- *Acrallentiginous melanoma* (the rarest form in white Caucasians and 35-60% in dark-skinned patients) develops frequently subungual and on palms or sols of feet (2). It appears as a flat, dark brown or black lesion with irregular borders (4). In the subungual subtype it appears as an approximately 3 mm wide linear pigmented streak (melanonychia) of the nail bed (Hutchinson's sign) (3). This subtype is characterized by a long horizontal growth phase that allows for early diagnosis, as vertical growth phase may associate metastasis (3). Wide excision of the subungual melanoma involves amputation of the distal phalanx, as the skin matrix is very thin and so the phalanx beneath it usually involved in the tumour process (7). Newer studies showed that amputation does not improve overall survival and that wide local excision with digit preserving might be enough, especially for melanoma *in situ* (13).
- *Amelanotic melanoma* is usually diagnosed late, in the vertical growth phase by imunohistochemical staining (no pigment for light microscopy diagnosis) (3).
- *Desmoplastic melanoma* is another rare form of melanoma with aggressive local growth but with rare metastasis. Differential diagnosis is difficult to realise with spindle cell tumours, common nevi, Spitz or blue nevi or haemangioma (14).
- *Ocular melanoma* (2-5%) presents with vision impedance that may permit earlier diagnosis (3).
- *Mucosal melanoma* (2-5%) has a poor prognosis as the diagnosis is usually long-delayed (3).

## Staging

Melanoma staging involves histological analysis of the full thickness of the tumour. This procedure involves analysing the Breslow thickness and Clark's level criteria. Breslow thickness measures the thickness of the tumour (in millimetres), while Clark's level confirms the level of invasion through the skin layers (15). It is presently considered that Breslow thickness is the most accurate criterium for the patient's prognostic (3). The second most important prognostic factor is the presence of ulceration on the surface of the tumour, which increases the risk of recurrence (16). For complete staging it is also necessary to assess the presence of regional nodes invasion and distant metastasis (Table 1).

Survival rate is strongly associated with stages of melanoma (Table 2). Patients with stage 1 disease have a five year survival rate of 90% in comparison with patients with stage 4 disease where the five year survival rate is only 5% (17).

## Treatment

The National Comprehensive Cancer Network does not recommend any routine previous laboratory or radiographic tests for primary melanoma. These can be done only if clinical examination reveals possible invasions of the regional nodes. If lymph nodes are enlarged and palpable, a fine needle or open biopsy can be also realised (19).

## Surgical treatment

The surgical treatment of melanoma consists of wide local excision of the primary tumour including the subcutaneous tissue down to, but not including the fascia. Excision margins depend on the tumour thickness that is assessed by the primary histopathological examination. The recommendation is to measure the margins before the resection, because skin can retract after excision (12). Orientation and description of the specimen is mandatory for the pathologist.

The histopathological examination must be realised in a permanent section, because frozen sections cannot differentiate normal from malign melanocytes, and therefore surgical margins and tumour thickness cannot be assessed.

Considering the Breslow thickness, a wide local re-excision might be necessary. These recommended clinical margins for re-excision are to ensure the microscopic clearance. For melanoma *in situ* a 0.5 cm margin is suitable in comparison with lesions smaller than 1mm in thickness, where a 1 cm margin is necessary. Margins in lesions between 1.01 and 2 mm vary from 1 to 2 cm. There are not enough large studies that can assess this limit. The theory reflects the fact that the greater the excision margins, the lower the risk of presence of the microscopic metastasis or recurrence. In cases where a 2 cm margin is difficult to achieve (*e.g.*, face), 1 cm margin can be adequate. Tumours between 2 and 4 mm thickness involve a 2 cm

| **AJCC TNM Melanoma Staging Classification, 2016** | | |
|---|---|---|
| ***Tumor Classification*** | ***Depth of Invasion (Thickness)*** | ***Clinic*** |
| Tis | Melanoma *in situ* | |
| T1 | ≤ 1 mm | a – without ulceration and mitosis <1/mm$^2$<br>b – with ulceration and mitosis >1/mm$^2$ |
| T2 | 1.01-2.0 mm | a – without ulceration<br>b – with ulceration |
| T3 | 2.01-4.0 mm | a – without ulceration<br>b – with ulceration |
| T4 | >4 mm | a – without ulceration<br>b – with ulceration |
| ***Node Classification*** | ***Number of metastatic lymph nodes*** | ***Clinic*** |
| N1 | 1 lymph node | a – micro metastasis (positive at pathology examination)<br>b – macro metastasis (positive at physical examination) |
| N2 | 2-3 lymph nodes | a – micro metastasis<br>b – macro metastasis<br>c – satellite (adjacentskin) metastasis or in-transit metastasis without metastatic lymph nodes |
| N3 | 4 or more metastatic lymph nodes | Satellite or in-transit metastasis with metastatic lymph nodes |
| Metastatic Classification | M1a – Distant skin, subcutaneous or lymph nodes metastases<br>M1b – Lung Metastases<br>M1c – Other viscera or distant metastases, as well as elevated serum LDH | |

**Table 1.** Melanoma staging. Modified from *NCCN Guidelines. Clinical practice guidelines in oncology: melanoma version 1.2017* (18)

| **According to the TNM scores above, melanoma stages include the following:** | |
|---|---|
| Stage 0 – Tis N0M0 | Stage IIB – T3b/T4a N0M0 |
| Stage IA – T1a N0M0 | *Stage IIC – T4b N0M0* |
| Stage IB- T1b/T2a N0M0 | Stage III – Any T ≥N1M0 |
| Stage IIA – T2b/T3a N0M0 | Stage IV – Any T Any N M1 |

**Table 2.** Melanoma stages. Modified from *NCCN Guidelines-Clinical practice guidelines in oncology: melanoma version 1.2017* (18)

| **Breslow Thickness** | **Oncologically safe margins** |
|---|---|
| *In situ* | 0,5 cm |
| < 1 mm | *1 cm* |
| 1,01-2 mm | 1-2 cm |
| 2,01-4 mm | 2 cm |
| >4 mm | 2 cm |

**Table 3.** Wide local excision margins for melanoma lesions (18)

surgical margin (16, 20) while those greater than 4 mm require a 2 cm margin depending on the region involved (16, 20) (Table 3).

Also, if the Breslow depth does not compel to deep resection of tumour, it is preferable to leave the fascia layer in place as the fascia could act as an additional barrier and prevent metastatic disease (3). Closure of the post-excisional defects should respect the reconstruction ladder, starting from primary closure when that is attainable to skin grafts orflaps, according to the complexity of the defect in question (1).

After excising a suspicious primary lesion that might require subsequently a sentinel lymph node biopsy, the recommendation is to close the defect using primary suture or skin grafts, because any undermining or flap creation might modify lymph drainage (18).

In case of subungual melanoma (3% of all melanomas) the correct treatment includes amputation of the affected digit proximally to the distal interphalangeal joint or the metatarsal joint for toes (5), as it is considered that the nail matrix is uniquely thin. In case of *in situ* subungual melanoma an excision of the lesion is adequately with periosteum preservation and covering using a skin graft (8).

The neck and scalp melanoma bares the worst prognosis with an erratic lymphatic drainage that could necessitate complete neck dissection. Moreover, excision must include the galea underlying the affected skin (3).

When the patient's general status does not favour a surgical intervention, lentigo malign and *in situ* melanoma can be treated with topical imiquimod or radiotherapy (3).

## Lymphadenectomy

It has been long proved that elective lymph node dissection does not improve long term survival for melanomas less than 1 mm thick as these have not yet metastasized to the lymph nodes, as well as for melanomas thicker than 4 mm thick which are already in a distant metastatic stage. Regarding melanomas with a Breslow grade of 0.76 to 1 mm, sentinel lymph node is recommended when one of the risk factors is present: ulceration, Clark level equal or greater than IV, male sex, mitotic rate higher than 1 and head and neck location (21).

The sentinel node biopsy is considered effective for staging and selecting patients for complete lymph node dissection. The lymph nodes status is considered the most important prognostic factor and it is presently the standard of care for melanoma patients at high risk of metastatic disease (4).

The sentinel node is the first lymphatic node to drain lymph from a certain region of the skin and it is highly predictive for the metastatic status of the entire lymphatic basin.

Patients with positive sentinel node will undergo regional lymphadenectomy. For negative sentinel node biopsy, the elective lymph node dissection is not beneficial to the patient (3).

Sentinel node biopsy is usually performed with preoperative lymphoscintigraphy and intraoperative lymphatic mapping with radiocolloid (Technetium – 99m) followed by isosulfan blue, both injected intradermally at the site of tumor's excision. A gamma probe will then identify the radiocolloid and the isosulfan blue will be directly visualized. These methods will permit the sentinel node biopsy through a limited incision with least possible morbidity (Fig. 2). The preoperative lymphoscintigraphy is useful in unpredictable drainage patterns as can be found on the trunk (20-35% of cases) and head and neck (60% of cases) (6). Sentinel node biopsy has a significant low complication rate (less than 5%) in comparison with elective regional lymphadenectomy (22).

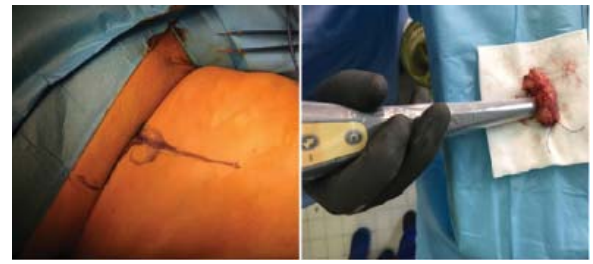

**Figure 2.** Excision of the sentinel lymph node using gamma probe

Recent studies showed that only 16 to 23% of the patients who underwent a regional lymphadenectomy have metastasis in the non-sentinel lymph nodes (23). A new study tried to assess the necessity of lymphadenectomy in comparison with observation and published part of the conclusions in June 2017. The second Multicenter Selective Lymphadenectomy Trial included patients of 18 to 75 years old, diagnosed with skin melanoma of intermediate thickness and with positive sentinel nodes. These were randomised in two groups, one with regional lymphadenectomy and the other with regular monitoring. The study showed that both groups, at three years, had the same survival rate (86%) but different rate of recurrences (32% vs 37%). The conclusions revealed that regional lymphadenectomy in patients with positive sentinel lymph node, does not increase melanoma survival rate, but lowers the local recurrence (24).

## Melanoma recurrence

Although surgery has a good rate of healing, almost 75%, there are also recurrences. These appear in average of 50% in the first year, 75% during the first three years and 90% within the first five years.

Local recurrences are defined as reappearing of melanoma cells near or in the same location, but with no widespread in the body (Fig. 3). Treatment of local recurrences is surgical with narrow excision, because it has not been seen any improvement in survival or in local control with a wider excision (25).

In some cases, the lymphatic space is also contaminated and malignant cells multiply and become palpable under the skin, subcutaneous or intradermally, being defined as in-transit metastasis if located at more than 2 cm of the primary tumour, but not beyond the regional nodes (26) (Fig. 4). These usually occur after the treatment of primary

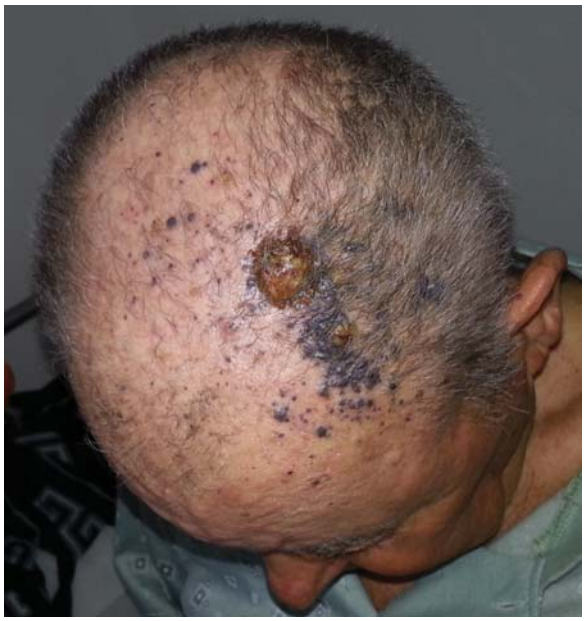

**Figure 3.** Local recurrence of a scalp melanoma

melanoma in approximately 10% of the patients with increased age or limb location and other aggressive pathological factors as high Breslow thickness, high mitotic rate and ulceration (27). The clinical manifestation represents just a part of other subclinical in-transit metastasis. Usually local excision is not sufficient; in-transit metastases having a high rate of recurrence and a lower prognosis, being classified as stage III (28). The treatment is usually chemotherapy and in some cases isolated lymph perfusion (29).

Nodal recurrences appear in patients where regional lymphadenectomy was not performed in proportion of 75% in comparison with patients where lymph node dissection was performed and the nodal recurrence is less than 20% (8). These are also treated surgically, by realising a lymph node dissection.

Distant metastases appear usually in the lungs, liver, brain, gastrointestinal tract and bone. Brain metastasis represents one of the main reasons for death in melanoma patients due to the blood brain barrier that reduces the treatment potency (30). Treatment consists of chemotherapy, radiotheraphy, surgery and target therapies. (31).

Some patients with melanoma recurrence of a single limb might be treated with isolated limb

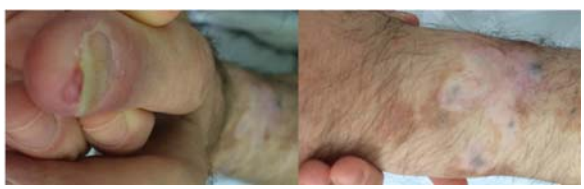

**Figure 4.** Forearm in-transit metastasis (right) of an index subungual melanoma (left)

perfusion, in order to prevent limb amputation. This method might be better than systemic chemotherapy because of the local action of a concentrated chemotherapeutic agent, with minimal body effects. Hyperthermia can also be associated to increase the response rate by improving the drug uptake through vasodilatation. Also, the temperature over 42 degrees is toxic for malignant cells, but can also increase local toxicity (32).

## Metastasizing melanoma without primary tumour

Metastatic melanomas of unknown primary tumour represent 2-6% of all melanoma cases (33). The metastases occur usually as cutaneous or subcutaneous tumours or as lymph nodes metastases. Their treatment and prognostic is similar with cutaneous melanoma with regional metastasis. The recommendation is to evaluate the entire skin and mucosa especially near the regional lymph nodes involved (33).

In order to prevent recurrences and to improve survival, especially in patients with stage IV of disease, numerous adjuvant therapies had been studied.

## Adjuvant treatment

### Radiotherapy

Adjuvant radiotherapy was not very often used in treating melanoma (34), but recent studies showed that in some cases this can be helpful, especially in local control of melanoma with high risk features as local ulceration, desmoplastic type, positive margins or extensive neurotropism (8). Also regional disease might influence these recommendations as extracapsular extension, more than 4 lymph nodes involved, size greater than 3 cm and recurrence after lymphadenectomy. In metastatic disease, radiotherapy can also be used in brain or bone metastasis (8).

### New target melanoma therapies

Although chemotherapy was the standard of care for treating advanced melanoma, nowadays this has been replaced in many cases with newer therapies. Dacarbazine is the standard chemotherapy agent in treating metastatic melanoma, having a higher response rate in some cases (between 30% and 50%), in association with other chemotherapeutics such as Avastine or Paclitaxel (35).

In the last years, numerous studies evaluated the possibility of using immunomodulation and target molecular therapies for treating melanomas. Target therapies block different substances and pathways in melanoma cells, obstructing the growth. Immunotheraphy improves the immune system and stimulates its ability to fight the cancer. In 2011, FDA approved some immunomodulators for

treating metastatic melanoma such as Ipilimumab, Peginterferon α2b and Vemurafenib. Other target therapies were approved since then, including Dabrafenib, Trametinib and Pembrolizumab (36).

Vemurafenib and Dabrafenib are BRAF inhibitors and action as a target therapy, being used in patients with BRAF mutations (approximately 50% of melanomas) and distant metastasis or unresectable melanoma, improving overall survival (37, 38).

Ipilimumab is a monoclonal antibody that up regulates the response of host to tumour cells, increasing survival, but with a small response rate (15-30% of the patients) (39).

Pembrolizumab is a humanized monoclonal immunoglobulin that decreases the size of the lesions and has a disease control rate of 51% (40).

Administration of Interferon α2b showed in some trials a survival benefit, being associated with chemotherapy (41, 42).

All of these target therapies have also side effects like skin toxicity (Vemurafenib), pyrexia (Dabrafenib), hepatitis, colitis and anaemia (Ipilimumab) (11).

In present, new therapies for treating metastatic and recurrent melanoma are in progress; examples include intratumoral therapies with IL-2, plasmid IL-12 electroporation, interferon or bacillus Calmette-Guerin (11).

Another innovation is the use of nanotechnology in treating melanoma. Nanoparticles can be used in drug distribution to the metastatic sites of melanoma, with an increased efficacy and decreased side effects (43).

## Follow up

There is no study that can assess a safe follow up for patients diagnosed with melanoma. National Comprehensive Cancer Network suggest that patients with stage O melanoma should have an annual skin check evaluation due to the increased risk of developing a new melanoma (44). Stage IA-IIA should receive a physical examination every 3 to 12 months for the first five years and then annually, with no additional imaging test (45). Stages IIB-IV should have a physical examination every 3 to 6 months for the first two years and 3 to 12 months for the next three years. In the first five years, the risk of recurrence is high, so additional imaging tests as chest x-ray and computed tomography are recommended every 3 to 12 months. Also, a magnetic resonance imaging of the brain is recommended annually (46).

An annual dermatologic check-up of the skin using digital dermoscopy or total body mapping is better to be done by all patients with melanoma, due to the increased risk of appearance of a new primary melanoma (47).

## Conclusions

Melanoma is one of the most aggressive skin cancers with an increasing incidence in the last years. Early diagnosis, proper surgical and medical treatments are important and have a great impact over patient survival. In advanced stages, melanoma is considered incurable, metastases lowering the survival rate in 80% of the cases to less than five years. New research in molecular medicine has led to creation of new therapies that can increase in time patients overall survival and quality of life.

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