An introduction in melanoma
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A brief history of cutaneous melanoma

Cancer has been described in humans as well as other vertebrates, preceding humankind itself.\(^1\) In humans, cancer was first documented in the Edwin Smith papyrus.\(^2\) Edwin Smith acquired this five meter long piece of papyrus in 1862 from an Egyptian merchant in antiquities in Luxor.\(^2,3\) The papyrus was later established to be written in the 16\(^{th}\) century B.C, being copied from an even older document written around 2500 B.C. It details the entire heritage of the famous Egyptian physician Imhotep, who lived around 2625 B.C. The document describes, amongst other diagnoses, fractures, suturing of wounds and cauterization with fire drills. It also includes a vivid description of what is to be believed the first documented cancer in men:

“If you examine [a case] having bulging masses on [the] breast and you find that they have spread over his breast; if you place your hand upon [the] breast [and] find them to be cool, there being no fever at all therein when your hand feels him; they have no granulations, contain no fluid, give rise to no liquid discharge, yet they feel protuberant to your touch, you should say concerning him: ‘This is a case of bulging masses I have to contend with...bulging tumors of the breast mean the existence of swellings on the breast, large, spreading and hard; touching them is like touching a ball of wrappings, or they may be compared to the unripe hemat fruit, which is hard and cool to the touch’”\(^2\)

Every case in the papyrus is followed by an extensive enumeration of therapies, but in this case, Imhotep falls silent. His brief conclusion states: “There is none.”

Etymologically, melanoma stems from the word ‘melanose’ as introduced in 1804 by Rene Laennec, the inventor of the stethoscope.\(^1\) Although the earliest physical evidence stems from the skeletons of pre-Colombian mummies (2400 years old), in whom diffuse melanotic metastases were found, cutaneous melanoma was not described as an entity until two millennia after the original description of cancer by Imhotep, when Hippocrates described ‘fatal black tumors with metastases’ in the 5\(^{th}\) century B.C.\(^4\) After these early observations, the medical profession grew silent on the topic for a long time. As with many diseases, surgeons were the physicians who made the first progress in treatment. The first reported surgical removal of melanoma was by the Scottish surgeon John Hunter 1787, although the tumor he
removed was not identified as a melanoma until 200 years later, when Bodenham reported that microscopic examination of the specimen confirmed that it was a melanoma.1,5

During the 19th century, large improvements were made in the documentation of melanoma based on thorough clinical observations. Despite numerous efforts and trials in treating the disease, patients with advanced melanoma had very poor prospects, as recognized early in Imhotep’s papyrus. Until far into the 20th century, a bitter statement made by the French historian Voltaire rang true:

“Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing.”

Prior to identifying any specific mutations as drivers in melanoma genesis and the role of the immune system in developing human cancer, the trial and error approach of cytotoxic agents utilized did little to improve the somber prognosis. Halfway through the 20th century William Norris identified that neither surgery nor medical treatments were effective once the melanoma was widely disseminated.4 He advocated surgical excision, as well as ablation using caustic agents. William Norris is also credited with the first case series of melanoma, describing genetic, clinical and epidemiologic features of this disease in eight patients.6 Herbert Lumley Snow published the first report on the rationale of a regional elective lymph node dissection (ELND) in 1892, postulating the “antipathy gland dissection” as a safe and easy procedure.7 This procedure, where lymphadenectomy was performed in select patients as their surgeons saw fit, was later abandoned when four prospective trials showed no impact on survival and replaced by the sentinel lymph node biopsy.9-10 This is different from a therapeutic lymph node dissection (TLND) for clinically apparent metastases, a delayed lymph node dissection (DLND) for metastases that become clinically apparent after the primary diagnosis, and completion lymph node dissection (CLND) which is done after a positive sentinel lymph node biopsy (SLNB).

Although wide local excision was used before, William Handley is widely considered as the father of this technique, describing the procedure in detail in 1907.14 He advocated the removal of 5 cm of subcutaneous tissue down to the level of muscle fascia along with radical removal of lymph nodes. His adage was upheld for nearly 50 years. In the 1960’s, Olsen and Wong published studies that established the 5 cm excision margin as a safe and effective procedure.15-16 Handley’s wide excisions were later abandoned after a series of randomized trials supported the safety of narrower margins.17-20 Current consensus in the majority of Western countries is to excise melanoma in situ with 5 mm margins, melanoma ≤1 mm thick with 1 cm margins, 1.01-2 mm with 1-2 cm margins and >2 mm with 2 cm margins.21-23 Since these resections margins are under debate, the MELMART trial was initiated in 2014 (NCT02385214). As smaller resection margins are expected to improve quality of life patients in this trial are randomized between a 1 cm and 2 cm excision margin and assessed for rate of local recurrence and melanoma specific survival.24

Although rare, spontaneous regression has been reported in melanoma. The reported incidence in primary melanoma ranges from 4-15%, however, regression of melanoma metastases is uncommon and reported in less than 1% of patients.25

Knowledge about and treatment options for melanoma were advancing slowly but surely, but during the 20th century surgeons became increasingly disappointed with the morbidity of lymph node dissections. Data became available that only 20% of all patients with melanoma harbored lymph node metastases. Randomized trials comparing comparing ELND to DLND failed to show a survival benefit.26-30 It was during this era that locoregional and systemic therapies started to emerge. In 1958, Creech and Kremetz published on isolated limb perfusion for in-transit disease, where the blood circulation of a limb is temporarily isolated using a tourniquet.31 This allows for higher chemotherapy concentrations than can be systemically administered. This method was refined in the early 1990’s, when isolated limb infusion was invented, which eliminates the extensive surgical procedure.32 These procedures have dramatically decreased the need for limb amputations. Chapter 4 will provide more detail on the development and success rates of these therapies.

The year 1962 saw the dawn of systemic therapies when a case series was published treating patients with melphalan, an alkylating chemotherapeutic agent, and autologous bone marrow transplants. Though melphalan showed some efficacy, duration of action was short and its use was limited by severe toxicity.1 In 1967 the FDA approved its first systemic therapy, hydroxyurea, for the treatment of metastatic melanoma.33 Hydroxyurea is a cytotoxic agent that acts as a ribonucleotide reductase inhibitor, thereby inhibiting DNA synthesis. Its efficacy is very limited34-35. Dacarbazine, an alkylating agent, was approved in 1976 and remained the standard therapy for decades.36

After the approval of hydroxyurea and dacarbazine, it took nearly 30 years for more drugs to come to market: interferon-α, a cytokine that enhances HLA antigen presentation, activates natural killer (NK) cells and also has a direct inhibiting effect on melanoma cells, was approved in 1996 and interleukin-2 (IL-2), an immuno-stimulatory cytokine mainly involved in T cell proliferation, was approved in 1998.37 Another decade passed before developments truly sped up. For the first time multiple promising agents for the treatment of metastasized melanoma progressed through trials simultaneously.
Since 2011, the US Food and Drug Administration (FDA) and the Europees Geneesmiddelen Agentschap (EMA) have approved nine different agents. That year was a landmark with the introduction of ipilimumab, an anti-CTLA-4 antibody, and vemurafenib, a BRAF inhibitor. In 2013 a second BRAF inhibitor, dabrafenib, was approved. Other approved drugs are the MEK inhibitors trametinib and cobimetinib, the anti-PD1 antibodies nivolumab and pembrolizumab and the intralesional oncolytic virus talimogene laherparepvec.

As melanoma is relatively insensitive to radiation therapy, it is rarely used for treatment. Newer approaches are being developed, such as adjuvant strategies. Adjuvant radiotherapy in patients undergoing a lymphadenectomy for a palpable lymph node field relapse decreased local relapse to 21%, as compared to 36% for observation alone, after six years of follow-up, but did not decrease overall relapse rate. In cutaneous melanoma, radiotherapy is therefore used to increase locoregional control after therapeutic lymphadenectomy and also to treat bone and brain metastases.

A more comprehensive overview of locoregional and systemic options will be provided in the paragraph ‘Treatment’ (page 25), after reviewing epidemiology, clinical presentation, staging, prognosis and pathology.

**Epidemiology**

In 2017, in the United States an estimated 87,110 people will develop melanoma and 9,730 people are expected to succumb to the disease in a population of 326 million people. For the Netherlands, the most recent available numbers are from 2016. In that year 6,787 people were diagnosed with melanoma of the skin and external genitalia in a population of 17 million people. More than a tenfold of that number are classified as living with the disease, which is largely driven by the excellent prognosis (>92% 5-year survival for melanomas ≤1 mm in depth) if melanoma is diagnosed at an early stage. Approximately 78% of all newly diagnosed patients present with stage I melanoma (paragraph ‘Staging’, page 17). Its incidence renders melanoma the 6th most common cancer, representing 4.5% of all new cancer cases in the US. The median age at diagnosis is 57 years and the median age at death is 67 years.

The lifetime risk of melanoma of the skin is 1 in 50 and still on the increase, though the rise in incidence has slowed down. In comparison, incidence was only 1 in 1500 in 1935 and 1 in 250 in 1980. Diagnoses of melanoma in situ are rising faster than other types of melanoma. The increase in incidence is therefore multifactorial and should be contributed to a combination of better screening and earlier detection and an increase in exposure to ultraviolet light which has long been known to be a risk factor for melanoma and nonmelanoma skin cancers. The popularity of tanning beds contributes to this increased exposure. Contrary to other skin cancers, which are mainly associated with cumulative sun damage, intermittent high sun exposure, as indirectly assessed by taking a history of sunburns, has been linked to melanoma. Sunburns in childhood carry the highest risk.

UVA, UVB and ultraviolet (UVR) solar radiation penetrate into the skin and cause DNA damage. The mechanism by which DNA damage occurs is complex, but a simplified explanation would be that UVR leads to single-strand breaks, double-strand breaks and cross-links between DNA strands; both UVA and UVB induce the synthesis of pyrimidine dimers; UVA in addition contributes through the formation of free radicals; and UVB also leads to the formation of 6,4 photoproducts, a specific link between two pyrimidine rings. Two of four base pairs used as a building block in DNA, i.e. cytosine and thymine, are pyrimidine derivatives. Formation of dimers interferes with base pairing during DNA replication and thereby leads to mutations. Free radicals, single-strand breaks and double-strand breaks lead to immediate DNA damage upon replication.

A small percentage of melanomas are discovered in a disseminated phase without a primary melanoma being identifiable. A large case series showed an incidence of 2.6% for these so-called melanomas of unknown primary. Based on mutational analysis, melanomas of unknown primary have a mutation profile consistent with cutaneous sun exposed melanomas and may arise in lymph nodes or as distant metastasis from cells that have migrated from the skin. Survival is similar to melanoma with macroscopic lymph node metastasis. When it comes to treatment decisions, these melanomas should therefore be regarded as cutaneous melanoma.

Men are more susceptible to developing melanoma than women (relative risk (RR) 1.74), with men developing melanoma most commonly on the trunk and women on the extremities. This is hypothesized to be caused by patterns in behavioral sun exposure, as recent years have seen an increase in trunk melanomas in women. Other risk factors include age (RR 1.02 per year increase), family history (RR 2.19 for positive family history), number of naevi (RR 3.08 with 10+ >3 mm naevi on extremities), hair color (as compared to light brown, RR 0.60 for black hair, RR 1.21 for blonde (non-significant) and 2.05 for red hair) and history of sunburns (RR 2.36 for >10 severe sunburns). Smoking is associated with an increase in Breslow thickness (0.25 mm), ulceration and positive SLNB.

Of all melanomas, 5-12% are estimated to be hereditary. The most common driver gene in this group of patients is cyclin-dependent kinase inhibitor 2A (CDKN2A), which codes for proteins acting as tumor suppressors in the cell cycle. Autosomal dominant inheritance of germline CDKN2A mutations has been implicated in approximately 20-40% of familial melanoma; the mutation frequency varies between different geographical regions. Other, more sporadic, entities are ocular melanoma, acral melanoma and mucosal melanoma, which carry different characteristics and a different prognosis. These entities fall outside the scope of this introduction.
Clinical presentation

The skin is the largest organ of the body and consists of the epidermis and dermis. Melanoma originates in melanocytes, found in the epidermis, which makes the tumor distinctly different from both carcinomas - originating in epithelial tissues - and sarcomas - arising in mesenchymal tissues. Approximately 25% of melanomas originate in pre-existing lesions, so the majority of tumors arise de novo with no identifiable precursor lesion. A de novo melanoma arises when an oncogenic stimulus, often excess sunlight, as described above, acts on these melanocytes, leading to proliferation of the mutated melanocytes.63

Clinically, the lesion progresses from a light tan macule, to a small pigmented macule without significant aplasia, to a lesion manifesting noticeable abnormalities as the mutated melanocytes spread throughout the epidermis.63 The tumor is usually dark in origin, reflecting the presence of melanin in the upper levels of the epidermis. Between 1.8 and 8.1% of melanomas is amelanotic, lacking the characteristic dark color.64 Metastasis occurs when the tumor starts extending to the dermis and subcutaneous fat, where it can invade blood vessels and lymphatics. This is also the stage at which ulceration, nodule formation and regression may occur.63

Diagnosing melanoma starts with a skin exam, sometimes aided by the use of a dermatoscope, a handheld device specifically designed to examine the skin using skin surface microscopy.65 Since the different clinical presentations of melanoma only constitute a few diagnoses out of the more than 1500 skin conditions that have been described, skin assessment is more accurate in the hands of an experienced clinician, leading to a lower number of false negative excised lesions.65 The number of melanocytic lesions that have to be excised to diagnose one melanoma, otherwise known as number needed to treat, varies highly depending on the experience of the assessing clinician, from 20-40 for general practitioners at nonspecialized clinics, to 19-28 for general practitioners at skin cancer clinics, to 4-8 for dermatologists at specialized clinics.65

The risk of a mole being melanoma can be assessed using the ABCD(E) rule, which encourages a systematic evaluation of the lesion in search for signs of asymmetry, border irregularity, color variation, diameter >6 mm and evolution (Figure 1).66 It is important to combine these factors as the sensitivity and specificity of the individual criteria are limited; sensitivities of 57%, 57%, 65%, 90%, and 84% and specificities of 72%, 71%, 59%, 63%, and 90% for the five traits have been reported, respectively.67,68 If a lesion is suspect for a melanoma, a biopsy will be done to obtain a histological diagnosis. Incisional as well as excisional biopsies may be done, however, excisional biopsy is preferred and recommended by the AJCC as it encompasses the entire lesion and provides the best information for pathological diagnosis and staging.53 The biopsy must achieve adequate depth and circumference, to facilitate complete tumor removal, and can be done using narrow margins. Microscopically, atypical melanocytes will be visible throughout the various layers of the skin, depending on the stage of progression and Breslow depth.69 Upon histological/pathological confirmation of a melanoma diagnosis and Breslow depth, re-excision with wider margins should be performed if necessary as described above.61-62 Incisional biopsy of the most atypical part of the lesion can be an option for large lesions, lesions that have a low suspicion for melanoma, or are located on face or acra.63 This type of biopsy has the risk of underestimating the true depth of a lesion as it samples only part of a lesion.

For high risk patients as identified by pathology results and clinical symptoms/exam findings, evaluation for disseminated disease is performed using imaging techniques, e.g. FDG-PET or CT-scans.69,70 Melanoma can metastasize to almost all organs, but the most frequently involved sites are liver, bones, lungs and brain. For the brain, MRI is the modality of choice. Due to inability to identify micrometastases and the low probability of metastasis in early stage disease, these imaging techniques have a limited role in stage I and II tumors.71,72

Staging

The first effort to use a staging system for melanoma was introduced by Wallace Clark in 1969, subdividing melanoma into five anatomic levels of invasion.73 Clark’s levels use the level of downward invasion of the melanoma. Five-year survival ranges from over 99% for Clark level I (melanoma in situ) to 55% for Clark level V. Clark concluded that ELND should be restricted to patients with level III, IV and V lesions.7 In 1970 Alexander Breslow introduced Breslow thickness as a measurement, which is still in use today (Figure 2).64 Breslow thickness

Figure 1 - ABCDE rule in melanoma66

![Image of ABCDE rule in melanoma](https://example.com/image1)

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is a quantitative measurement of the total vertical depth of a melanoma, as measured in millimeters, and has become a major prognostic factor for localized melanoma. It is also used to identify patients who benefit from sentinel lymph node biopsy after surgery.

The AJCC introduced a more precise staging system in 1998 and has updated this system since. The 7th edition of the melanoma staging system was published in 2009. The 8th edition will be implemented at the start of 2018. The AJCC staging system uses three parameters, local advancement (T), a combination of Breslow depth and ulceration, lymph node status (N) and distant metastasis (M). It is therefore also referred to as the TNM staging system. Regional metastasis is defined as metastasis to the regional lymph nodes, the location of which depends on the location of the primary melanoma, or in-transit/satellite metastasis, which is metastasis in between the primary melanoma and the regional lymph node station. Distant metastasis is all other skin and lymph node metastasis and also includes visceral metastasis. The three parameters (T, N and M) are then combined into four categories (I-IV, Figure 3). Stage I represents limited local disease, stage II locally advanced disease, stage III regionally advanced disease and stage IV distant metastasis. The AJCC staging system, and before that the Clark and Breslow systems, have guided patient selection in many trials.
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Step by step this has led to a better understanding of cellular pathways and possible actionable targets. Figure 4 shows a simplified representation of eight pathways identified in melanoma. Our understanding of the molecular background of cancer has advanced since the publication of this model, but it still serves as a good base for pathways found in melanoma. Abnormalities in the MAPK pathway, also known as Ras-Raf-MEK-ERK pathway, are found in 80% of patients with melanoma.

Prognosis

Melanoma has an excellent prognosis when discovered at an early stage, however, overall survival (OS) drops sharply as stage progresses. From a cellular perspective, metastases are inefficient and uncommon. Only 0.01%-0.03% of cells in a primary tumor metastasize to other organs, offering an explanation for the relatively low rate of tumors that metastasize. Although melanoma is well known for its capability of late metastasis, the vast majority of metastases happen early in the disease.

For stage IA, IB, IIA, IIB, and IIC 5-year survival rates are 97%, 92%, 81%, 70% and 53%, respectively. Five-year survival for locoregional metastasis is 78% (stage IIA), 59% (stage IIB) and 40% (stage IIC). Once melanoma has metastasized distantly, 5-year survival drops to 15-20%, although these rates are expected to improve upon the recent introduction of BRAF-targeted drugs, checkpoint inhibitors and combination therapies. Greater Breslow thickness, tumor location, gender, tumor ulceration, microsatellites, mitotic rate, regression, sentinel lymph node, number of tumor-infiltrating lymphocytes and angiolymphatic invasion have all been associated with prognosis. Out of these, long-term follow-up reveals the strongest predictors for recurrence are Breslow depth (as compared to Breslow depth ≤1 mm, odds ratios [OR] for 2-4 mm and >4 mm are 2.84, 6.08 and 8.81, respectively), ulceration (OR 2.41 for ulcerated tumors vs. non-ulcerated tumors) and sentinel lymph node status (2.74 for positive SLNB vs. negative SLNB). Once metastasis has occurred, the site of first metastasis is the most important prognostic factor (hazard ratio (HR) 1.3 for metastasis to the regional lymph nodes vs. satellite/in-transit recurrence, and HR 5.5 for distant metastasis vs. satellite/in-transit recurrence, p < 0.001).

Pathology, molecular biology and actionable targets

After biopsy the diagnosis of a skin lesion depends on pathologic assessment. The Edwin Smith Papyrus is the earliest source of pathological anatomy, however, a pivotal development in current tissue diagnosis was the invention of the microscope, which changed concepts of disease from whole organs to separate cells and enabled cytological and histological assessment of tumors. Paraffin embedding was added to the repertoire by Edwin Klebs in 1869. Cytological characteristics of melanoma include the presence of atypical and necrotic melanocytes and melanocytes undergoing mitosis. Histologically, melanoma is classified based on asymmetry, poor circumscription and the presence of irregularly distributed melanocytes occupying the epidermis, dermis and adjacent tissues. Melanin is irregularly distributed in the lesion. Chemical and immunohistochemical stains may aid the diagnosis. Various markers are used, such as S-100B, HMB45, Mart-1, tyrosinase, MITF, NKI/C3, CD10 antigen and vimentin. To optimize sensitivity and specificity a combination of these diagnostic aids should be used.

Recent years have seen the emergence of molecular biology, which has the potential to identify gene mutations that can be used as therapeutic targets. In 2010, a melanoma cell line was the first cell line being reported in a whole genome sequencing study cataloguing the somatic mutations in cancer. Step by step this has led to a better understanding of cellular pathways and possible actionable targets. Figure 4 shows a simplified representation of eight pathways identified in melanoma.
Although NRAS mutations were the first oncogenes described in melanoma in 1984, the development of targeted therapy in metastatic melanoma truly has its footing with the identification of activating mutations in BRAF, a serine threonine kinase, in 2002 by Davies et al. 88 BRAF was first identified in 1988 as the transforming gene in a sample of Ewing’s sarcoma. 89 Mutations in exon 15 of the BRAF gene are now known to occur in 40-60% of cutaneous melanomas, with the most common being the V600E mutation, an amino acid substitution at position 600 in BRAF from a valine to a glutamic acid, in >85% of these patients. 90 This gain of function change leads to constitutive activation of the MAPK pathway, resulting in cell growth, proliferation and increased invasive potential. BRAF is a promising target for systemic treatments as these tumors are generally dependent on a single oncogene, like Bcr-Abl in CML and c-KIT in gastrointestinal stromal tumors. While BRAF mutations alone are not able to transform melanocytes into malignant melanoma cells, they create a more aggressive phenotype of melanoma and prior to the development of targeted agents patients with metastatic melanoma harboring BRAF mutations had worse overall survival than the average population. 91 Curiously enough, BRAF is not exclusively found in melanomas, but is also present in the majority of benign naevi. Most of these naevi are in a state of permanent growth arrest (senescence) following the acquisition of mutant BRAF, which explains why so few naevi progress to melanoma. 92 The molecular disease model also demonstrates the benefit of combination therapy. By e.g. combining BRAF inhibitors and MEK inhibitors, the MAPK pathway is inhibited on two separate levels. This increases response rates and delays the onset of resistance, as further discussed in the paragraph ‘Epidemiology’ (page 14).

Another topic of interest in tumor biology is biomarkers, as these would be able to predict prognosis and, in an ideal situation, will assist in selecting patients for systemic treatment based on anticipation of response, thereby tailoring oncologic treatment to the patient. Lactate dehydrogenase (LDH) and S-100B have been found to serve as biomarkers and may be used to measure response to therapy. Increased levels in peripheral blood are associated with worse outcome. 93 LDH, which is included in the AJCC staging system, can be very useful for detecting distant metastasis; however, it is also associated with other malignancies and has low sensitivity. 94 S-100B is located in the cytoplasm of melanoma cells and its presence in peripheral blood is thought to be caused by loss of integrity of these cells. It is strongly correlated with both tumor burden and survival. 95 In a recent small patient series, preoperatively measured S-100B was the strongest predictor for non-sentinel node positivity in patients planned for CLND. 96 Other implied biomarkers are PD-1 and PD-L1 expression on the tumor, which have been used in phase 3 studies of agents directed against these proteins. PD-L1 expression did have an effect on overall response rate to PD-L1 inhibitors in a review (45% for PD-L1 positive patients vs. 27% in PD-L1 negative patients), a pattern that can be seen in the treatment of other tumor types as well. 97 As responses are still seen in the PD-L1 negative group, this marker is not yet ready to be used to select patients. As of yet, these biomarkers have not resulted in a better selection of patients or seen a translation into survival benefit and their use is mainly prognostic, however, as more data become available utility of biomarkers may expand.

Melanoma and the immune system

Tumors may evolve using a process called immunoediting, which consists of three phases: elimination, equilibrium and escape. 31 Through the process of immunosurveillance (elimination), the immune system continuously checks cells to distinguish invading cells, such as bacteria and viruses, from the body’s own and tumor cells from their non-cancerous counterparts.
To do this, it uses checkpoints; molecules on immune cells that need to be activated or inactivated to start an immune response. These checkpoints use the proteins that are expressed on the cellular surface or foreign cells to recognize and eliminate threats. The phrase ‘immune checkpoints’ thus refers to a plethora of pathways in the immune system that regulate immune responses (Figure 5). Immune tolerance and evasion by tumor cell populations can be achieved through these immune checkpoints. Cytokines have similar actions, but typically have diverse functions on immune cell populations, including immune suppression (e.g. IL-6 and IL-8) and stimulation of T cell activity and proliferation (IL-2). Both cells in the immune system and tumor cells express immune checkpoint molecules, which can have either stimulatory or inhibitory effects on immune cells. E.g. PD-1 on physiological cells acts as an off-switch to keep the immune system from attacking the own body. When tumor cells express PD-L1, one of the ligands of the PD1 receptor, the binding of these two proteins leads to the immune system not reacting to the tumor cell. The tumor cells surviving the elimination phase enter into equilibrium between immunologic pressure and tumor growth. It is thought that this process may last up to many years, before the tumor acquires insensitivity to immunologic detection and/or elimination through genetic or epigenetic changes, escapes the equilibrium and starts to grow uncontrollably.

T cells require three signals for optimal T cell recognition and generation of an adaptive T cell immune response: first, recognizing antigen presented by major histocompatibility complexes (MHCs); then, a signal activating T cells, e.g. interaction of the CD28 costimulatory marker on T cells with CD80/CD86 on antigen-presenting cells. 4-1BB and OX40 can also initiate this step. Third, amplification of T cell receptor signaling and secretion of cytokines (e.g. IL-2), which then differentiate and activate T cells. T cell activation leads to release of cytotoxic granules (e.g. granzyme and perforin) and direct induction of apoptosis (e.g. Fas-Fas ligand interactions), leading to tumor cell death.

Melanoma is known to be a tumor with a high mutational load and should thus be recognized by the immune system as foreign. The fact that the tumor is able to evade the immune system provides possibilities in priming the immune system. Cytokine therapies such as IL-2 and interferon-α have served as proof of principle that the immune system can be stimulated to produce antitumor responses against melanoma and other tumor types. While IL-2 has the potential to produce durable responses in patients with advanced melanoma, objective responses occur in less than 20% of patients and serious toxicities are observed in most patients. The search for more effective and tolerable immunotherapies was rewarded with the development of CTLA-4 and PD1/PD-L1 antibodies.

The immunoglobulin CTLA-4 (CD152) is a transmembrane receptor exclusively expressed on T cells. CTLA-4 competes with the costimulatory CD28 molecule for binding CD80/CD86, leading to downregulation of T cell receptor signaling. CTLA-4 knockout mice experience lethal systemic immune hyperactivation, thereby demonstrating the importance of the immunoglobulin. In response to the CD28-CD80/CD86 interaction, tumor cells can develop resistance by aberrantly overexpressing inhibitory ligands (e.g. PD-L1) that downregulate T cell effector function through T cell exhaustion or anergy. The binding of ligand PD-L1 on antigen presenting cells and tumor cells to PD1 on T cells delivers an inhibitory signal to the T cell, inhibiting T cell receptor signaling, activation of IL-2 production and T cell proliferation. Under normal physiological circumstances, the main role for PD1 is to limit effector T cell responses in peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity, thereby protecting against immune-mediated tissue damage. PD1 is a transmembrane protein expressed on activated T cells, B cells and monocytes. Binding of anti-PD-L1 to PD1 downregulates T cell activation, so blocking either PD1 or PD-L1 interrupts this signal, leading to activation of T cells and removing the inhibitory signal that keeps the immune system from attacking the tumor. The paragraph ‘Epidemiology’ (page 14) will provide more details on clinical efficacy of these agents.

The other ligand that has been described for PD1 is PD-L2. PD-L2 is not as widely expressed as PD-L1 and its role in cancer genesis is less clear. While studies have found that patients with tumors expressing PD-L1 have an impaired survival, no such correlation has been found for PD-L2. It is too early to say whether PD-L2 is a viable target. Antibodies against PD-L2 are being developed, as are antibodies against some of the other receptors shown in Figure 5, such as OX40 and 4-1BB.

**Treatment**

A broad range of therapies have been used over the years to treat melanoma, however, Imhotep’s somber treatment statement - ‘There is none’ - rang true until into the 20th century. Surgery is still the mainstay of melanoma treatment (paragraph ‘Epidemiology’, page 14). For patients with isolated in-transit metastasis (i.e. no other identified metastases) in the extremities and liver metastasis, locoregional perfusion/infusion techniques or intralesional injection may be used (paragraph ‘Epidemiology’, page 14). As mentioned in the paragraph ‘A brief history in cutaneous melanoma’ (page 11), the 2000’s have seen the dawn of new checkpoint blockade and BRAF-targeted systemic therapies. This will be further discussed in the paragraph ‘Epidemiology’ (page 14).

**Surgical treatment**

Surgery is a cornerstone in melanoma treatment. As described in the paragraph ‘A brief history in cutaneous melanoma’ (page 11), for stage I-II patients, surgical excision with 5 mm margins for melanoma in situ is advocated, 1 cm margins for melanomas ≤1 mm, 1-2 cm margins for melanoma 1.01-2 mm and 2 cm margins for melanomas ≥2 mm thick, combined with a sentinel node biopsy in melanomas ≥1 mm in depth. For select stage III-IV patients, surgery provides an improved chance at long term survival, therefore metastasectomy should be considered in patients with limited metastasis. Most locoregional disease will...
be amenable to resection aiming to render the patient free of disease. However, some patients will present with unresectable bulky adenopathy due to surgical limitations such as involvement of neurovascular structures. Similarly, as many as 24% of patients with recurrent locoregional melanoma have satellite and/or in-transit disease not amenable to complete resection.

The newest development in surgical treatment is to perform robotic-assisted or videoscopic surgeries. This has mainly been described for inguinal lymphadenectomies and allows for less invasive procedures while maintaining an adequate lymph node yield. Shorter hospital stays and less wound complications have been described in a small number of patient reports, however, more extensive data are needed to establish the role of these procedures in melanoma treatment.

Sentinel lymph node biopsy

The sentinel lymph node biopsy (SLNB) is an intraoperative procedure where the status of the draining lymph node basin is assessed by excising the first node draining a tumor, as identified by a combination of radioactive tracer and dye. The procedure was made possible by the discovery of lymphoscintigraphy in 1977 and first described by Morton in 1992. The goals of SLNB include accurate staging, enhancing regional disease control, identifying patients for adjuvant treatment regimens and improving survival. Ten year survival for sentinel node negative and sentinel node positive patients is 85.7% and 63.1%, respectively, making it the single most important predictive factor for survival. Morton pioneered the procedure and dedicated his life to continued improvements in the SLNB procedure, right up until his death in 2014.

Before the SLNB was common practice in patients with melanomas ≥1 mm Breslow depth, as advocated by the AJCC, many surgeons favored ELND as consensus was that this improved outcomes. Physicians observed that lymph node metastasis often precedes more widespread metastatic disease, and hypothesized that removal of lymph nodes therefore may prevent systemic metastasis. The procedure was abandoned after four trials did not show survival benefit, although the fact was recognized that regional lymph node positivity is strongly associated with a worse prognosis. As compared with patients who never developed nodal metastases after wide excision of the primary without ELND, the HR for death was 1.25 in patients with histologically positive nodes at ELND and 2.11 in patients who developed node metastases during follow-up and underwent a DNLN.

The SLNB procedure has revolutionized surgical treatment of melanoma as it has made the ELND largely obsolete, with much less morbidity. During the procedure, the first lymph node or group of lymph nodes to drain lymphatic flow from the primary tumor site is identified using radioactive blue dye, 1% isosulfan blue with the addition of Tc99m sulfur colloid, and resected. The radioactive tracer allows for creating a map of lymphatic drainage using lymphoscintigraphy before surgery and identifying the sentinel lymph node during surgery using a handheld scanner with a gamma sensor probe. The blue dye allows for visual identification of the sentinel lymph node and distinguishing lymphatic tissue from surrounding tissues. Using a combination of both tracer and dye garners higher identification rates than using either technique alone. Drainage to more than one lymph node basin occurs in 15-27% of patients. The excised tissue is examined postoperatively, as the sensitivity for melanoma detection has been found to be higher in formalin-fixed tissue as opposed to frozen tissue. Frozen tissues provide a suboptimal morphology, requires embedding in paraffin which leads to unexamined sections and may lack the subcapsular region of the lymph node, which is where micrometastases often are found.

The procedure is aimed at identifying occult lymph node metastases. If the sentinel node is positive, patients will undergo CLND with removal of all lymph nodes in the basin, as identified in the NCCN guidelines. The only exceptions to these are enrollment into a clinical trial and severe comorbidities precluding surgery. The procedure is highly reliable, with the ability to find the sentinel lymph node in 96% of patients. SLNB is recommended in patients with tumors ≥1 mm thick. The MSLT-I trial looked at wide local excision, nodal observation and TLND compared to wide local excision, SLNB and immediate lymphadenectomy for nodal metastases. Ten year disease free survival was significantly improved in the SLNB arm in patients with intermediate thickness (1.20-3.50 mm, HR 0.76) and thick (>3.50 mm, HR 0.70) melanomas. There was no difference in melanoma-specific survival rates or OS after ten years.

Of the patients who do undergo CLND, additional positive lymph node nodes are found in 20%. In patients with melanoma ≥1 mm, the sentinel lymph node is only positive in 5% of cases. These observations led to the design of the MSLT-II trial, which randomized patients with a positive SLNB between CLND and ultrasound monitoring of the lymph node basin. Ultrasound can detect metastases as small as 4 mm. The primary endpoint is melanoma-specific survival. Results are still awaited.

The optimal timing to perform the SLNB procedure after excisional biopsy has not been established, however, consensus is that the procedure should be done as soon as possible. A cohort study in 1015 patients did not identify time interval from primary excision to SLNB as a prognostic factor for survival after a follow-up of three years. Morbidity of the SLNB is relatively limited, with wound infections, seroma, postoperative bleeding and erysipelas reported in 2% of patients and mild lymphedema in 6-11%. CLND leads to a marked increase in lymphedema, with 7% of patients reporting symptoms after axillary node dissection and 64% after inguinal node dissection, and wound complications (infection, seroma, necrosis, hematoma) in 51% of patients with inguinal lymph node dissection. TLND leads to a higher frequency of lymphedema and longer hospitalization as compared to CLND.
Locoregional treatment

Patients with limited locoregional disease often experience relatively few symptoms, which has prompted physicians to look into alternative treatment modalities. Treatment modalities described in this population include: intralesional injection for limited cutaneous metastases, (hyperthermic) isolated limb perfusion (HILP/ILP) and isolated limb infusion (ILI) for bulky disease limited to the extremities and percutaneous hepatic perfusion (PHP) for patients with isolated liver metastases.\(^{1,23,106-107,130-141}\) Locoregional therapy has several advantages over systemic therapy, as local drug administration allows for delivery of an increased concentration of the agent and reduced systemic exposure, thereby both increasing efficacy and lowering toxicity.\(^{106,134}\) These treatments can be repeated multiple times, depending on response and toxicity.

Intralesional injection was first described by Coley, who reported regression of locally advanced tumors after injection of mixed bacterial toxins in 1893.\(^{141}\) The ideal agent will express a bystander effect, where uninjected distant lesions exhibit a response.\(^{190,197}\) Since then, numerous agents have been tested, but the most promising data have been found for PV-10 and talimogene laherparepvec (TVEC).\(^{106,107,131,144-146}\) The latter was FDA approved in 2015.\(^{33}\)

PV-10 (rose bengal) is a xanthine dye which creates reactive oxygen by reacting with visible and ultraviolet light, thereby mediating phototoxic reactions and inducing autolysis in lysosomes of cancer cells, which selectively absorb the agent.\(^{195,147}\) Its predecessor was first patented back in 1882 as a wool dye and the first clinical application of rose bengal was to combat ocular pneumococcal infection in 1914.\(^{148}\) Other applications included use as an ophthalmic diagnostic agent, a marker for impaired liver function (now redundant) and a food dye. Its anti-carcinogenic effects were not discovered until the 1980s, when the Japanese Ministry of Health and Welfare decided to look into the safety of artificial food colorings. Akihiro Ito evaluated rose bengals tumorigenicity in mice and found, contrary to his expectation, dose-dependent survival increases for mice who received daily rose bengal after 82 weeks of exposure.\(^{148}\)

TVEC is an oncolytic, immune-enhanced herpes simplex virus type 1, selectively infecting cancer cells and destroying the cells by direct effects on metabolic processes and inducing immune responses.\(^{191}\) TVEC has shown an OS benefit as compared to GM-CSF (23.3 months vs. 18.9 months) in patients with stage IIB/IIIIC/IV-M1a cutaneous head and neck melanoma in its randomized phase 3 trial.\(^{193}\) A retrospective subgroup analysis suggests that the results in melanomas of the head and neck may be even better.\(^{197}\)

Regional therapies were first reported in the 1950’s when open cannulation (i.e. placing a cannula in a blood vessel using an open surgical procedure, as opposed to percutaneous placement) and surgical control of the vessels were achieved to provide intra-arterial regional chemotherapy.\(^{199}\) The first techniques described used open procedures, requiring a laparotomy for hepatic perfusion and an incision in the groin/axilla for HILP/ILP.\(^{134,147,149}\) These techniques were later refined using a percutaneous approach for PHP and ILI, which decreased the duration of the procedures and associated morbidity and mortality.\(^{192,196}\)

The extremities are particularly suitable for perfusion and infusion techniques as the vascular in- and outflow can be isolated using an extremity tourniquet. The systemic leak rate is less than 1%.\(^{137}\) The chemotherapeutic agents most widely used in ILI and HILP are melphalan combined with tumor necrosis factor-α (TNFα) and dacitoximycin.\(^{131,133,135-140,149}\) Reported results for ILI demonstrate complete response (CR) rates ranging from 23% to 44% and partial responses (PR) from 27% to 56% with a median duration of response between 12-18 months.\(^{139,141,142}\) ILP improves response rates as compared to ILI, but not PFS or OS.\(^{150}\) Burden of disease is a prognostic factor for response.\(^{134,144,149}\)

Although percutaneous perfusions have been described for other organs, the liver is specifically suitable for this approach because venous outflow into the systemic circulation for the entire liver is via the hepatic veins into the inferior vena cava, vascular isolation of the liver can be achieved via balloon occlusion of the inferior vena cava. This also allows for filtering the chemotherapeutic agent with a veno-venous bypass before it reaches systemic circulation in order to limit systemic toxicity. PHP is especially important in uveal melanoma, where 95% of patients that develop metastatic disease will have liver metastases, which in 80% of cases will be the only site of distant disease. Even large tumors, covering more than 50% of the liver, can be treated this way.\(^{106,137}\) The overall response rate (ORR) for this procedure is 60% and disease control rate is 90%.\(^{134}\) A retrospective cohort reported a significantly improved PFS for PHP of 245 days, compared to 52 days for chemoembolization and 54 days for yttrium-90, however, it should be taken into account that not all patients are candidates for PHP and more (randomized) research is needed in this area.\(^{155}\)

Adjuvant and neo-adjuvant treatment

Until recently, adjuvant (i.e. post-surgery) and neoadjuvant (i.e. pre-surgery) systemic therapies had not shown an improvement in survival. Up until 2015, high dose interferon-α during one year was the only adjuvant therapy approved by the FDA.\(^{98,196}\) A pooled analysis of all randomized trials involving high dose interferon-α (n = 4) conducted by the Eastern Cooperative Oncology Group (ECOG) showed a significant decrease in relapse free survival (RFS), but not OS. Study E1684 compared adjuvant high dose interferon-α to observation and reported a HR for recurrence-free survival (RFS) of 1.38 in favor of interferon-α. E1690 compared three groups; observation vs. low dose interferon-α (no benefit) and high dose interferon-α; the HR for RFS was 1.24 (non-significant). Neither study reported a statistically significant OS benefit. E1694 compared interferon-α to GMK vaccine and demonstrated both improved RFS (HR 1.33) and OS (HR 1.32). E2696 included three groups; GMK vaccine alone vs. GMK with either concurrent or sequential interferon-α. This study showed neither RFS nor OS improvement.\(^{157}\)
The most extensive data on this topic, however, come from a meta-analysis of all randomized controlled trials published between 1990 and 2008 (n = 14) and involved 8122 patients. In these trials, 17 comparisons were made between interferon-α and a comparator. Disease free survival was improved in 10/17 comparisons (HR 0.82) and OS was improved in 4/14 comparisons (HR 0.89).165 Discontinuation rates of 37% have been reported because of toxicity.166 Based on these data, the benefit of adjuvant treatment with interferon-α has always remained controversial.

In 2015, the FDA approved adjuvant use of ipilimumab for stage III melanoma patients based on a phase 3 trial conducted by Eggermont et al.33,159 Patients who had undergone complete resection of stage III melanoma were randomized between 10 mg/kg ipilimumab and placebo. After a median follow-up of 5.3 years, RFS was 41% vs. 30% and 5-year survival was 65% vs. 54%, both statistically significant with approximately 25% risk reduction. However, over 40% of patients treated with ipilimumab in this study experienced a treatment-related grade 3-5 adverse event. This has placed concern over the routine use of ipilimumab 10mg/kg in a clinical setting. Ipilimumab has been directly compared to high dose interferon-α in the ECOG 1609 study, but the results have yet to be reported.

Regarding neoadjuvant therapy, small prospective studies with temozolomide, interferon-α, and biochemotherapy - a regimen containing multiple chemotherapeutic agents in combination with interferon-α - have demonstrated tumor burden reduction and occasional pathologic complete responses in resectable stage III patients. ORR’s of 16% for temozolomide, and 26% for biochemotherapy were shown.34,35 For high-dose interferon-α, an objective clinical response of 55% was reported.152

This landscape may change when results from trials using BRAF-targeted therapy and anti-PD1 therapy become available.

Systemic therapy in advanced melanoma

Systemic therapy is the primary treatment for patients with unresectable locoregional and metastatic melanoma. Prior to the recent therapeutic advantages, cytotoxic agents were the first choice for treatment in advanced melanoma. Chemotherapeutic agents used for melanoma treatment include dacarbazine, cisplatin, temozolomide, nitrosoureas ( fotemustine, carmustine and lomustine) and taxanes (docetaxel and paclitaxel). ORR’s range from 10-20%.35 With the exception of dacarbazine, none of these have received a formal approval by the FDA.31 Although the antimetabolite hydroxyurea received FDA approval as well, based on efficacy in combination with radiotherapy, consensus is that hydroxyurea does not show efficacy in metastatic melanoma as monotherapy.36,35 Out of the enlisted options, the two main drugs that have been used are dacarbazine and temozolomide. Dacarbazine was introduced in 1972 and FDA approved in 1976.167 It yielded a response rate of 16% and the median OS was 4.5-6 months. Long term responses are extremely rare, with less than 2% of patients being alive after six years.164-66 Although never formally approved, temozolomide has shown similar efficacy to dacarbazine and has the added advantages of crossing the blood brain barrier and being an oral agent.165 While older regimens such as biochemotherapy have fallen out of favor due to associated toxicities and unclear benefit over other options, carboplatin plus paclitaxel is another regimen that has been used based on an ORR of 11% and median PFS of 17.9 weeks.167 No chemotherapy regimen has demonstrated an improvement in overall survival.163 Targeted agents, such as BRAF and MEK inhibitors, selectively inhibit a mutated protein or activated pathway that is unique to the tumor, as opposed to chemotherapy, which targets all rapidly dividing cells. For the majority of mutations shown in Figure 4 (e.g. P13K, CDK4/6 and mTOR) targeted inhibitors exist, but so far these have not proven a benefit in melanoma.97 Other mutations such as NRAS, KRAS and HRAS have not yet seen successful therapies specifically targeting the mutation.

The first BRAF inhibitor proceeding to phase 3 trials was sorafenib, which was added to a carboplatin/paclitaxel regimen.251 Due to its low potency and low selectivity for BRAF V600E it failed to achieve its goals. Phase 3 randomized studies of BRAF inhibitors vemurafenib and dabrafenib vs. dacarbazine have shown objective response rates of 50-53% in metastatic BRAF V600E mutant melanoma patients.31,38 Although responses seen using BRAF monotherapy can be dramatic, the majority of patients develop resistance, with a median PFS of five months in the earlier trials and seven to nine months in the later trials.37,38,168 Like immunotherapy, BRAF inhibitors have also shown improved survival in melanoma patients, with 84% of vemurafenib patients alive after six months, compared to 64% of patients on dacarbazone. Resistance against BRAF inhibitors may be intrinsic or acquired. Most mechanisms lead to reactivation of the MAPK pathway or activation of PI3K/akt/mTOR pathway. The addition of MEK inhibitors increases response rates to 68% and extends the median PFS to 9-13 months.19,40,29,68 The importance of combination therapies becomes apparent when looking at the pathways in Figure 4, as melanoma develops resistance in >95% of patients treated with chemotherapy, interferon-α and IL-2 and >75-80% in patients treated with BRAF-targeted therapy or ipilimumab.20,38 In the case of treatment with BRAF and MEK inhibitors, vertical blockade of the MAPK pathway increases efficacy and delays the onset of resistance. As introduced in the paragraph ‘A brief history in cutaneous melanoma’ (page 11), another strategy has been to target the immune system to drive anti-tumor immune responses against melanoma tumors based on its established immunogenicity. The first systemic immunotherapeutic agents that demonstrated clear activity in patients with advanced melanoma were interferon-α and high dose interleukin-2 (IL-2). FDA approved in 1995 (as adjuvant therapy) and 1998, respectively. IL-2 has a response rate of 16% and interferon-α of 23%.35,169 Both agents did improve long term survival in a subset of patients (~5%), however, median survival still was only six and twelve months, respectively.99,171 The current decennium has seen a second wave of immunotherapies. Ipilimumab, an anti-CTLA-4 antibody, was FDA approved in 2011. It was the first drug to show an OS benefit for melanoma, though it was still limited by the low percentage of responders, with an ORR of 10-
Pembrolizumab and nivolumab, both blocking the checkpoint molecule PD1, received FDA approval in 2014. Agents that act on PD1 and PD-L1 may only be the beginning of a renewed exploration into using the immune system as a tool against cancer. Of note, responses to immunotherapy cannot always be measured by using the traditional response evaluation criteria in solid tumors (RECIST), as pseudoprogression has been reported. Therefore, other response criteria such as immune-related response criteria (irRC) and immune-related RECIST (irRECIST) have been developed.  

Both pembrolizumab and the combination nivolumab/ipilimumab have shown improved PFS and OS when directly compared to ipilimumab. Robert et al. reported a 12-month survival rate of 74% for pembrolizumab every two weeks, 68% for pembrolizumab every three weeks and 58% for ipilimumab in patients with unresectable stage III or stage IV melanoma who had received no more than one previous systemic treatment for advanced disease. Larkin et al. reported a PFS of 11.5 months for nivolumab/ipilimumab, 6.9 months with nivolumab only and 2.9 months with ipilimumab only in previously untreated melanoma patients with unresectable stage III or stage IV melanoma. ORR in frontline settings is 40-45% with nivolumab and pembrolizumab monotherapy and up to 60% with nivolumab/ipilimumab. PD-1 and PD-L1 antibodies have shown efficacy in a range of tumor types, e.g. lung cancer and Merkel cell carcinoma, although response rates have not been as high as those seen in melanoma (33-40%).

Other immunogenic treatment modalities in melanoma are tumor specific vaccines, which have been largely abandoned due to disappointing results, and tumor-infiltrating lymphocytes (TIL), which have shown promising results in phase 1/2 trials. The presence of lymphocytic infiltrates within tumors is associated with better outcomes in several tumor types, including metastatic melanoma. This has led to the development of autologous TIL, with lymphocytes being grown from resected lesions. Patients are treated with a lymphodepleting regimen and infused with TIL, followed by IL-2 to support the continued growth and activity of the infused TIL. The optimal regimen has not been established yet. Reported ORRs range from 21-72% is treated patients, but have to be interpreted with caution, as TIL cannot be grown for all patients included in trials, which introduces a bias in the reported outcomes. Rosenberg et al. reported a 5-year survival rate of 93% in the 20/93 heavily pretreated patients who developed a complete response. A phase 3 trial comparing TIL to ipilimumab in patients with unresectable stage IIIC or stage IV melanoma is in progress (NCT02278887).

The clinical development of checkpoint immunotherapies and targeted therapies has surely improved outcomes for melanoma patients. Median OS of 24 months or longer have now been achieved in clinical trials of dabrafenib plus trametinib and nivolumab plus ipilimumab. In the nivolumab/ipilimumab phase 2 and 3 studies, median OS has not been reached.

**Clinical challenge: melanoma brain metastasis**

In absolute numbers, melanoma is the third most frequently metastasized cancer to the brain, after breast cancer and lung cancer. Over a third of patients with advanced melanoma will develop brain metastases during the course of their disease, and even higher rates have been observed at autopsy. Historically, the prognosis of patients with melanoma brain metastases (MBM) has been poor, with median OS ranging from 2-5 months from time of diagnosis. Patients with solitary or oligometastatic disease amenable to surgery or stereotactic radiosurgery (SRS) typically have better survival than the general MBM population, with median OS reported from 7-10 months. This is likely reflective of improved local MBM control and patient selection. The criteria for SRS are not set in stone; traditionally SRS was considered for patients with ≤3 MBM and no lesions >3 cm in diameter, but the current limit is more fluid and patient-specific. When surgical resection or SRS are not an option, whole brain radiation therapy (WBRT) has been used, at the cost of neurocognitive deficits. The molecular biology of MBM is not well understood and research has garnered conflicting data. Data on molecular markers have demonstrated an increased rate of MBM in patients whose disease harbor BRAF V600 and NRAS mutations, as well as shorter time to MBM with loss of PTEN/PI3K pathway activation - although this has been controversial with other reports showing no clear correlation between BRAF mutations and MBM incidence. Systemic treatment of MBM comes with specific challenges and lack of response may be due to inadequate blood brain barrier penetration, drug efflux pumps, intrinsic resistance or protection against drug-induced apoptosis from specific cells in the brain microenvironment, such as astrocytes. Phase 1 and retrospective data with BRAF-targeted therapy have shown that the brain is an important location for progression, with MBM development occurring in 20-43% patients at time of progression, thereby raising questions about the relationship between treatment regimens and MBM development, as addressed in chapter 8. Past systemic therapies have demonstrated limited benefit in patients with active MBM. Most chemotherapeutic agents have minimal to no activity in treating MBM. Among those that have modest activity, such as temozolomide and fotemustine, the objective MBM response rates have ranged from 7% to 12%. The addition of WBRT has provided marginal benefit to patients. Similarly disappointing results have been seen in systemic therapy with high-dose interleukin-2 (IL-2), with a combined intra- and extra-cranial response rate of 6% in patients with active MBM. Furthermore, chemotherapy and IL-2 regimens have demonstrated low overall success in preventing the development of MBMs. In a prospective study designed to evaluate the MBM incidence between cisplatin/temozolomide/IL-2 and cisplatin/dacarbazine/IL-2, 49% of assessable melanoma patients developed disease located in the central nervous system and there was no significant difference between the arms. Interestingly, at least two
Table 1 - Historical landmarks in melanoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>3550 BC</td>
<td>Imhotep documents the first known case report of cancer</td>
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<tr>
<td>1400 BC</td>
<td>Hippocrates documents the first known case report of melanoma</td>
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<tr>
<td>1787</td>
<td>John Hunter reports a surgical removal of melanoma</td>
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<tr>
<td>1812</td>
<td>René Laennec first describes melanoma as a disease entity</td>
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<tr>
<td>1857</td>
<td>William Norris published the first melanoma case series in the English literature</td>
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<tr>
<td>1840</td>
<td>Samuel Cooper notes that early surgical removal of melanoma “is the only chance for benefit.”</td>
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<tr>
<td>1892</td>
<td>Herbert Lumley Snow advocates for “anticipatory gland dissection” before gland enlargement</td>
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<tr>
<td>1907</td>
<td>William Handley advocates for wide excision</td>
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<tr>
<td>1958</td>
<td>Edward Krementz publishes first case series of isolated limb perfusion with melphalan</td>
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<tr>
<td>1967</td>
<td>FDA approval of hydroxyurea for advanced melanoma</td>
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<tr>
<td>1968</td>
<td>Donald Morton publishes first series of patients treated with BCG vaccination</td>
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<tr>
<td>1969</td>
<td>Ion Gresser describes the role of interferons in antitumor immunity</td>
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<tr>
<td>1969</td>
<td>Wallace Clark notes the pathologic heterogeneity of melanoma and levels of invasion that correlate with prognosis</td>
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<tr>
<td>1970</td>
<td>Alexander Breslow describes the relationship between tumor thickness and prognosis</td>
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<tr>
<td>1974</td>
<td>Donald Morton describes the first successful clinical application of immunotherapy directed against a metastatic human cancer</td>
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<tr>
<td>1976</td>
<td>FDA approval of dacarbazine for advanced, metastatic melanoma</td>
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<tr>
<td>1978</td>
<td>John Kirkwood initiates high dose interferon studies in patients with high risk of relapsed melanoma</td>
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<tr>
<td>1980</td>
<td>First version of the AJCC staging system for melanoma</td>
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<tr>
<td>1990</td>
<td>Ferdy Lejeune publishes on locoregional use of tumor necrosis factor</td>
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<tr>
<td>1992</td>
<td>Donald Morton publishes technical details regarding the use of intraoperative sentinel lymph node mapping</td>
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<td>1992</td>
<td>Danielle Lienard reports success with a combination of TNF-α, interferon-γ and melphalan in isolated limb perfusion</td>
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<tr>
<td>1996</td>
<td>The FDA approves high dose interferon for adjuvant treatment of high-risk melanoma</td>
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<tr>
<td>1998</td>
<td>The FDA approves high dose bolus IL-2 for advanced, metastatic melanoma</td>
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<tr>
<td>2002</td>
<td>Helen Davies describes a high frequency of the BRAF mutation in melanoma</td>
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<tr>
<td>2005</td>
<td>Boris Bastian publishes the first report that melanomas are genetically heterogeneous</td>
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<tr>
<td>2006</td>
<td>Donald Morton publishes evidence in favor of sentinel lymphadenectomy with early nodal dissection</td>
</tr>
<tr>
<td>2011</td>
<td>The FDA approves three drugs; pegylated interferon for high-risk resected disease, ipilimumab for advanced, metastatic disease and vemurafenib for advanced, metastatic disease</td>
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<tr>
<td>2013</td>
<td>The FDA approves two drugs: trametinib and dabrafenib for BRAF mutated unresectable or metastatic melanoma</td>
</tr>
<tr>
<td>2014</td>
<td>The FDA approves pembrolizumab and nivolumab for unresectable or metastatic melanoma</td>
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<tr>
<td>2015</td>
<td>The FDA approves talimogene laherparepvec for unresectable recurrent melanoma and comitnib for BRAF V600E or V600K mutated melanoma and ipilimumab for adjuvant treatment of stage III resected melanoma</td>
</tr>
<tr>
<td>2017</td>
<td>&gt;600 active trials in melanoma on clinicaltrials.gov</td>
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Adapted and updated from Lee et al.7

Retrospective studies have shown that patients demonstrating extracranial disease response to a systemic therapy have longer survival from MBM diagnosis.79

With regards to BRAF-targeted therapies and immune checkpoint therapies, the majority of patients enrolled on the registration protocols did not have a history of MBM and all patients were required to have prior MBMs treated with surgery and/or SRS. The effects of these therapies in MBM populations have been subsequently studied in smaller patient groups. Phase 2 studies of immuno-oncology and BRAF agents conducted in patients with active MBM have shown lower clinical activity than in non-MBM populations. These include objective MBM responses from as low as 5-22% with ipilimumab and pembrolizumab monotherapies, to as high as 39% with BRAF-targeted therapy; median OS ranged from 3-7 months from time of diagnosis for BRAF and ipilimumab studies, but has not yet been reached in the phase 2 pembrolizumab study after a median follow-up of 11.6 months.79-101 Despite these results, retrospective data has suggested that survival outcomes are much improved when MBM patients have been managed with SRS and immunotherapy (ipilimumab) with median OS ranging from 12.4 to 21 months.202-204 Trials are ongoing with dabrafenib plus trametinib and nivolumab plus ipilimumab in patients with active MBM. Up to 60% of brain metastasis patients die of extracranial disease progression.205 This suggests that MBM prevention and/or better control of disease in MBM patients could lead to improved outcomes, particularly with newer, more effective therapies. Real world data in large patient groups treated with recently approved therapies, which can be found in this dissertation, are largely missing.

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1. An introduction in melanoma

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