Abstract. This article reviews the epidemiology, pathogenesis, diagnosis, prognostic factors and treatment of metastatic melanoma, including the most recent developments in the specific field. It examines the sequential and non-linear models of development and progression of melanoma and the main molecular disorder involved in these processes. Clinical and diagnostic aspects have been divided according to clinical staging. Surgical resectability, the site and number of metastases, the number of involved organs, the duration of remission, serum lactate dehydrogenase levels and tumor doubling-time have the greatest prognostic value. Surgical treatment has been analyzed considering its rational function and examining all sites involved in metastasis. We also discuss the palliative role of radiotherapy in relation to various metastatic sites, chemotherapy and recently introduced targeted-therapy. The association of newer drugs and new biological therapies such as ipilimumab and vemurafenib have improved the treatment landscape of stage IV melanoma.

Over the last decades of the twentieth century, melanoma incidence increased in Caucasian populations; thus, this type of cancer has become a significant public health problem worldwide in fair-skinned populations (1). Incidence rates per 100,000 patients vary between 21.9 in USA to 55.9 in Australian males. Differently, in Asia, the incidence of cutaneous melanoma (CM) is significantly lower (incidence rates of 2 to 5 per 1,000,000 patients/year (2). CM is the most common cause of mortality from skin cancer in Caucasian populations. The incidence rate of melanoma changes in relation to race shows that white populations have an approximately 10-fold greater risk than black, Asian or Hispanic populations. However, both White and African Americans develop plantar melanoma with a similar risk, while mucosal melanoma is more common in non-White populations (3).

The median age at the time of diagnosis is 57 years and the incidence increases between the ages of 25 and 50 years (1). Distant metastatic melanoma (DMM) has an overall survival rate of only 5-10% of cases at 5-years; median survival is 6 to 10 months depending on the site of metastasis (4). CM can metastasize to any organ or tissue. In 42% to 59% of patients, the initial sites of distant metastases are skin, subcutaneous tissue and distant lymph nodes; the most common sites of visceral metastases, in order of frequency, are the lung, liver, brain, bone and intestine. Metastasis to heart, pancreas, adrenal kidney and thyroid (in clinical series before 1985) were rare but frequent at autopic examination. This discrepancy not only shows the aggressive behavior of metastatic melanoma but also suggests an underestimation of metastatic disease. Now, with the use of computed tomography (CT) and 2-(18F)-fluoro-2-deoxy-D-glucose positron-emission tomography (PET) and PET-CT, more cases are being diagnosed (5-8).

Many prognostic factors have been identified predicting survival of patients with DMM: these include surgical resectability, response to chemotherapy, serum lactate dehydrogenase (LDH) levels, site of first metastasis, number of metastases and duration of remission (9-11).

Regarding the sites of distant metastasis, analysis of the melanoma database of the American Joint Committee on Cancer (AJCC) showed three groups of patients with different prognoses: patients with skin, subcutaneous tissue
Oncogenic mutation of progression of melanoma can be simplified as follows: The main molecular disorders involved in development and pathogenesis of melanoma. A recent study of 200 patients with stage IV melanoma at the University of Alabama, 1-year survival rate was 36% for patients with one metastatic site, 13% for patients with two sites and 1% for patients with three or more sites (13). In contrast to this study, a multivariate analysis conducted at the John Wayne Cancer Institute showed that the number of metastatic sites is not a significant independent prognostic factor and suggests that some sites of metastases have a dominant-negative effect on survival (14).

The most effective therapeutic approach for metastatic melanoma is surgery, whenever possible, because it limits the progression of disease, and interrupts metastatic progression without precluding new systemic therapies (15).

A certain degree of consensus has been established about diagnostic procedures, treatment and prognostic factors of DMM but several diagnostic and therapeutic aspects are still unclear. This article could be a valid tool for daily clinical practice for patients with melanoma because it combines a review of the most recent literature with the experience of a multidisciplinary group dealing with diagnosis and therapy of melanoma.

Pathogenesis

The main molecular disorders involved in development and progression of melanoma can be simplified as follows: Oncogenic mutation of BRAF gene and, in particular, gene re-arrangement of chromosome 9p21 with the resulting production of a protein called AKT3 are involved in melanocytic proliferation; mutation or epigenetic silencing of CDKN2A (cyclin-dependent kinase inhibitor) with the consequent functional deficit of p16, amplification of CCND1, and inactivation of TP53 through a de-regulation of the p14 CDKN2A–MDM2-p53 pathway are implicated in the alteration of apoptosis and cellular survival (intermediate neoplastic phase); activating mutation of NRAS gene and c-KIT aberration contribute to neoplastic transformation; gene silencing of p16 CDKN2A, functional loss of (PTEN), activation of PI3K-AKT pathway and MIFT gene amplification have a role in the acquisition of malignant phenotype with melanoma progression.

A combination of these processes represents a linear model of melanoma genesis (16, 17). However, a non-linear model of neoplastic progression for melanoma development has been proposed, hypothesizing that the alteration of stem cells might produce melanoma cells in the superficial or vertical growth phase, or directly produce metastatic cells (Figure 1) (17-20).

Diagnosis and Staging

Laboratory test and biomarkers. There is no universal agreement to the usefulness of laboratory tests such as lactate dehydrogenase (LDH) or alkaline phosphatase (ALP) for DMM screening. High levels of LDH identify patients with a poor prognosis and the sixth edition of the AJCC staging system for melanoma considers serum LDH levels a good tool for characterizing the subpopulation of patients with M1c disease (21, 22).

The most useful biomarkers for early detection of melanoma metastases are melanocyte lineage/differentiation antigens such as S-100 β protein and melanoma inhibitory activity (23). The sensitivity for detecting new metastases was 29% for S-100 β protein, 24% for the multi-marker reverse transcription polymerase chain reaction (RT-PCR), 22% for melanoma inhibitory activity, 17% for ALP and 2% for LDH. The diagnostic accuracy was 86% for melanoma inhibitory activity, 84% for S-100 β protein, 79 % for ALP, 77% for LDH and 72% for RT-PCR (24, 25). At present, although four different assays for measurement of S-100 β protein have been designed and many studies support that S-100 β assay has sensitivity, it is not used as a routine clinical tool to diagnose metastases in high-risk patients (21, 22, 23, 26).

During the past decade, many other markers of malignant melanoma have been investigated: a circulation immune complex composed of TA90 (a tumor-associated 90 kDa glycoprotein antigen and its immunoglobulin G antibody) or IL8, IL10, intercellular adhesion molecule 1 (ICAM1), and lipid-associated sialic acid in plasma (LASA-P), but these have uncertain significance and are not routinely used in clinical practice (27-30).

Recent studies have been conducted on serum proteomic fingerprinting analysis and this approach might become a useful tool to identify high-risk patients with melanoma who are candidates for adjuvant therapy (31, 32).

Imaging. Imaging studies should be undertaken on the basis of specific symptoms. Overall, the best approach to identify
the presence of DMM is the use of total-body PET/CT scan. This examination combines the anatomic imaging of CT with the functional imaging of PET and reduces PET scan limits (33-37).

Magnetic resonance imaging (MRI) with gadolinium is considered the most sensitive examination to detect cerebral metastases and to distinguish metastases from melanoma from other types of metastases (38-40).

Ultrasound (US) of the lymph nodes in patients with CM is still controversial, because it is considered excessively operator-dependent (41, 42). Fine-needle aspiration cytology (FNAC) associated with US or CT is very accurate at obtaining cytological diagnosis of metastatic melanoma (41, 43, 44).

Clinical staging. Clinical staging of patients with melanoma is based on history, physical examination and evaluation of diagnostic examination. At the end of clinical staging, patients with metastases can be categorized into three groups. Table I shows a brief description of the latest version of AJCC melanoma staging system. Table II shows the clinical and diagnostic aspects of each clinical stage.

**Surgical Treatment**

Surgery is the only potentially curative treatment for patients with stage I and stage II melanoma and it is also the most effective therapy for those with stage III disease. In patients with stage IV melanoma, the role of surgery is less clear. In patients with distant metastases, surgery can have a palliative or a curative purpose. In the first option, resectable distant metastases that are symptomatic or might become symptomatic should be treated with surgery to obtain a better quality of life. In the second case, cytoreductive surgery is proposed to make the patients disease-free and, in selected cases, as a preparatory therapy prior to systemic treatment or radiotherapy. A 5-year survival rate of 20% to 30% after complete surgical resection has been recorded. This outcome is not currently achievable with any other systemic treatment (45-52).

It has been observed that, initially, most patients have only one to three synchronous metastases at a single organ site. In these patients, surgical treatment may prevent metastatic cascade to other sites and, if recurrence occurs, a secondary metastasectomy may be advantageous in an apparently
Table II. Clinical and diagnostic aspects of distant metastases according to AJCC substage for melanoma.

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence (%)</th>
<th>Anatomic site</th>
<th>Clinical manifestation</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td><strong>MELANOMA M1a</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin/ subcutaneous metastases (57, 58)</td>
<td>Clinical series: 42-59 Autopic series: 50-75</td>
<td>Single Multiple</td>
<td>Pigmented nodule/s (0.52 cm) with or without pain</td>
<td>Physical examination US PETCT FNAC PETCT FNAC US/CT guided</td>
</tr>
<tr>
<td>Distant lymph nodes (48, 59, 60-62)</td>
<td>Clinical series: 42-59 Autopic series: 50-75</td>
<td>Laterocervical Axillary Inguinal Popliteal Mediastinum Retroperitoneum Pelvis</td>
<td>Invasion or displacement adjacent organs</td>
<td>Physical examination US PETCT FNAC PETCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MELANOMA M1b</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lung Pleura Mediastinum (63, 64, 66, 67, 68, 69, 70)</td>
<td>Clinical series: 18-36 Autopic series: 70-87</td>
<td>Single Multiple</td>
<td>Asymptomatic (75%) Cough Dyspnea Hemoptysis Fever Chest pain</td>
<td>Chest radiographs during follow-up CT PETCT</td>
</tr>
<tr>
<td><strong>MELANOMA M1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain (71, 72, 73, 74, 75)</td>
<td>Clinical series: 12-20 Autopic series: 36-54</td>
<td>Single: 35% Multiple: 65%</td>
<td>Headache Early-morning pain/nausea Visual changes Endocrin hypertension from hemorrhage Papilledema Focal neurologic defects Diabetes insipidus</td>
<td>CT MRI</td>
</tr>
<tr>
<td>Leptomeningeal (72, 73, 79, 81)</td>
<td>Clinical series: - Autopic series: 50</td>
<td>Single: rare Multiple: frequent</td>
<td>Confusion Audiovestibular symptoms Meningeal irritation</td>
<td>CT MRI</td>
</tr>
<tr>
<td>Gastrointestinal tract (83, 84, 85, 86, 87, 88)</td>
<td>Clinical series: 10 Autopic series: 50</td>
<td>Stomach: 7%-26% Small intestine: 6%-58% Colon: 14%-26%</td>
<td>Early-morning pain/nausea Visual changes Endocrin hypertension from hemorrhage Papilledema Focal neurologic defects Diabetes insipidus</td>
<td>CT MRI</td>
</tr>
<tr>
<td>Liver+biliary tract/spleen (89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100)</td>
<td>Clinical series: 14-20 Autopic series: 54-77</td>
<td>Liver +biliary tract: more frequent Spleen: rare</td>
<td>Headache Early-morning pain/nausea Visual changes Endocrin hypertension from hemorrhage Papilledema Focal neurologic defects Diabetes insipidus</td>
<td>CT MRI</td>
</tr>
<tr>
<td>Heart and pericardium (106)</td>
<td>Clinical series: &lt;1 Autopic series: 40-45</td>
<td>Right side: frequent Left side: rare</td>
<td>Headache Early-morning pain/nausea Visual changes Endocrin hypertension from hemorrhage Papilledema Focal neurologic defects Diabetes insipidus</td>
<td>CT MRI</td>
</tr>
<tr>
<td>Bone (101, 102, 103, 105)</td>
<td>Clinical series: 11-17 Autopic series: 23-49</td>
<td>Axial skeleton Pelvis Skull</td>
<td>Fractures Pain Neurological symptoms</td>
<td>CT MRI</td>
</tr>
<tr>
<td>Others (109, 110, 111, 112, 113, 114, 115)</td>
<td>Rare</td>
<td></td>
<td></td>
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</tbody>
</table>

disease-free patient. However, if surgical treatment fails, the patient becomes a candidate for systemic therapy (46, 47, 49-51, 53, 54). The rational function of surgical resection of DMM is multifactorial and summarized in Figure 2.

Selection of patients. Many prognostic factors can be considered in the evaluation of a patient’s eligibility for curative surgery: i) Site: median and 5-year progressive survival decrease according to the involved site (13, 14, 47). ii) Number of metastases: median survival falls from 23 to 8 months in patients with more than three metastases in a single organ compared to patients with single metastasis (13, 47). iii) Number of involved organs: the involvement of more than three organs reduces the median survival from 7 to 2 months (13, 14, 47, 50). iv) Disease-free interval: 5-year survival amounts to 15% if the disease-free interval is less than 36 months and goes up to 30% when it is greater than 36 months (47, 51). v) LDH: in patients with liver metastases, an increase of LDH reduces median survival from 11 to 3 months (13, 14, 21, 22, 23, 47). vi) Tumor doubling-time (TDT): the median and 5-year survival is zero if the TDT is less than 60 days; it goes up to 20.7%, if the TDT is 60 days or more (55, 56). vii) Performance status: patients undergoing surgery should have a good performance status to reduce intraoperative risks (13, 14).

Surgery for stage IV M1a melanoma

Skin: Metastases should be removed before they become bulky and symptomatic. The elective treatment is surgical removal with a rim of normal tissue (at least 1 cm or >1 cm for larger lesions). If metastases are multiple and sequential, in one or more areas, it may be necessary to resort to electrochemotherapy, locoregional or systemic chemotherapy. When patients undergo surgery, they have a median survival rate of 2 years (range 3 to 180 months) from the onset of metastases (57, 58).

Lymph nodes: Surgical treatment for M1a lymph node metastases is complete dissection (cervical, axillary, and inguinal lymph nodes) (48, 59, 60-62).

Table III. Specific protein inhibitors of the most important pathways of signal transduction under investigation in clinical trials.

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Phase of study</th>
</tr>
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<tbody>
<tr>
<td>BRAF</td>
<td>Non-selective</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Selective</td>
<td>XL281</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verumafenib (Zelborac©)</td>
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<tr>
<td></td>
<td></td>
<td>GSK2118436</td>
</tr>
<tr>
<td>MEK</td>
<td>AZD6244</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>GSK1120212</td>
<td>I, II, III: ongoing</td>
</tr>
<tr>
<td></td>
<td>PDO325901</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>AS703026</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>E6201</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>CMG162</td>
<td>I, II</td>
</tr>
<tr>
<td></td>
<td>GDC0973</td>
<td>I</td>
</tr>
<tr>
<td>NRAS</td>
<td>R116777</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>CMG162</td>
<td>I, II</td>
</tr>
<tr>
<td>PI3K</td>
<td>GDC0941</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>XL147</td>
<td>I</td>
</tr>
<tr>
<td>AKT</td>
<td>MK-2206</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>GSK690693</td>
<td>I</td>
</tr>
<tr>
<td>GNAC e GNA11</td>
<td>MEK inhibitors</td>
<td></td>
</tr>
<tr>
<td>(uveal melanoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-KIT</td>
<td>Dasatinib</td>
<td>II: negative</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>II: positive</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td>III: ongoing</td>
</tr>
<tr>
<td></td>
<td>Masitinib</td>
<td>III: ongoing</td>
</tr>
</tbody>
</table>

PI3K: Phosphoinositide 3-Kinase. AKT: Protein Kinase B. GNA11: Guanine nucleotide-binding protein subunit alpha-1. c-KIT: Tyrosine-Protein Kinase Kit

Surgery for stage IV M1b melanoma

Patients with pulmonary metastases have a longer survival rate than patients with metastases at other visceral sites. The median survival in patients who undergo complete surgical excision is equal to 28 months. Generally, pulmonary
metastases are multiple and bilateral and can be associated with hilar or mediastinal node metastases.

Surgery can give a survival benefit to a small number of selected patients who have a limited number of metastases with an acceptable residual lung capacity.

The 5-year survival rate amounts to 20-39%. Criteria for surgical excision should include an absence of metastases in other organs, prolonged TDT, the possibility of complete resection or palliation of symptoms (63, 64).

Especially for lung metastases, TDT can be a useful method for identifying suitable patients for metastasectomy. TDT is calculated by measuring the changing diameters of each nodule. Median survival after pulmonary metastasectomy correlates with TDT: patients with slow-growing tumor have better survival (56, 65). Minimally-invasive thoracoscopic-assisted resection is often used for these procedures. Lobectomy is rarely performed to obtain clear margins, and pneumonectomy is almost never recommended (63, 64, 66).

Endobronchial metastases or the more infrequent metastases to the trachea or larynx might be treated, after endoscopy with biopsy, by endoscopic fulguration, laser excision, external-beam radiation or implants. Segmental resection or pneumonectomy may sometimes be useful to treat endobronchial metastases (67-70).

Surgery for stage IV M1c melanoma

**Brain:** Involvement of cerebral parenchyma is common in patients with stage IV melanoma and life expectancy ranges from two to seven months in relation to the extent of disease and the response to treatment. Surgical excision is the elective treatment for metastases larger than 3.5 cm and symptomatic metastases.

Surgery alleviates symptoms and prevents neurological damage but should be considered as treatment-of-choice only for patients with a limited number of metastases in easily accessible sites, and in the absence of other systemic localizations. In fact, bleeding during surgical excision, because of the hemorrhagic nature of metastases, may be the major cause of symptoms. After surgery, patients survive on average approximately six months (71-75). Whole-brain radiotherapy after surgery reduces the incidence of relapses but it does not seem to improve survival (76, 77).

**Spinal cord:** Spinal cord metastases are rare and need immediate surgical decompression, radiotherapy and high doses of corticosteroids. An important randomized study concludes that patients with spinal cord compression, treated with decompressive surgery, corticosteroids and post operative radiotherapy, regain the capacity to walk more often and maintain it longer than patients treated with radiation and corticosteroids alone (78-82).

**Gastrointestinal tract:** About 50% of patients with stage IV melanoma have gastrointestinal metastases. In nearly all cases, intestinal involvement is symptomatic, and surgery, both curative and palliative, is the elective treatment. When surgical resection is curative, mean survival amounts to 15-49 months after surgery, compared with 5-8 months in patients who do not undergo surgery (83-85).

Extensive procedures such as esophagogastrectomy or subtotal gastrectomy should be performed only when long-term survival is considered possible. Segmental resection or partial gastrectomy should be used in the presence of bleeding. Sometimes, if the main symptom is obstruction, it may be necessary to perform a by-pass (thereby preventing a short bowel syndrome) (86-88).

**Liver, biliary tract and spleen:** Patients with liver metastases have an average survival rate of 2-4 months (89). A prospective study of 1,750 patients with hepatic metastases conducted at the John Wayne Cancer Institute and at the Sydney Melanoma Unit demonstrated that the median overall survival rate was 28 months for patients who underwent surgical resection and four months for patients who underwent exploration only (90).

Surgery is only recommended for isolated liver metastases; for patients who have multiple metastases, new techniques such as cryosurgery or radiofrequency ablation can be considered (91-96). Patients with symptomatic localized gallbladder metastases can benefit from cholecystectomy (97, 98).

Splenic metastases are rare but patients who undergo splenectomy have a mean survival of 20 months, in comparison with seven months for those not nominated for surgery (89-100).

**Bone:** Bone metastatic melanoma permits survival of only four to six months, and the survival of these patients is even shorter when other sites are involved. Treatment is related to the severity of symptoms, the site of metastases and the performance status of patients, and has mainly a palliative purpose.

Surgery is limited to operative bone fixation, joint replacement, repair with methyl methacrylate, or use of external braces or casts (11, 17, 101-104). De-compressive laminectomy and postoperative irradiation may be necessary in patients with fractures of vertebrae causing compression of spinal cord (104, 105).

**Other sites:** The heart, pericardium, kidney and urinary tract, endocrine organs, breast, ovaries, uterus, vagina, testes, penis, oral cavity, pharynx, eye and orbit can be sites of metastasis. Surgical treatment, both palliative and curative, may be considered in relation to the uniqueness of the lesion and the general condition of the patient (7, 17, 106-115).

Radiotherapy

Melanoma is generally considered a relatively radioresistant tumor. Retrospective clinical studies have shown that the standard treatment is effective in only 40% of irradiated sites. In the remaining cases, the lack of response could be due to
the presence of hypoxic cell fractions and cell clones with the ability to repair the damage from radiation (6, 7, 15, 116).

Radioresponsiveness, however, varies from case to case. The main problem concerns the optimal dose (single and total dose). High single doses should be used to obtain an optimal response. The most recent radiation treatment protocols require individual doses of between 5 and 9 Gy. The total dose seems less important than the single dosage. The total dose varies depending on the type of fractionation. Currently, amounts up to 6 Gy twice a week for a total dose of 36-42 Gy are mainly used.

Overgaard et al. has proposed 9 Gy in three sessions within 96 h, up to a dose of 27 Gy in eight days (117, 118). This scheme, of short duration, produces more than 90% complete and partial responses (116, 117).

Bentzen et al. (119) designed a clinical trial to monitor the outcome of radiotherapy: the tumor control probability (TCP) on 239 treated lesions was analyzed, observing that the treatment time does not affect TCP, while it is influenced by the single-fraction dose (6 Gy are considered the ideal dose) and the size of the tumor (119).

Patients can obtain clinical benefit from radiation of symptomatic metastases and radiotherapy is usually used in addition to systemic therapy (116, 120).

Skin and subcutaneous metastases: Single lesion or small clusters of lesions are treated with a single dose of 8 Gy that can be repeated once or twice. Larger or deeper lesions may require 20 Gy in five fractions in one week or 24 to 30 Gy in 4 to 5 fractions at two fractions per week. Multiple skin or subcutaneous metastases involving wide areas are not usually treatable with radiotherapy (57, 116).

Lymph node metastases: The majority of lymph node metastases can be treated with 20 Gy in five daily fractions. A bolus may be needed in case of fungation (116, 121).

Brain metastases: In view of the predominantly palliative purpose of radiotherapy for brain metastases, treatments are more concentrated in time than in other cases and should be performed using single doses of 4-6 Gy for 2-3 times a week, up to a total dose of 20-30 Gy. Another scheme involves 4 Gy for five sessions on consecutive days. Generally, radiation therapy is associated with corticosteroids and anti-convulsant therapy and it is excluded in patients with poor performance status (74, 76, 116, 122-125). During the London Conference on the treatment of brain metastases, the following indications were established: i) surgery in single localizations, in symptomatic patients, with good performance status; ii) whole-brain radiotherapy for patients with more than four brain metastases; iii) stereotactic radiotherapy for patients with a lower number of lesions.

Good palliation can be obtained with doses of 30 Gy in 10 fractions in two weeks. Daily multiple fractions do not improve palliative response. The traditional treatment of multiple lesions barely changes survival; the only common observation is a variation of survival in the case of single localization without other metastases, especially when it is removed or irradiated with stereotactic radiotherapy (126). Stereotactic therapy is a recent and complex technique based on focused radiation beams targeting a well-defined tumor and using extremely detailed imaging scans. Radiation oncologists perform stereotactic treatments, often with the help of a neurosurgeon (127, 128).

There are two types of stereotactic radiation: stereotactic radiosurgery is when a single radiation treatment is performed (122, 128, 129) and fractionated stereotactic radiotherapy refers to several stereotactic radiation treatments (130-132).

Stereotactic radiosurgery, in terms of survival, leads to the same results compared to surgery but with a considerable difference in costs (122, 128, 129).

Malignant spinal cord compression: For patients who are not candidates for surgery and those who refuse surgical treatment, radiotherapy can be appropriate. The treatment scheme involves 30 Gy at the depth of compression in 10 fractions at five fractions per week, in association with steroid therapy. A 67% response rate, in terms of improvement of compression symptoms and pain, was reported. If neurological deterioration continues, during radiation therapy, emergency surgical decompression must be performed (80, 133).

Bone metastases: In cases of bone metastases, single doses of 4 Gy seem to be sufficient and a total dose of 30 Gy must be achieved. If pathological fractures of long bones are found, prophylactic internal fixation followed by postoperative radiotherapy should be considered (116).

Systemic Treatment

The medical treatment of patients with stage IV melanoma can take advantage of using chemotherapy, ipilimumab, tyrosine kinase inhibitors drugs or including patients in clinical trials.

Chemotherapy: Dacarbazine and its equivalent temozolomide, nitrosoureas (especially fotemustine), cisplatin, carboplatin, vinblastine, vindesine and paclitaxel have shown some activity in melanoma therapy. Dacarbazine, temozolomide and fotemustine, and more rarely paclitaxel, are mostly used in monochemotherapy, all others are used in combination (134, 135).

Chemotherapy has never been shown to increase the overall survival in metastatic melanoma. Dacarbazine at a dose of 1,000 mg/mq every 28 days or 850 mg/mq every 21 days and temozolomide at a dose of 200 mg/mq/day for five days every 28 days, remain the gold standard in almost all phase III studies.

Fotemustine. Fotemustine at a dose of 100 mg/mq (day 1, 8, 15), followed after five weeks by maintenance with 100 mg/mq every 21-28 days is also used outside experimental protocols.
Based on the results of comparative studies, temozolomide and fotemustine are considered equivalent to dacarbazine, with the only difference being that fotemustine is not registered in all countries. Dacarbazine achieves a response rate that ranges from 10 to 25% with a 1-year survival of 27% and median survival of 5.6 to 11 months (136). Temozolomide has a similar efficacy but it is able to pass the blood-brain barrier and has the advantage of oral intake (137). Fotemustine has a response rate of approximately 15% with a time-to-progression and median duration of responses similar to dacarbazine (138). Polychemotherapy generally leads to a higher response rate and improves progression-free survival compared to monochemotherapy but with greater toxicity and no increase in overall survival (134, 135).

**Ipilimumab:** Ipilimumab was the first drug to show an advantage in overall survival in patients with metastatic melanoma (139). It is a monoclonal antibody that binds to (CTLA4) and blocks the inhibitory signal to T-lymphocytes, thus promoting the T-cell antitumor response. It is administered intravenously at a dose of 3 mg/kg every 21 days four times and in combination with dacarbazine. Toxicity is immune-mediated and, in particular, can involve the gastrointestinal tract, skin, liver and endocrine system (140).

**Vemurafenib:** Vemurafenib is able to target melanoma with a mutation in codon 600 of *BRAF*, which is found in 50-66% of cases and has been shown to be superior to dacarbazine in prolonging overall survival (84% vs. 64% at one year), with quick responses recorded in 80% of patients (1.45 months) (141). Unfortunately, some resistance mechanisms can arise very rapidly, so that the progression-free survival ranges from 5 to 7 months. The drug is taken orally continuously, at a dose of 960 mg twice a day and, frequently, toxicity appears at skin (where the onset of squamocellular carcinoma is also possible) and articular levels (142, 143).

**Dabrafenib:** Like vemurafenib, dabrafenib is a BRAF inhibitor used in cases that have a mutation at codon V600. It has been recently approved by the Food and Drug administration (FDA) for the treatment of metastatic melanoma, following the results of a phase III study in which an increased progression-free survival compared to dacarbazine (5.1 months vs. 2.7 months) was demonstrated, with a response rate of 52% and median response duration of five months. It is taken orally, at a dose of 150 mg twice daily. The most commonly encountered side-effects are hyperkeratosis, fever, headache, arthralgia, alopecia and palmpoplantar eritrodisestesia. However, cases of cutaneous squamous cell carcinoma have also been found (144).

**Trametinib:** Trametinib is an inhibitor of (MEK) that was recently approved by the FDA for the treatment of metastatic melanoma with mutation of BRAF (V600E or V600K) that have not been previously treated with a BRAF inhibitor. Compared to chemotherapy (paclitaxel or dacarbazine), trametinib led to an increase in progression-free survival (4.8 vs. 1.5 months) and a higher response rate (22% vs. 8%) (145). In patients previously treated with a BRAF inhibitor, trametinib did not demonstrate any sort of activity. It is taken orally at dose of 2 mg daily. The most frequently observed toxicities include rash, diarrhea, and lymphedema (146).

**Ongoing clinical trials:** Several clinical trials are underway to evaluate the activity of new drugs or drug combinations already used in monotherapy of metastatic melanoma. In particular, the combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib seems to be promising. In a phase III study, this drug association has been shown to be superior to dabrafenib only in terms of progression-free survival (9.4 months vs. 5.8 months) and response rate (76% vs. 54%) (147). Another group of new drugs in development for the treatment of metastatic melanoma is represented by PD1 antibodies. These drugs lead to increased antitumor immune activity by blocking this receptor, which mediates the inhibitory signal to activate T-lymphocytes. In the phase I study, patients who took nivolumab (a PD1 inhibitor) at a dose of 3 mg/kg had a median survival of 20.3 months with a survival rate at two and three years of 44% and 40%, respectively (148). Recently, data from a combination study of nivolumab and ipilimumab have shown that this therapy is active in metastatic melanoma, causing a rapid and important response in the majority of patients (149). Another antibody against PD1, which currently stands at an advanced stage of study, is lambrolizumab. In a phase I study, this drug led to a response rate of 52% at a dose of 10 mg/kg every two weeks, with a median duration of 11 months at the time of the analysis (150). Table III shows the specific protein inhibitors of the most important pathways of signal transduction that are under investigation in clinical trials for metastatic melanoma.

**References**


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