Actas Dermosifiliogr. 2010;**101(2)**:129-142

ACTAS
Dermo-Sifiliográficas

Full English text available at
www.elsevier.es/ad

CONSENSUS STATEMENT

# Initial Evaluation, Diagnosis, Staging, Treatment, and Follow-up of Patients with Primary Cutaneous Malignant Melanoma. Consensus Statement of the Network of Catalan and Balearic Melanoma Centers

**C. Mangas,[a,*] C. Paradelo,[a] S. Puig,[b] F. Gallardo,[c] J. Marcoval,[d] A. Azon,[e] R. Bartralot,[f] S. Bel,[g] X. Bigatà,[h] N. Curcó,[i] J. Dalmau,[j] L.J. del Pozo,[k] C. Ferrándiz,[a] M. Formigón,[l] A. González,[m] M. Just,[n] A. Llambrich,[o] E. Llistosella,[p] J. Malvehy,[q] R.M. Martí,[r] M.E. Nogués,[s] R. Pedragosa,[t] V. Rocamora,[u] M. Sàbat,[v] and M. Salleras[w]**

[a]*Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*
[b]*Unitat de Melanoma, Hospital Clínic i Provincial de Barcelona, Barcelona, Spain*
[c]*Hospital del Mar, IMIM, Barcelona, Spain*
[d]*Hospital Universitari de Bellvitge, Barcelona, Spain*
[e]*Hospital Sant Joan de Reus, Reus, Barcelona, Spain*
[f]*Hospital Vall d'Hebron, Barcelona, Spain*
[g]*Hospital Comarcal d'Amposta, Amposta, Tarragona, Spain*
[h]*Hospital de Mataró, Mataró, Barcelona, Spain*
[i]*Hospital Mútua de Terrassa, Terrassa, Barcelona, Spain*
[j]*Hospital Santa Creu i Sant Pau, Barcelona, Spain*
[k]*Hospital Universitari Son Dureta, Palma de Mallorca, Spain*
[l]*Consorci Sanitari de Terrassa, Terrassa, Barcelona, Spain*
[m]*Consorci Sanitari Integral, L'Hospitalet de Llobregat, Barcelona, Spain*
[n]*Hospital de Figueres, Figueres, Girona, Spain*
[o]*Hospital Son Llàtzer, Palma de Mallorca, Spain*
[p]*Hospital Universitari Dr. Josep Trueta, Girona, Spain*
[q]*Hospital Clínic i Provincial de Barcelona, Barcelona, Spain*
[r]*Hospital Universitari Arnau de Vilanova, Lleida, Spain*
[s]*Hospital d'Igualada, Igualada, Barcelona, Spain*
[t]*Hospital Plató, Barcelona, Spain*
[u]*Hospital de Manacor, Manacor, Mallorca, Spain*
[v]*Hospital ParcTaulí, Sabadell, Barcelona, Spain*
[w]*Hospital Sagrat Cor, Barcelona, Spain*

*Corresponding author.
*E-mail address:* cris_mangas@yahoo.es (C. Mangas).

**KEYWORDS**
Melanoma;
Consensus statement;
Management

**Abstract**
This consensus statement on the management of primary cutaneous melanoma that we present here was based on selection, discussion, review, and comparison of recent literature (including national and international guidelines). The protocols for the diagnosis, treatment, and follow-up used in the hospital centers throughout Catalonia and the Balearic Isles belonging to the Network of Catalan and Balearic Melanoma Centers were also considered. The main objective of this statement was to present the overall management of melanoma patients typically used in our region at the present time. As such, the statement was not designed to be an obligatory protocol for health professionals caring for this group of patients, and neither can it nor should it be used for this purpose. Professionals reading the statement should not therefore consider it binding on their practice, and in no case can this text be used to guarantee or seek responsibility for a given medical opinion. The group of dermatologists who have signed this statement was created 3 years ago with the aim of making our authorities aware of the importance of this complex tumor, which, in comparison with other types of cancer, we believe does not receive sufficient attention in Spain. In addition, the regular meetings of the group have produced interesting proposals for collaboration in various epidemiological, clinical, and basic applied research projects on the subject of malignant melanoma in our society.


**PALABRAS CLAVE**
Melanoma;
Documento
de consenso;
Manejo

## Valoración inicial, diagnóstico, estadificación, tratamiento y seguimiento de los pacientes con melanoma maligno primario de la piel. Documento de consenso de la "Xarxa de Centres de Melanoma de Catalunya i Balears"

**Resumen**
El documento de consenso respecto al manejo del melanoma primario de la piel, que detallamos a continuación, nace de la puesta en común, aceptación, revisión y confrontación con la literatura reciente (incluyendo guías clínicas nacionales e internacionales), así como de los protocolos de diagnóstico, seguimiento y tratamiento consensuados en los diferentes centros hospitalarios de toda Cataluña y Baleares pertenecientes a la Xarxa de Centres de Melanoma de Catalunya i Balears. El objetivo principal de este documento es exponer de forma conjunta el manejo habitual del paciente con melanoma que actualmente se realiza en nuestro medio. Sin embargo, este documento no pretende, ni puede, por lo que tampoco debiera ser usado como un protocolo de obligado cumplimiento por los profesionales que atendemos a este grupo de enfermos. En este sentido, cabe mencionar que la consulta de este documento por parte del profesional no es vinculante para su acción, y en ningún caso este texto podrá ser utilizado para garantizar o buscar responsabilidades del juicio médico concreto. El grupo de dermatólogos que firman dicho documento se formó hace ahora tres años, con la intención de dar a conocer a nuestras autoridades la importancia de este complejo tumor, que en nuestro país creemos que se encuentra erróneamente infravalorada con respecto a otros tipo de cáncer. Además, fruto de las reuniones periódicas del grupo, han surgido también interesantes propuestas de colaboración en distintos proyectos de investigación epidemiológica, clínica y básica aplicada en torno al melanoma maligno en nuestra sociedad.


## Identification and Follow-up of Suspicious Lesions or Individuals at High Risk for Developing Melanoma

While the usefulness of screening the general population for melanoma has not been established, regular dermoscopic monitoring by a dermatologist of individuals at high risk for developing malignant melanoma (MM) is generally recommended; this group includes patients with multiple clinically atypical moles and those with a personal or family history of MM.[1-3] Physicians should draw up a surveillance plan for patients in this high-risk group to ensure early identification of malignant lesions or lesions with a risk of developing into melanoma (lesions that meet the ABCDE criteria of asymmetry, border irregularity, color variegation, diameter >6mm, or rapid evolution). Taking into account the presence of one or more of the following known risk factors for developing MM, the plan should define the type and frequency of follow-up in each case (6-monthly or annual visits), specify whether manual or digital dermoscopy (body mapping) should be used,[4] and include a family risk study[5-10]:

**Table 1** Incidence of *CDKN2A* Mutations Detected in the Blood of Patients with Melanoma[a]

| | CDKN2A Mutations | |
|---|---|---|
| | % | Relative |
| **Risk** | | |
| **Sporadic melanoma** | | |
| Total | 2.3 | – |
| Women | 1.2 | 0.53 |
| Men | 3.8 | 1.66 |
| Not multiple | 1 | 0.88 |
| Multiple (2 melanomas) | 10 | |
| Multiple (3 or more) | 27.8 | 16.34 |
| Age >40 y | 1.1 | 0.45 |
| Age <40 y | 5 | 2.21 |
| **Familial melanoma** | | |
| Two family members with melanoma | 19 | – |
| Three family members with melanoma | 25 | – |
| Three or more family members with melanoma | 43.7 | – |
| Four family members with melanoma | >75 | – |

[a]Data obtained from the study of over 700 cases of sporadic melanoma, over 150 cases of multiple melanomas, and more than 50 families with familial melanoma studied in our area.[16]

1. Phenotype: light eye color, fair skin phototype (I or II), blonde or red hair, the presence of multiple freckles or solar lentigines, numerous typical nevi (>50), numerous clinically atypical nevi (as per the ABCDE criteria), dysplastic nevi syndrome (>100 nevi including 1 or more with a diameter >6mm and 1 or more with a dysplastic histology)
2. History of MM and/or multiple neoplasms in a first-degree relative
3. Personal history of MM

A personal history of MM increases the individual's risk of developing a second primary melanoma by a factor of 10, with maximum risk occurring during the 2-year period following diagnosis of the first primary lesion. Patients with a family history of MM who have multiple atypical nevi are at increased risk for developing melanoma. In our region (Catalonia and the Balearic Islands), some of the families with familial melanoma have been found to have mutations in the *CDKN2a* and *CDK4* genes, which are associated with a lifetime risk of developing melanoma ranging from 60% to 90% (Table 1). In these probands with a high level of suspicion and in patients with multiple primary melanomas, genetic diagnosis should be carried out in the context of a genetic counseling program. The Hospital Clínic in Barcelona has a genetic counseling program that deals specifically with familial melanoma and similar services exist throughout Spain.[16] Other centers offering such counseling include the Instituto Valenciano de Oncología (Valencia), the Hospital Virgen de la Arrixaca (Murcia), and other centers in the Basque Country, Madrid, and Galicia.

## Diagnosis and Clinical Staging of Primary Melanomas

### Preoperative Assessment of the Primary Tumor

When dealing with a melanocytic lesion and clinical suspicion of MM, the medical history obtained from the patient should include the following details:

1. Evolution of the lesion, including the following information in addition to any other relevant details: the chronology of the lesion; the signs or symptoms that gave rise to the consultation; the presence or absence of bleeding, itching, or pain; any changes in the color, shape, or size of the lesion; the existence of a precursor lesion and any prior manipulation or treatment of the lesion
2. The results of the macroscopic study of the tumor including details of the site, findings on palpation, the presence of papules or nodules, size, pigmentation, clinical type, ulceration, areas of regression, adjacent nevi, etc
3. Description of the results of epiluminescence microscopy (dermoscopy)
4. Graphic documentation of the evidence that gave rise to clinical suspicion of MM

### Clinical Diagnosis and Skin Biopsy

All lesions suspected of being MM should be biopsied, and specimens should be sent to the pathology department for histologic confirmation of the diagnosis. Whenever possible the biopsy should be excisional and include the entire lesion, with margins between 2 mm and 5 mm to avoid modifying the lymphatic drainage of the affected area. Avoid manipulation of the suspicious lesion with needle pricks, curretage, shave excision, and treatment with electrocoagulation, laser, cryotherapy, or any other technique that might complicate correct histological study of the excised sample. Occasionally (when clinical suspicion is low or when the lesion is located on the face or any area where excision would result in disfigurement) an incisional biopsy may be carried out (punch biopsy). In such cases, the thickest portion of the lesion should be biopsied (as assessed by palpation or using dermoscopic criteria).

### Pathologic Diagnosis

The pathology report on an malignant melanocytic lesion should conform to the consensus guidelines published recently by various Spanish working groups.[18,19] According to these recommendations, all pathology reports must include the characteristics listed in Table 2, and negative results must be explicitly noted. When a value cannot be identified in the histologic specimen, this fact must also be explicitly noted in the report. When a patient who has been diagnosed with MM in another hospital is referred for follow-up and/or sentinel node biopsy (SNB), the referral hospital should request a slide and/or the paraffin block for reassessment.

**Table 2** Histopathologic Characteristics that Must be Included in the Pathology Report of Melanomaa

| |
|---|
| Macroscopic description of the anatomical site and the biopsy sample |
| Type of excision (incisional or excisional biopsy, shave excision, curretage, etc) |
| Clinicopathologic type |
| Tumor thickness (Breslow depth) |
| Level of invasion (Clark) |
| Mitotic rate (number of mitoses per $mm^2$) |
| Vertical growth phase (yes/no) |
| Ulceration (yes/no) |
| Regression (yes/no) |
| Lymphocytic invasion (yes/no) |
| Vascular involvement (yes/no) |
| Perineural involvement (yes/no) |
| Histologically confirmed satellite metastasis |
| Width of disease-free excision margins in mm (lateral and deep) |
| Precursor lesion (melanocytic nevus) (yes/no) |
| **Optional Information** |
| Plasmacytic infiltration |
| Semiquantitative assessment of regression and inflammatory infiltration |
| Melanoma cell types and variants (nevoid, balloon cell, small cell, folliculotropic, spitzoid, etc.) |

[a]Taken from our protocol for pathology reports in primary melanoma[18]

## Initial Assessment of the Melanoma Patient

### Medical History

The preliminary clinical assessment of all patients diagnosed with melanoma should include a detailed medical history with particular attention paid to all aspects pertinent to MM. In addition to other clinical characteristics, the following should be noted:

1. Personal and family history of MM or dysplastic nevus syndrome
2. Personal and familiar history of cancer
3. Skin phototype
4. Habits of exposure to sun (pattern of solar exposure: intermittent, chronic, etc), amount of time spent outdoors in work and leisure activities, number of severe sunburns, use of UV-A tanning lamps, etc)
5. The symptoms that gave rise to the consultation (itching, pain, bleeding, changes in the color or size of the lesion, etc)
6. Site and diameter of the lesion
7. Presence of areas suggestive of regression
8. Presence of clinically atypical nevi
9. Presence of a precursor lesion

A general clinical history should also be recorded and should include information on any symptoms that might suggest the presence of metastasis (toxic syndrome, localized pain, cough, neurological symptoms, bleeding in the digestive tract, etc) and any concomitant diseases, particularly conditions that might limit future medical or surgical treatment.

### Physical Examination

The dermatological examination should be complete and include the scalp, genital region, and oral mucosa. Particular attention should be paid to the detection of possible precursor lesions (clinically atypical nevi), additional suspicious pigmented lesions, and possible cutaneous metastases of the primary melanoma. Patients should also undergo a general physical examination with particular attention to the examination of the regional lymph nodes and the presence of subcutaneous masses or nodules.

### Additional Investigations in the Study of Initial Spread

The clinical and pathologic classification currently recommended for staging patients with MM is the American Joint Committee on Cancer (AJCC) prognostic staging system (seventh classification) published in 2009 (Table 3).[20,21] Prior pathologic examination of the primary tumor and of an SNB (if indicated) are necessary for the application of this system.

### Lymph Node Staging. Indications for Sentinel Node Biopsy

Sentinel node technology has made possible selective assessment of the regional lymph nodes at greatest risk for metastasis due to lymphatic spread, thereby limiting the need for radical surgical intervention (lymphadenectomies) and/or adjuvant treatments in patients in whom metastasis is detected.[22] Consequently, the chief utility of SNB in patients with MM, almost universally accepted by the scientific community, is its role as a precise staging tool, and its use is essential in the case of patients participating in clinical trials.[6-10,22-24] However, some authors consider the routine use of SNB to be controversial because it has not yet been shown to have any beneficial impact on overall survival.[25-30]

### Criteria for Sentinel Node Biopsy

Table 4 summarizes the currently accepted criteria for the selection of candidates for SNB in MM.[31]

In the preliminary assessment of tumor spread in patients without clinically evident nodal involvement, ultrasound of the regional nodal basin should not replace SNB in routine clinical practice. Ultrasound can, however, be useful before SNB when clinical palpation is problematic (in obese patients and patients with prior surgery in the area to be explored, such as those who have undergone inguinal herniorraphy) and in hospitals that do not perform SNB or refer patients to other centers for SNB.[32-34] SNB is not recommended in patients at low risk for MM (stages 0 and IA) and when there is no clinical suspicion of nodal involvement. In the protocols of some hospitals, SNB may be indicated in invasive low-risk primary tumors (Breslow

**Table 3** Current Clinicopathologic Classification for Melanoma Published by the American Joint Committee on Cancer (AJCC)[a]

| T Classification | Thickness, mm (Breslow Depth) | Ulceration Status/Mitoses |
|---|---|---|
| T0 | No evidence of any primary tumor | Either |
| Tis | In situ | Either |
| T1 | ≤ 1 | a: without ulceration and with mitosis <1/mm$^2$<br>b: with ulceration or mitoses \> 1/mm$^2$ |
| T2 | 1.01–2.0 | a: without ulceration<br>b: with ulceration |
| T3 | 2.01–4.0 | a: without ulceration<br>b: with ulceration |
| T4 | > 4.0 | a: without ulceration<br>b: with ulceration |
| N Classification | No. of Metastatic Nodes | Nodal Metastatic Burden |
| N1 | 1 node | a: micrometastasisb<br>b: macrometastasisc |
| N2 | 2-3 nodes | a: micrometastasisb<br>b: macrometastasisc<br>c: in transit or satellite metastases without metastatic nodes |
| N3 | 4 or more metastatic nodes, or matted nodes, or in transit or satellite metastases with metastatic nodes | |
| M Classification | Site | Serum Lactate Dehydrogenase |
| M1a | Distant skin, subcutaneous, or nodal metastases | Normal |
| M1b | Lung metastases | Normal |
| M1c | All other visceral metastases | Normal |
| | Any distant metastases | Elevated |

| Clinical Staging | | | | Pathologic Staging | | | |
|---|---|---|---|---|---|---|---|
| | T | N | M | | T | N | M |
| 0 | Tis | N0 | M0 | 0 | Tis | N0 | M0 |
| IA | T1a | N0 | M0 | IA | T1a | N0 | M0 |
| IB | T1b | N0 | M0 | IB | T1b | N0 | M0 |
| | T2a | N0 | M0 | | T2a | N0 | M0 |
| IIA | T2b | N0 | M0 | IIA | T2b | N0 | M0 |
| | T3a | N0 | M0 | | T3a | N0 | M0 |
| IIB | T3b | N0 | M0 | IIB | T3b | N0 | M0 |
| | T4a | N0 | M0 | | T4a | N0 | M0 |
| IIC | T4b | N0 | M0 | IIC | T4b | N0 | M0 |
| III | Tx | N0 | M0 | IIIA | T1-4a | N1a | M0 |
| | | | | | T1-4a | N2a | M0 |
| | | | | IIIB | T1-4b | N1a | M0 |
| | | | | | T1-4b | N2a | M0 |
| | | | | | T1-4a | N1b | M0 |
| | | | | | T1-4a | N2b | M0 |
| | | | | | T1-4a | N2c | M0 |
| | | | | | T1-4b | N2c | M0 |
| | | | | IIIC | T1-4b | N1b | M0 |
| | | | | | T1-4b | N2b | M0 |
| | | | | | Tx | N3 | M0 |
| IV | Tx | Nx | M1 | | Tx | Nx | M1 |

[a]Adapted from Balch et al.[20]
[b]Micrometastases are diagnosed by pathologic and/or immunohistochemical examination of the nodes dissected in the course of sentinel node biopsy.
[c]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension in the pathologic examination.

depth <1 mm, nonulcerated) if there is clear evidence of histologic regression or other features indicating a poor prognosis.[35-40] The best time to obtain a SNB is during the definitive surgical excision procedure undertaken to increase the safety margins around a primary tumor (or during the definitive wide excision of a tumor when the initial biopsy was incisional). Pathologic examination of sentinel lymph nodes should be exhaustive, and requires an approach that

**Table 4** Recommended Criteria for the Selection of Patients with Malignant Melanoma for Sentinel Node Biopsy[a]

| |
|---|
| **Indications** |
| Primary cutaneous melanoma ≥IB (AJCC 2009), and no clinically palpable regional lymph nodes[b] |
| **Relative Contraindications[c]** |
| Metastatic disease |
| Alteration of the lymphatic drainage of the area: |
| Wide excision of the primary tumor (margins >1 cm) |
| Reconstruction with grafts or flaps |
| Active infection |
| Radical surgery or radiotherapy of the nodal basin to be examined |
| The patient's general condition and any underlying disease |
| Pregnancy[d] |

[a]Derived from Mangas et al.[31]
[b]When there is doubt, prior ultrasound-guided fine needle aspiration is recommended.
[c]Individual assessment by a multidisciplinary committee is recommended.
[d]There is no experience of the use of radiopharmaceuticals in pregnant women. Breastfeeding is not a contraindication to the use of radiopharmaceuticals.

differs substantially from the conventional assessment of other node samples.[41,42] Protocols for the evaluation of sentinel lymph nodes specify multiple-level sectioning of each block and the combined use of hematoxylin#-eosin and immunohistochemical stains. Freezing sentinel lymph node samples to obtain perioperative reports is not recommended.[36,43]

## Additional Investigations for Visceral Staging

In addition to the physical examination and the pertinent medical history obtained during the preliminary assessment, the following investigations should also be carried out to complete staging in all patients diagnosed with invasive MM except those with stage 0 melanoma in situ[6-10,22,44-47]:

1. Standard workup including complete blood count and biochemistry, which should include alkaline phosphatase, gamma-glutamyltransferase, and lactate dehydrogenase (LDH). Measurement of other markers, such as S-100β, melanoma inhibitory activity, and reverse transcription polymerase chain reaction of tyrosinase messenger RNA in circulating blood, should also be considered.[36,48]
2. Posteroanterior and lateral plain chest radiograph
3. Electrocardiogram (in cases in which SNB is indicated as part of the preoperative preparation and in candidates for adjuvant treatment [interferon])

In patients with low-risk or medium-risk MM (stages IA, IB, and IIA), no additional tests and examinations are routinely carried out, although some hospitals recommend abdominal ultrasound in stages IB and IIA. When there are clinical grounds for suspecting metastasis, the additional tests required in each case to confirm diagnosis and facilitate staging should be ordered (computed tomography [CT], ultrasound, nuclear magnetic resonance imaging [MRI], scintigraphy, etc). In patients with high-risk invasive melanoma (stages IIB, IIC, and III), further investigation is recommended even in patients with a normal physical examination on diagnosis because of the high probability of occult distant metastasis. The following examinations are recommended at the initial visit prior to definitive surgical treatment (SNB or lymphadenectomy): chest, abdominal, and pelvic CT (or chest CT and abdominal ultrasound), cranial MRI or CT (optional), cervical CT (in the case of tumors on the head or neck), and bone scintigraphy (optional).[6-10,44-47,49-54] In our region, positron emission tomography (PET) is only ordered for melanoma patients who have distant metastasis, either during initial staging and/or when there is a suspicion of recurrence, and only when a curative therapeutic approach is under consideration depending on the results of the investigation (for example when surgical intervention is being considered for a single metastasis or when the images obtained with other methods are unclear).[55-59]

However, with the greater availability of this imaging method and its use in combination with other techniques (PET-CT), it is now possible to evaluate on a case-by-case basis the usefulness of the technique in the initial assessment of high-risk melanoma (AJCC stages IIB, IIC, and III) and in patients in whom nodal metastases are detected at initial presentation, especially in the case of melanoma of unknown origin (see below).[57-59]

### Notification of Local and National Registers

When staging is complete, the relevant local and national cancer or melanoma registers should be notified of the diagnosis of MM.

## Treatment of Patients with Localized MM

Invasive MM is a complex tumor that must be managed by a multidisciplinary team of specialists. Whenever possible, the team should be coordinated and organized into specialist committees.

### Treatment of the Primary Tumor

The treatment for primary cutaneous melanomas is wide local excision of the tumor. Radiotherapy and other treatments (imiquimod, cryotherapy, etc) are only used to treat primary tumors when surgery is not feasible (inoperable patients) or when complete extirpation of the lesion would be highly disfiguring (for example a large lentigo maligna on the face). The ideal procedure is en bloc resection with margins no greater than 0.5 cm when the suspicious lesion is being biopsied (an excisional biopsy). This margin will be adequate in the case of the thinnest tumors (melanoma in situ) and will not affect

the lymphatic drainage of the area around the tumor in patients who subsequently undergo procedures such as lymphoscintigraphy and the identification and biopsy of sentinel nodes. The interval between the diagnostic biopsy and the definitive surgical intervention should always be as short as possible. Once the lesion has been excised and the diagnosis of MM confirmed, a re-excision procedure is scheduled to increase the safety margins of the initial excisional biopsy. The lateral margin width should be measured from the scar of the simple excision, discounting the 2 to 5 mm margin extirpated during the initial tumor resection from the total width required. The minimum safety margin is dictated by the thickness of the tumor measured using a micrometer (Breslow depth). The deep excision extends down to the muscle fascia but does not include it.[6-10,22,23] Several randomized controlled trials have shown that the ideal lateral margin in each case will depend on the depth of the lesion (Breslow depth) and that increasing safety margins beyond 3 cm is not associated with any benefit.[60-68] Analysis of past experience has led to a reduction in the margins previously recommended (Table 5). Patients in the studies cited above were stratified according to the classification systems in use at the time, which did not take into account the importance of ulceration of the primary tumor in staging disease. Data are now needed from similar studies taking into account the TNM staging of the tumor, but to date no such studies have been published. When SNB is indicated (as per the above criteria), the safety margins should ideally be increased when the sentinel biopsy procedure is carried out or, if this is not possible, following SNB. Surgical treatment of the primary tumor must sometimes be adapted to the anatomical peculiarities associated with the site, certain large tumors, or the patient's medical situation. In the case of subungual tumors, amputation below the distal interphalangeal joint is recommended. However, in the case of stage 0 subungual tumors (melanoma in situ), a conservative surgical approach should be considered (extirpation plus graft or plastic surgery). Likewise, when the melanoma is located on other sites on the fingers or on the palms, soles, or other areas of the hands or feet, a conservative treatment of the limb should be considered as long as complete excision with adequate safety margins can be achieved. Acceptable reconstructive techniques include grafts, flaps, and healing by second intention. In the case of tumors on the fingers, a disarticulation proximal to the tumor can also be performed.[69] Mohs micrographic surgery has also been shown to be a valid option when a tumor proves difficult to delimit or is located at an anatomical site where it may be difficult or disfiguring to ensure adequate safety margins using other methods.[70-72]

**Table 5** Recommended Increased Safety Margins After Simple Excision According to the Breslow Depth of the Primary Tumor

| Breslow Depth | Recommended Lateral Margins, cm | Observations |
|---|---|---|
| 0 | 0.5 | |
| ≤1 mm | 1 | |
| 1-2 mm | 1 | 2 cm where feasible depending on the site |
| 2.01-4.00 mm | 2 | 3 cm in some hospitals |
| > 4.00 mm | 2 | 3 cm in some hospitals |

## Treatment of Nodal Disease

Metastasis to the regional lymph nodes is treated by surgery (lymphadenectomy), which in selected cases may be followed by an adjuvant treatment (radiation therapy, immunotherapy, etc). The different lymphadenectomy procedures used depending on the anatomic area of the lymphadenopathy are shown in Table 6. Selective lymph node dissection should be performed when there is no clinical evidence of regional disease but the histopathologic study of the sentinel node or nodes reveals the presence of micrometastases. Therapeutic lymphadenectomy is indicated in patients with obvious lymph node involvement (clinical suspicion after palpation or on the basis of ultrasound, CT, or PET findings) that has been confirmed histologically (percutaneous fine needle aspiration biopsy [FNAB] or ultrasonically-guided FNAB depending on the site).[6-10,22,23] The following relative contraindications should be taken into account when indicating lymphadenectomy:

**Table 6** Recommended Type of Lymphadenectomy Depending on the Site of the Metastatic Nodes

| Site | Type of Lymphadenectomy |
|---|---|
| Intraparotid lymph nodes | Parotidectomy (superficial rather than complete when possible) + modified cervical dissection |
| Cervical lymph nodes | One-sided dissection of cervical nodes |
| Axillary lymph nodes | Axillary block dissection |
| Inguinal lymph nodes | Inguinal dissection. The iliac nodes (superficial and/or deep) may be included after taking into account the radiographic image and the opinion of the committee |
| Lymph nodes located outside the standard groups (popliteal, cubital, posterior triangle lymph node, etc.) | Complete nodal dissection as far as possible |

a) known distant metastasis; b) long-term survival unlikely for other causes; and c) the patient's general state of health and disease status (which should be evaluated on a case-by-case basis by a committee).

## Available Adjuvant Treatments

### Adjuvant Radiotherapy

Radiation therapy of the affected parts of the lymphatic system (after lymphadenectomy) reduces the likelihood of nodal recurrence by 20%- 50% in some groups of patients with stage III disease who are considered high risk.[73-75] It is therefore contemplated in the following cases:

1. Lymph node recurrence (irrespective of the prior clinical and pathologic staging of the case)
2. Lymph node metastasis with extracapsular spread in the histopathologic study.
3. Metastases in more than 3 nodes in the same lymph node chain
4. Lymph node macrometastasis (1 or more clinically enlarged lymph nodes of >3 cm in diameter)[75]

If the patient is a candidate for interferon treatment, radiation therapy should be completed before this is started to avoid any risk of demyelination.[76]

## Interferon-α

### Adjuvant Therapy with High-Dose Interferon-α

Adjuvant high-dose interferon-α-2b has been shown to improve disease-free survival and also, albeit only in some studies, overall survival.[77-88] The approved indications in Spain for high-dose interferon therapy are situations involving melanoma with a high risk of recurrence. It is, therefore, indicated in the following cases:

1. Patients with regional node metastases, in-transit metastases, or satellite metastasis who are disease free after surgery (stage III)
2. Patients with an ulcerated primary tumor (or local recurrence) greater than 2 mm (stage IIB) or a lesion greater than 4 mm (stages IIB-IIC)

However, because of the high toxicity of this therapy (see the Summary of Product Characteristics) the clinician must always evaluate the patient's age and disease status and exclude pregnant women and patients with concomitant disease, a second neoplasm, or evidence of distant metastasis.[88] Early start of treatment is recommended following a diagnosis of melanoma (within 8 weeks of diagnosis or the definitive surgical intervention). The 2-phase treatment regimen approved for high-dose interferon (known as the Kirkwood Schema) starts with an initial induction phase involving the administration of a higher dose (20 MU/m$^2$) administered intravenously 5 times a week for 4 weeks followed by a lower maintenance dose (10MU/m$^2$) administered subcutaneously 3 times a week for 48 weeks. The aim of treatment is to maintain the highest dose tolerated by the patient, but the dose may have to be adjusted depending on toxicity (see Summary of Product Characteristics). Before starting treatment, a general blood workup should be obtained including thyroid hormones, complete liver function and lipid tests, and hepatitis B and C serology. Patients should have an electrocardiogram, and some hospitals also recommend prior examination of the ocular fundus. Laboratory tests should be performed weekly to monitor toxicity during the induction phase and, depending on tolerance, monthly or bimonthly thereafter.

### PEGylated Interferon-α-2b

PEGylated interferon-α-2b has been shown to have an efficacy similar to that of conventional interferon-α-2b in the treatment of the various diseases for which the latter is indicated (melanoma and chronic hepatitis caused by the hepatitis C virus) and it offers a more comfortable dosage regimen and lower toxicity. This in turn facilitates longer treatment regimens than those currently used and the possibility of prolonging the benefits of interferon treatment (the disease-free period). Although the use of PEGylated interferon-α-2b is currently only approved in the treatment of chronic hepatitis caused by the hepatitis C virus, it is expected that healthcare authorities will also approve it for patients with melanoma.[87]

### Other Adjuvant Treatments

Adjuvant treatments other than interferon-α-2b should only be used in the context of a clinical trial. Currently, these alternatives are based on cell immunotherapy and the use of targeted agents, such as anti-cytotoxic T-lymphocyte antigen-4 antibodies.

### Treatment of Patients with Metastatic Melanoma

Whenever possible, patients with metastatic disease should be included in clinical trials. The best candidates for systemic palliative treatment are patients in good general health with low tumor load. When a patient does not fulfill the criteria for enrolment in a clinical trial, other alternatives may be considered, including no treatment and symptomatic treatment, given the scant efficacy of palliative treatment in stage IV melanoma.

### Surgery of Metastasis

Complete surgical resection is the only treatment for metastatic melanoma consistently associated with an improvement in 5-year survival. While it is not considered curative, surgical resection of metastases does prolong the patient's survival.[89] Surgical excision of metastasis should be considered for single lesions located in soft tissues, nonregional lymph nodes,[89] the lung,[90] and/or in selected cases when metastasis affects the central nervous system (see below) or digestive tract (especially in the case of bleeding metastases).[91] Surgery should only be performed

in patients in good general health and when the foreseeable disease-free interval is long and the growth of the lesions is not rapid.

### Palliative Radiation Therapy

The indications for radiation therapy in metastatic melanoma include the following[74,75]:

1. Multiple inoperable subcutaneous metastases
2. Single metastasis occurring after excision
3. Local recurrence of the primary tumor, visceral metastases (bone with spinal cord compression, multiple cerebral lesions), or inoperable lymph node involvement

The dose and fractionation of radiation therapy will vary mainly according to the site of the tumor, the foreseeable risk of complications, and the aim of treatment (radical, complementary, or palliative). Whenever possible, a hypofractionated treatment regimen should be used. In the case of brain metastases, holocranial radiotherapy, surgery, and radiosurgery should be considered depending on the clinical situation. Surgery followed by holocranial radiotherapy is the first-line treatment for patients with a single metastasis greater than 3 cm, a marked mass effect, and disease controlled on other levels. Radiosurgery is a therapeutic option in the case of a single metastasis with a diameter of less than 3 cm. The standard treatment for multiple metastases is radiation therapy with or without chemotherapy,[92] but the benefits of prior radiosurgery in selected patients with 2 or 3 metastases should not be ruled out.

### Regional Hyperthermic Perfusion with Cytostatic Agents in the Treatment of Malignant Melanoma of the Limbs

Isolated limb perfusion with cytostatic agents is indicated in patients with local recurrence or in-transit metastasis disseminated throughout a limb following the extirpation of at least 1 lesion when disease is localized within the limb. The drug combination that appears to be most effective in regional perfusion is melphalan plus tumor necrosis factor $\alpha$.[93]

### Chemotherapy

In view of the poor results obtained with chemotherapy in patients with stage IV MM (no chemotherapy regimen has significantly improved survival in this group), phase II trials of new drugs are justified, even as first-line treatments.[94] The chemotherapy treatment regimens currently most recommended are those that include dacarbazine. Except in the context of experimental protocols, dacarbazine is considered to be the standard chemotherapy agent and it is approved by the health authorities.[94] Dacarbazine has been shown to achieve a 10.2% to 20% response in phase III trials.

### Temozolomide

Temozolomide has demonstrated efficacy similar to that of dacarbazine in phase III trials (clinical response rate of 13%).[95] It is used particularly when an oral regimen is preferable and is prescribed in the context of compassionate use programs since its use has not been approved by the regulatory agencies. The advantage of this agent is that it crosses the blood-brain barrier, and so could reduce the risk of recurrence in the central nervous system.[96]

### Fotemustine

Fotemustine, an agent approved for the treatment of patients with melanoma, has been shown in randomized controlled trials to have some benefit over dacarbazine and furthermore it can be used to treat patients with brain metastases.[97] This drug can be considered for first- or second-line use depending on the presence of brain metastases. The chief adverse effect is myelotoxicity.

### Polychemotherapy

Combination chemotherapy regimens (cisplatin + vinblastine + dacarbazine [CVD], cisplatin + carmustine + vinblastine + dacarbazine [CBVD], and cisplatin/dacarbazine) have in general been shown to be associated with higher response rates than dacarbazine alone in phase II trials, but have not been shown to be superior with respect to single-agent therapy with dacarbazine in phase III trials.[98] Moreover, because they are associated with increased toxicity, these regimens are not recommended for routine treatment. At this time, the combination that has been shown to obtain the highest rate of overall responses in a number of studies is dacarbazine + carmustine + cisplatin + tamoxifen, although this regimen has also failed to demonstrate improved survival in phase III trials.

## Immunotherapy

### Single-Agent Interleukin-2

Intravenous infusion of high doses of interleukin-2 is associated with a 15% response rate, with complete responses in one third of these patients.[99] Of these complete responses, 70% are durable and, in some cases, represent a cure. However, the high toxicity of this regimen (with deaths from toxicity in around 0.5%-2% of patients) makes close management in an intensive care unit essential, and this type of care is only available in highly specialized hospitals serving a large number of patients. Owing to its high toxicity and the lack of any comparative studies with dacarbazine and/or polychemotherapy regimens, treatment with interleukin-2 has not yet been approved by the European regulatory agencies.

### Interferon-$\alpha$

Single-agent therapy with interferon-$\alpha$, which has not been approved in the treatment of metastatic melanoma, has obtained a 10% to 15% response rate in phase I and phase II trials, but has not yet been compared with DTIC or polychemotherapy.[100] Neither the addition of this agent to chemotherapy regimens (single-agent dacarbazine,

dacarbazine-cisplatin-tamoxifen, or CBVD) nor its use in combination with interleukin-2 has shown any significant benefit in phase III trials. Consequently, its use is not recommended outside of the clinical trial setting.

### Vaccines

Phase II trials are currently underway in our region using heterologous cell vaccines[101] and autologous dendritic cells pulsed with heterologous or autologous tumor.[102] These may benefit some patients with small tumor masses or slowly-progressing disease.

### Biochemotherapy

The term biochemotherapy refers to regimens that combine dacarbazine and/or polychemotherapy with interferon-$\alpha$ (subcutaneous) or interleukin-2 (intravenous or subcutaneous) at variable doses. These treatment regimens are associated with high response rates (33%-64%) and considerable toxicity in phase II trials.[103,104] However, since no phase III study has to date been published that shows a significant benefit over chemotherapy in terms of either disease progression or survival, the routine use of biochemotherapy cannot be recommended.[105]

### Other Treatments

There are several phase II and a few phase III trials currently underway with the goal of establishing the role of new treatments for metastatic melanoma.[94] The treatments investigated in these trials range from immunotherapeutic agents to targeted therapies (for example, sorafenib, oblimersen, paclitaxel, and anti-CTLA-4 antibodies). The use of these treatments outside of the clinical trial setting is currently not justified.

## Follow-up of Patients with Melanoma

The objective of follow-up in patients diagnosed with MM, as in other neoplastic diseases, is twofold. The first goal is the diagnosis of recurrence (local, regional, or distant) through the additional investigations and tests appropriate to the natural history of the process. The second aim is early diagnosis of a second melanoma. The simplest and most efficient methods should be used, and these may vary from one hospital to another. Prompt diagnosis is essentially justified if there is a possibility of effective rescue treatment. However, to date regular follow-up of these patients has not been shown to increase survival.[6-10,106]

Although there is no consensus on which additional investigations should be considered routine practice, there is nonetheless general agreement that the use of such investigations should be guided in each case by prognostic factors and, especially, clinical and pathologic staging.[6-10,22] The following should be included at each patient visit: an update of the patient's medical history designed to detect the signs and symptoms indicative of recurrence; a detailed examination of all areas of the skin; palpation of regional nodal basins or—depending on its availability in the hospital and the characteristics of the patient (for example in obese patients)—ultrasound assessment of the affected nodal basins.[22,33,34,107] In addition, all patients should receive instruction on how to carry out a monthly self-examination and implement effective photoprotection. The patient looks for changes in pigmented macular lesions and monitors the appearance of any change in superficial lymph nodes. The hospital should also have a fast track system that affords these patients rapid access to a specialist if any unexplained signs or symptoms arise so that they do not have to wait for a routine visit.[108]

Follow-up visits should be scheduled for a period of at least 5 years for patients in stages 0 and IA and for at least 10 years in patients with disease at more advanced stages. Because of the risk of a second melanoma, lifetime surveillance is necessary in patients diagnosed with MM (regardless of stage) who have a family history of melanoma or who have other suspicious lesions (clinically atypical nevi).[22,109] The clinical follow-up regimens used in different hospitals can be summarized as follows:

1. Melanoma in situ. Annual follow-up for 3 to 5 years, without further investigations
2. Low-risk melanoma (stage IA). Follow-up for 5 to 10 years. Schedule: every 3 to 6 months for the first 2 years and every 6 months for the following 3 years (further follow-up, when necessary, is annual). Standard blood workup + LDH: 6-monthly to annual for the first 2 years and annually for the following 2 years. Chest radiograph with optional abdominal ultrasound annually for the first 5 years
3. Intermediate-risk melanoma (stages IB and IIA). Follow-up for 10 years. Schedule: every 3 to 6 months for the first 3 years, twice yearly for the next 2 years, and annually for the last 5 years. Standard blood workup + LDH 2 to 4 times a year for the first 3 years, then twice yearly for 2 years, and annually during the last 5 years. Chest radiograph with optional abdominal ultrasound twice a year for the first 3 years, annually for the following 2, and chest radiography only for the last 5 years
4. High-risk melanoma (stages IIB, IIC, and III). Follow-up for 10 years. Schedule: every 3 to 4 months for the first 3 years, twice yearly for the next 2 years, and annually for the last 5 years. Standard blood workup + LDH 2 to 4 times a year for the first 3 years, then twice yearly for 2 years, and annually during the last 5 years. Chest and abdominal CT (or chest radiograph with abdominal ultrasound in stages IIB and IIC) once or twice yearly for the first 3 years, annually for the following 2 years (not required during the last 5 years of surveillance)

Some hospitals also perform a scintigraphic bone scan and a cranial brain MRI scan (more sensitive) or cranial CT annually in patients in high-risk stages.

In addition to LDH, Other optional markers that may be monitored are tyrosinase, S-100$\beta$ (a 50% increment in S-100$\beta$ is highly indicative of disseminated disease, although this test is currently only performed in clinical trials).[48,110-112] Other additional examinations are ordered depending on clinical findings and laboratory test results.

## Melanoma of Unknown Primary Origin

Melanoma of unknown primary origin is defined as the presence of metastases of melanoma (confirmed by histology) in the lymph nodes or in subcutaneous or visceral sites without evidence of a primary lesion; these cases represent between 2% and 6% of all melanoma patients.[113-116] The prognosis in these patients does not differ substantially from that of patients with primary melanomas diagnosed at a similar AJCC stage.[114] Although the strictest definition excludes cases with a history of excision of a probably melanocytic lesion without histologic confirmation, the clinical approach for this su bgroup of patients does not differ from that used in patients with melanoma of unknown primary origin in the strict sense. In all patients diagnosed with metastatic melanoma without a known primary tumor, a series of examinations should be undertaken to rule out a noncutaneous melanoma, which is often not clinically evident. These should include complete examination of the skin and mucous membranes with particular attention to affected nodal basins (when applicable) and to less accessible areas, such as the genitals and scalp. Otolaryngologic, ophthalmologic, gynecological, and digestive tract (gastroscopy and colonoscopy) examinations must also be performed.[117] The AJCC staging system is used in this group of patients; disease is considered to be stage III if there is localized metastases to the skin and subcutaneous tissue and stage IV when there is visceral metastasis.[20] Additional examinations are indicated to provide data for initial staging depending on the AJCC stage and the clinical signs; these do not differ from those used in patients with a known primary melanoma.[117,118] The treatment of patients with melanoma of unknown primary origin should be determined on the basis of the same criteria used to determine optimum treatment in patients with a known primary cutaneous melanoma. When feasible, radical excision of the initial lesion or lesions is the first line treatment.[119]

## Conflict of Interest

The authors declare no conflicts of interest.

## REFERENCES


1. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Arch Dermatol. 1998;134: 1563-70.
2. Bafounta M, Beauchet A, Aegerter P, Saiag P. Is dermoscopy useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of the diagnostic tests. Arch Dermatol. 2001;137:1343-50.
3. Puig S, Argenziano G, Zalaudek I, Ferrara G, Palou J, Massi D, et al. Melanomas that failed dermoscopic detection: a combined clinicodermoscopic approach for not missing melanoma. Dermatol Surg. 2007; 33:1262-73.
4. Malvehy J., Puig S. Follow up of melanocytic skin lesions with digital dermoscopy. Clin Dermatol. 2002;20:297-304.
5. Markovic SN, Erickson LA, Rao RD, Weenig RH, Pockaj BA, Bardia A, et al, Melanoma Study Group of the Mayo Clinic Cancer Center. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. Mayo Clin Proc. 2007;82:364-80.
6. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. N Engl J Med. 2004;351:998-1012.
7. Garbe C, Hauschild A, Volkenandt M, Schadendorf D, Stolz W, Reinhold U, et al. Evidence-based and interdisciplinary consensus-based German guidelines: systemic medical treatment of melanoma in the adjuvant and palliative setting. Melanoma Res. 2008; 18:152-60.
8. Clinical Practice Guidelines in Oncology. Melanoma. V.2.2008. National Comprehensive Cancer Network (NCCN). Available from: www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf.
9. Australian CancerNetwork. Melanoma Guidelines Revision Working Party. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington (2008). Available from: www.cancer.org.au.
10. Guía de Prevención y Tratamiento del Melanoma Cutáneo de la Comunidad Valenciana, Valencia (2006). Available from: www.biblioteca.sp.san.gva.es.
11. Ruiz A, Puig S, Malvehy J, Lázaro C, Lynch M, Giménez-Arnau MA, et al. CDKN2A mutations in Spanish cutaneous malignant melanoma families and patients with multiple melanomas and other neoplasia. J Med Genet. 1999;36:490-4.
12. Rizos H, Puig S, Badenas C, Malvehy J, Darmanian AP, Jiménez L, et al. A melanoma-associated germline mutation in exon 1ß inactivates p14ARF. Oncogene. 2001; 20:5543-7.
13. Goldstein AM, Chan M, Harland M, Gillanders EM, Hayward NK, Avril MF, et al. Melanoma Genetics Consortium (GenoMEL). High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. Cancer Res. 2006; 66:9818-28.
14. Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT, et al, Study Group LM, Genomel MG. Features associated with germline CDKN2A mutations: A GenoMEL study of melanoma-prone families from three continents. J Med Genet. 2007;44:99-106.
15. Goldstein AM, Chaudru V, Ghiorzo P, Badenas C, Malvehy J, Pastorino L, et al. Cutaneous phenotype and MC1R variants as modifying factors for the development of melanoma in CDKN2A G101W mutation carriers from 4 countries. Int J Cancer. 2007;121:825-31.
16. Puig S, Malvehy J, Badenas C, Ruiz A, Jiménez D, Cuéllar F, et al. Role of the CDKN2A locus in patients with multiple primary melanomas. J Clin Oncol. 2005;23:3043-51.
17. Malvehy J, Puig S, Argenziano G, Marghoob AA, Soyer HP, on behalf of the International Dermoscopy Society Board members. Dermoscopy report: Proposal for standardization Results of a consensus meeting of the International Dermoscopy Society. J Am Acad Dermatol. 2007;57:84-95.
18. Protocolo de informe anatomopatológico del melanoma primario de la piel. Available from: www.academia.cat/societats/anatomia/proto.htm.
19. Nagore E, Monteagudo M, Pinazo MI, Botella-Estrada R, Oliver V, Bañuls J, et al. Propuesta de protocolo para el informe histológico del tumor primario de los pacientes con un melanoma cutáneo del Grupo de Trabajo para el Melanoma Cutáneo de la Comunidad Valenciana. Actas Dermosifiliogr. 2007;98:459-65.
20. 20. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009 Dec 20;27(36): 6199-206.

21. Morton DL, Wen Dr, Wong JH, Economou JS, Cagle LA, Storm FK, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127:392-9.
22. Balch CM. Cutaneous melanoma. In: Greene FL, Page DL, Fleming ID, Balch CM, Haller DG, Morrow M, editors. AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer Verlag; 2002. p. 209-17.
23. Thompson JF, Scoyler RA, Kefford RF. Cutaneous melanoma. Lancet. 2005;365:687-701.
24. Balch CM, Soong S, Atkins MB, Buzaid AC, Cascinelli N, Coit DG, et al. An evidence-based staging system for cutaneous melanoma. CA Cancer J Clin. 2004;54:131-49.
25. Medalie N, Ackerman AB. Sentinel node biopsy has no benefit for patients whose primary cutaneous melanoma has metastasized to a lymph node and therefore should be abandoned now. Br J Dermatol. 2004;151:298-307.
26. McMasters KM, Reintgen DS, Ross MI, Gershenwald JE, Edwards MJ, Sober A, et al. Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. J Clin Oncol. 2001;19:2851-5.
27. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, et al. Sentinel node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355:1307-17.
28. Thomas JM, Patocskai EJ. The argument against sentinel node biopsy for malignant melanoma. Its use should be confined to patients in clinical trials. Br Med J. 2000;321:3-4.
29. Gutzmer R, Al-Ghazal M, Geerlings H, Kapp A. Sentinel node biopsy in melanoma delays recurrence but does not change melanoma-related survival-a retrospective analysis of 673 patients. Br J Dermatol. 2005;153:1137-41.
30. Thompson JF, Stretch JR, Uren RF, Ka VS, Scoyler R. Sentinel Node Biopsy for melanoma: where have we been and where are we going. Ann Surg Oncol. 2004;11:147S-51S.
31. Mangas C, Paradelo C, Rex J, Ferrándiz C. La biopsia del ganglio centinela: su papel diagnóstico y pronóstico en el melanoma maligno. Actas Dermosifiliogr. 2008;99:331-48.
32. Rossi CR, Mocellin S, Scagnet B, Foletto M, Vecchiato A, Pilati P, et al. The role of preoperative ultrasound scan in detecting lymph node metastasis before sentinel node biopsy in melanoma patients. J Surg Oncol. 2003;83:80-4.
33. Bafounta ML, Beauchet A, Chagnon S, Saiag P. Ultrasonography or palpation for detection of melanoma nodal invasion: a meta-analysis. Lancet Oncol. 2004;5:673-80.
34. Starritt EC, Uren RF, Scolyer RA, Quinn MJ, Thompson JF. Ultrasound examination of sentinel nodes in the initial assessment of patients with primary cutaneous melanoma. Ann Surg Oncol. 2005;12:18-23.
35. Nagore E, Oliver V, Botella R, Insa A, Fortea JM. Factores pronósticos en el melanoma maligno cutáneo localizado: estudio de 639 pacientes. Med Clin (Barc). 2005;124:361-7.
36. Carlson JA, Ross JS, Slominski A, Linette G, Mysliborski J, Hill J, et al. Molecular diagnostics in melanoma. J Am Acad Dermatol. 2005;52:743-75.
37. Alonso SR, Ortiz P, Pollán M, Pérez-Gómez B, Sánchez L, Acuña MJ, et al. Progression in cutaneous malignant melanoma is associated with distinct expression profiles. Am J Pathol. 2004;164:193-203.
38. Yee VS, Thompson JF, McKinnon JG, Scoyler RA, Li L.X, McCarthy WH, et al. Outcome in 846 cutaneous melanoma patients from a single center after a negative sentinel node biopsy. Ann Surg Oncol. 2005;12:1-11.
39. Wong SL, Brady MS, Busam KJ, Coit DG. Results of sentinel lymph node biopsy in patients with thin melanoma. Ann Surg Oncol. 2006;13:1-8.
40. Avilés JA, Lázaro P. Pronóstico del melanoma cutáneo según el servicio quirúrgico: estudio comparativo en un hospital de tercer nivel. Actas Dermosifiliogr. 2006;97:247-52.
41. Cook MG, Green MA, Anderson A, Eggermont AM, Ruiter DJ, Spatz A, et al. The development of optimal pathological assessment of sentinel lymph nodes for melanoma. J Pathol. 2003;200:314-9.
42. Spanknebel K, Coit DG, Bieglick SC, Gonen M, Rosai J, Klimstra DS. Characterization of micrometastatic disease in melanoma sentinel lymph nodes by enhanced pathology. Am J Surg Pathol. 2005;29:305-17.
43. Roberts AA, Cochran AJ. Pathologic analysis of sentinel lymph nodes in melanoma patients: current and future trends. J Surg Oncol. 2004;85:152-61.
44. Hafner J, Schmid MH, Kempf W, Burg G, Künzi W, Meuli-Simmen C, et al. Baseline staging in cutaneous malignant melanoma. Br J Dermatol. 2004;150:677-86.
45. Yancovitz M, Finelt N, Warycha MA, Christos PJ, Mazumdar M, Shapiro RL, et al. Role of radiologic imaging at the time of initial diagnosis of stage T1b-T3b melanoma. Cancer. 2007; 110:1107-14.
46. Wang TS, Johnson TM, Cascade PN, Redman BG, Sondak VK, Schwartz JL. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. J Am Acad Dermatol. 2004;51:399-405.
47. Gold JS, Jaques DP, Busam KJ, Brady MS, Coit DG. Yield and predictors of radiologic studies for identifying distant metastases in melanoma patients with a positive sentinel lymph node biopsy. Ann Surg Oncol. 2007;14:2133-40.
48. Sopena J, Nogueira E, Carpio D, Sanmartín O, Sevilla A, Guillén C. Desarrollo de un test para la detección y cuantificación de células de melanoma en sangre periférica mediante el análisis del RNAm de la tirosinasa por RT-PCR y empleo de un secuenciador automático. Actas Dermosifiliogr. 1999;90:419-31.
49. Buzaid AC, Sandler AB, Mani S, Curtis AM, Poo WJ, Bolognia JL, et al. Role of computed tomography in the staging of primary melanoma. J Clin Oncol. 1993;11:638-43.
50. Aloia TA, Gershenwald JE, Andtbacka RH, Johnson MM, Schacherer CW, Ng CS, et al. Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. J Clin Oncol. 2006;24:2858-65.
51. Miranda EP, Gertner M, Wall J, Grace E, Kashani-Sabet M, Allen R, et al. Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph node rarely identifies systemic disease. Arch Surg. 2004;139:831-6.
52. Buzaid AC, Tinoco L, Ross MI, Legha SS, Benjamin RS. Role of computed tomograpy in the staging of patients with local-regional metastases of melanoma. J Clin Oncol. 1995;13: 2104-8.
53. Johnson TM, Fader DJ, Chang AE, Yahanda A, Smith JW, Hamlet KR, et al. Computed tomography in staging patients with melanoma metastatic to regional nodes. Ann Surg Oncol. 1997;4:396-402.
54. Choi EA, Gershenwald JE. Imaging studies in patients with melanoma. Surg Oncol Clin N Am. 2007;16:403-30.
55. Clark PB, Soo V, Kraas J, Shen P, Levine EA. Utility of fluorodeoxyglucose F18 positron emission tomography in initial evaluation of patients with T2 to T4 melanoma. Arch Surg. 2006;141:284-8.
56. Wagner JD, Schauwecker D, Davidson D, Logan T, Coleman JJ, Hutchins G, et al. Inefficacy of F-18 fluorodeoxy-D-glucose-positron emission tomography scans for initial evaluation in early-stage cutaneous melanoma. Cancer. 2005;104:570-9.
57. Maubec E, Lumbroso J, Masson F, Suciu V, Kilb F, Mamelle G, et al. F-18 fluorodeoxy-D-glucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm. Melanoma Res. 2007; 17:147-54.

58. Brady MS, Akhurst T, Spanknebel k, Hilton S, Gonen M, Patel A, et al. Utility of preoperative 18F-fluorodeoxyglucose-positron emission tomography scanning in high-risk melanoma patients. Ann Surg Oncol. 2006;13:525-32.
59. Prichard RS, Hill AD, Skehan SJ, O'Higgins NJ. Positron emission tomography for staging and management of malignant melanoma. Br J Surg. 2002;89:389-96.
60. Veronesi U, Cascinelli N, Adamus J, Balch C, Bandiera D, Barchuk A, et al. Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. N Engl J Med. 1988;318:1159-62.
61. Veronesi U, Cascinelli N. Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. Arch Surg. 1991;126:438-41.
62. Balch CM, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Drzewiecki K, et al. Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4mm). Results of a multi-institutional randomized surgical trial. Ann Surg. 1993; 218:262-9.
63. Heaton KM, Sussman JJ, Gershenwald JE, Lee JE, Reintgen DS, Mansfield PF, et al. Surgical margins and prognostic factors in patients with thick (>4 mm) primary melanoma. Ann Surg Oncol. 1998;5:322-8.
64. Cohn-Cedermark G, Rutqvist LE, Andersson R, Breivald M, Ingvar C, Johansson H, et al. Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8–2.0mm. Cancer. 2000;89: 1495-501.
65. Balch CM, Soong SJ, Smith T, Ross MI, Urist MM, Karakousis CP, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. Ann Surg Oncol. 2001;8:101-8.
66. Khayat D, Rixe O, Martin G, Soubrane C, Banzet M, Bazex JA, et al. French Group of Research on Malignant Melanoma. Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2.1 mm thick). Cancer. 2003;97:1941-6.
67. Haigh PI, DiFronzo LA, McCready DR. Optimal excision margins for primary cutanous melanoma: a systematic review and meta-analysis. Can J Surg. 2003;46:419-26.
68. Thomas JM, Newton-Bishop J, A'Hern R, Coombes G, Timmons M, Evans J, et al. Excision margins in high-risk malignant melanoma. N Engl J Med. 2004;350:757-66.
69. Mehrara BJ, Abood AA, Disa JJ, Pusic AL, Halvorson E, Cordeiro PG, et al. Thumb reconstruction following resection for malignant tumors. Plast Reconstr Surg. 2008;121:1279-87.
70. Zitelli JA, Brown C, Hanusa BH. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. J Am Acad Dermatol. 1997;37:236-45.
71. Dawn ME, Dawn AG, Miller SJ. Mohs surgery for the treatment of melanoma in situ: a review. Dermatol Surg. 2007;33: 395-402.
72. Broadland DG. The treatment of nail apparatus melanoma with Mohs micrographic surgery. Dermatol Surg. 2001;27: 269-73.
73. Stevens G, McKay MJ. Dispelling the myths surrounding radiotherapy for treatment of cutaneous melanoma. Lancet Oncol. 2006;7:575-83.
74. Stevens G, Hong A. Radiation therapy in the management of cutaneous melanoma. Surg Oncol Clin N Am. 2006;15: 353-71.
75. Berk LB. Radiation therapy as primary and adjuvant treatment for local and regional melanoma. Cancer Control. 2008;15: 233-8.
76. Conill C, Jorcano S, Domingo-Domènech J, Marruecos J, Vilella R, Malvehy J, et al. Toxicity of combined treatment of adjuvant irradiation and interferon alpha2b in high-risk melanoma patients. Melanoma Res. 2007;17:304-9.
77. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith Tj, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol. 1996;14:7-17.
78. Grobb JJ, Dreno B, de la Salmoniere P, Delaunay M, Cupisol D, Guillot B, et al. Randomized trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. Lancet. 1998;351: 1905-10.
79. Pehamberger H, Soyer H, Steiner A, Kofler R, Binder M, Mischer P, et al. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. J Clin Oncol. 1998;16:1425-9.
80. Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Emstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/ S9111/C9190. J Clin Oncol. 2000;18:2444-58.
81. Kirkwood JM, Ibrahim J, Lawson DH, Atkins MB, Agarcala SS, Collins K, et al. High-dose interferon alfa-2b does not diminish antibody response to GM2 vaccination in patients with resected melanoma: results of the Multicenter Eastern Cooperative Oncology Group Phase II Trial E2696. J Clin Oncol. 2001;19:1430-6.
82. Cascinelli N, Belli F, MacKie RM, Santinami M, Bufalino R, Morabito A. Effect of long term adjuvant therapy with interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomized trial. Lancet. 2001; 358:866-9.
83. Lens MB, Dawes M. Interferon alpha therapy for malignant melanoma: a systematic review of randomized clinical trials. J Clin Oncol. 2002;20:1818-25.
84. Hancock BW, Wheatley K, Harris S, Ives N, Harrison G, Horsman JM, et al. Adjuvant interferon in high-risk melanoma: the AIM HIGH Study--United Kingdom Coordinating Committee on Cancer Research randomized study of adjuvant low-dose extended-duration interferon Alfa-2a in high-risk resected malignant melanoma. J Clin Oncol. 2004;22:53-61.
85. Kirkwood JM, Manola J, Ibrahim J, Sondak V, Emstoff MS, Rao U, et al. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high dose interferon for melanoma. Clin Cancer Res. 2004;10:1670-7.
86. Eggermont AM, Suciu S, MacKie R, Ruka W, Testori A, Kruit W, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomized controlled trial. Lancet. 2005;366:1189-96.
87. Eggermont AM, Suciu S, Santinami M, Testori A, Kruit WH, Marsden J, EORTC Melanoma Group. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet. 2008;372:117-26.
88. Botella-Estrada R. Controversias sobre el interferón en el tratamiento adyuvante del melanoma. Actas Dermosifiliogr. 2004; 95:597-605.
89. Blazer DG, Sondak VK, Sabel MS. Surgical therapy of cutaneous melanoma. Semin Oncol. 2007;34:270-80.
90. Conill C, Gimferrer JM, Marruecos J, Domingo-Domenech J, Vilella R, Catalan M, et al. Clinical outcome after surgical resection of lung metastases from melanoma. Clin Transl Oncol. 2007;9:48-52.
91. Wood TF, DiFronzo LA, Rose DM, Haigh PI, Stern SL, Wanek L, et al. Does complete resection of melanoma metastatic to solid intra-abdominal organs improve survival?. Ann Surg Oncol. 2001;8:658-62.

92. Conill C, Fernández-Ibiza J, Malvehy J, Puig S, Sánchez M, Castel T. Temozolomida en pacientes con metástasis cerebrales de melanoma tratados con irradiación holocraneal. Med Clin (Barc). 2004;122:413-5.
93. Grünhagen DJ, de Wilt JH, van Geel AN, Eggermont AM. Isolated limb perfusion for melanoma patients--a review of its indications and the role of tumour necrosis factor-alpha. Eur J Surg Oncol. 2006;32:371-80.
94. Tawbi HA, Kirkwood JM. Management of metastatic melanoma. Semin Oncol. 2007;34:532-45.
95. Quirt I, Verma S, Petrella T, Bak K, Charette M. Temozolomide for the treatment of metastatic melanoma: a systematic review. Oncologist. 2007;12:1114-23.
96. Conill C, González-Cao M, Jorcano S, Puig S, Malvehy J, Marti R, et al. Temozolomide as prophylaxis for melanoma brain metastases. Melanoma Res. 2004;14:73-4.
97. Avril MF, Aamdal S, Grob JJ, Hauschild A, Mohr P, Bonerandi JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol. 2004;22:1118-25.
98. Lens MB, Eisen TG. Systemic chemotherapy in the treatment of malignant melanoma. Expert Opin Pharmacother. 2003;4: 2205-11.
99. Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K, the members of the Melanoma Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Single-agent interleukin-2 in the treatment of metastatic melanoma. Curr Oncol. 2007;14:21-6.
100. Krown SE, Burk MW, Kirkwood JM, Kerr D, Morton DL, Oettgen HF. Human leukocyte (alpha) interferon in metastatic malignant melanoma: the American Cancer Society phase II trial. Cancer Treat Rep. 1984;68:723-6.
101. Vilella R, Benítez D, Mila J, Vilalta A, Rull R, Cuéllar F, et al. Treatment of patients with progressive unresectable metastatic melanoma with a heterologous polyvalent melanoma whole cell vaccine. Int J Cancer. 2003;106:626-31.
102. Vilella R, Benítez D, Mila J, Lozano M, Vilana R, Pomes J, et al. Pilot study of treatment of biochemotherapy-refractory stage IV melanoma patients with autologous dendritic cells pulsed with a heterologous melanoma cell line lysate. Cancer Immunol Immunother. 2004;53:651-8.
103. Legha SS, Ring S, Eton O, Bedikian A, Buzaid AC, Plager C, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. J Clin Oncol. 1998;16:1752-9.
104. Cao MG, Malvehy J, Marti R, Conill C, Sánchez M, Martín M, et al. Biochemotherapy with temozolomide, cisplatin, vinblastine, subcutaneous interleukin-2 and interferon-alpha in patients with metastatic melanoma. Melanoma Res. 2006; 16:59-64.
105. Eton O, Legha SS, Bedikian AY, Lee JJ, Buzaid AC, Hodges C, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol. 2002;20:2045-52.
106. ESMO Guidelines Working group, Jost L. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2007;18(Suppl 2): ii71-3.
107. Machet L, Nemeth-Normand F, Giraudeau B, Perrinaud A, Tiguemounine J, Ayoub J, et al. Is ultrasound lymph node examination superior to clinical examination in melanoma follow-up? A monocentre cohort study of 373 patients. Br J Dermatol. 2005;15:66-70.
108. Moore Dalal K, Zhou Q, Panageas KS, Brady MS, Jaques DP, Coit DG. Methods of detection of first recurrence in patients with stage I/II primary cutaneous melanoma after sentinel lymph node biopsy. Ann Surg Oncol. 2008;15:2206-14.
109. Einwachter-Thompson J, Mackie RM. An evidence base for reconsidering current follow-up guidelines for patients with cutaneous melanoma less than 0.5 mm thick at diagnosis. Br J Dermatol. 2008;159:337-41.
110. Auge JM, Molina R, Filella E, Bosch E, González Cao M, Puig S, et al. S-100b and MIA in Advanced Melanoma in relation to prognostic factors. Anticancer Research. 2005;25:1779-82.
111. Domingo-Domènech J, Castel T, Auge JM, García-Albeniz XA, Conill C, Puig S, et al. Prognostic implications of protein S-100 beta serum levels in the clinical outcome of high-risk melanoma patients. Tumour Biol. 2007;28:264-72.
112. Cao MG, Auge JM, Molina R, Martí R, Carrera C, Castel T, et al. Melanoma inhibiting activity protein (MIA), beta-2 microglobulin and lactate dehydrogenase (LDH) in metastatic melanoma. Anticancer Res. 2007;27:595-9.
113. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998;83:1664-78.
114. Katz KA, Jonasch E, Hodi FS, Soiffer R, Kwitkiwski K, Sober AJ, et al. Melanoma of unknown primary: experience at Massachusetts General Hospital and Dana-Farber Cancer Institute. Melanoma Res. 2005;15:77-82.
115. Vijuk G, Coates AS. Survival of patients with visceral metastatic melanoma from an occult primary lesion: a retrospective matched cohort study. Ann Oncol. 1998;9: 419-22.
116. Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeutic management of cancer of an unknown primary. Eur J Cancer. 2003;39:1990-2005.
117. Henry F, Piérard-Franchimont C, Arrese JE, Claessens N, Paquet P, Piérard GE, Groupe Mosan d'Etude des Tumeurs Pigmentaires. How I explore… an orphan metastasis from melanoma. Rev Med Liege. 2002;57:405-7.
118. Schlagenhauff B, Stroebel W, Ellwanger U, Meier F, Zimmermann C, Breuninger H, et al. Metastatic melanoma of unknown primary origin shows prognostic similarities to regional metastatic melanoma: recommendations for initial staging examinations. Cancer. 1997;80:60-5.
119. Vélez A, Walsh D, Karakousis CP. Treatment of unknown primary melanoma. Cancer. 1991;68:2579-81.