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PRACTICAL DERMATOLOGY

Study and Treatment of Locally Advanced Melanoma

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Abstract. Locally advanced melanoma is characterized clinically by the appearance of in-transit or satellite metastases, and is considered stage IIIB or IIIC according to the 2002 classification of the American Joint Committee on Cancer. Despite the absence of distant metastases, the management of locally advanced melanoma is complicated and the disease is associated with a reduction in overall survival. The initial step in the approach to the patient with locally advanced melanoma involves restaging in order to exclude the presence of distant metastases. Positron emission tomography-computed tomography is currently accepted as the most accurate restaging technique. Surgical excision of the metastases continues to be the treatment of choice for locally advanced melanoma. In the case of unresectable metastases, hyperthermic isolated limb perfusion with melphalan with or without tumor necrosis factor has achieved complete responses in up to 60% of patients treated, with very rare severe locoregional and systemic toxic effects. Radiation therapy, chemotherapy, and biochemotherapy are options that, even though they have not been tested in patients with only in-transit metastases, may have a role in unresectable, locally advanced melanoma without distant metastases. In any case, therapeutic options for locally advanced melanoma should be individualized, and should take into consideration the availability of each of these techniques as well as the experience of the health care team.

Key words: melanoma, locally advanced melanoma, in-transit metastasis, satellitosis, isolated limb perfusion.

MELANOMA LOCALMENTE AVANZADO. ESTUDIO Y TRATAMIENTO

Resumen. El melanoma localmente avanzado representa un estadio clínico caracterizado principalmente por la presencia de metástasis en tránsito o satelitosis, estadios IIIB o IIIC de la clasificación *American Joint Committee on Cancer* de 2002, y que en ausencia de metástasis a distancia, representa un acortamiento en la supervivencia del paciente y un escenario clínico de manejo complejo.

La aproximación al paciente en este estadio debe iniciarse con una reestadificación que permita descartar la presencia de metástasis a distancia, para lo que se acepta como técnica con mayor validez la tomografía por emisión de positrones-tomografía computarizada. La exéresis quirúrgica de la/s metástasis continúa siendo considerada el tratamiento de primera elección en la enfermedad localmente avanzada.

En caso de metástasis irresecables la perfusión hipertérmica del miembro aislado con melfalán con o sin factor de necrosis tumoral, proporciona porcentajes de respuesta completa del 60 %, con toxicidad sistémica y locorregional grave muy poco frecuente. La radioterapia, quimioterapia y bioquimioterapia son alternativas terapéuticas que, aunque no han sido estudiadas exclusivamente en el paciente con metástasis en tránsito, pueden tener un papel en la enfermedad localmente avanzada irresecable sin metástasis a distancia.

En cualquier caso, las opciones terapéuticas en el melanoma localmente avanzado clínico deben ser individualizadas para cada paciente y teniendo en cuenta la disponibilidad de cada una de las técnicas y la experiencia del equipo de profesionales con cada una de ellas.

Palabras clave: melanoma, melanoma localmente avanzado, metástasis en tránsito, satelitosis, perfusión del miembro aislado.

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Despite its low incidence (5 to 7 cases annually per 100000 population in Spain), cutaneous melanoma is the neoplastic disease that accounts for the highest percentage of skin cancer deaths.[1] However, the prognosis for patients with melanoma varies a great deal depending

on clinical stage, ranging from a survival rate almost comparable to that of the general population of the same age for patients with early-stage melanoma to a rate of less than 10% at 5 years in patients with advanced disease characterized by distant metastasis.[2] Intermediate clinical stages characterized by disease localized in a single region of the body are associated with a significant reduction in survival and are complicated to manage. These are the cases classified as locally advanced melanoma (LAM), the subject of this review.

Locally Advanced Melanoma

The difficulties of managing LAM start with the very definition of this clinical concept, which is applied differently in the different studies and articles on this topic. In the broad sense, the term LAM refers to cases of primary or recurrent melanoma without systemic or distant metastasis, that is, cases in which disease is limited to a specific region of the body. In spite of this absence of distant metastasis, the clinical situations that fall into this category are associated with a poor prognosis and a significantly reduced overall survival rate.

The initial clinical and prognostic evaluation of melanoma differentiates between local, locoregional, and systemic disease, with survival rates at 5 years of 95%, between 50% and 75%, and less than 25%, respectively.[2] Traditionally, locoregional disease was divided into the following 3 types: local recurrence, satellite metastasis, and in-transit metastasis (Table 1, Figures 1 and 2). Each one of these clinical situations may or may not be accompanied by corresponding regional lymph node involvement, and the prognostic implications of such involvement will be different in each case. However, the most recent classification published in 2002 by the American Joint Committee on Cancer (AJCC) differentiates—from a prognostic standpoint—between local recurrence on the

Table 1. Definitions of In-Transit and Satellite Metastasis and Local Recurrence

Concept	*Definition*	*Mechanism*	*AJCC 2002 TNM Stage*[2]
Local recurrence	Regrowth of a tumor on or within 2 cm of the surgical scar caused by excision of the primary tumor	Persistence Incomplete excision	–
Satellite metastasis	Cutaneous or subcutaneous metastasis within a radius between 2 and 5 cm of the primary tumor	Infiltration of the lymphatic system	N2c → IIIB N3 (+ lymph node disease) → IIIC
In-transit metastasis	Cutaneous or subcutaneous metastasis developing more than 5 cm from the primary tumor along the pathway between primary tumor and the corresponding regional lymph node station.	Infiltration of the lymphatic system	N2c → IIIB N3 (+ lymph node disease) → IIIC

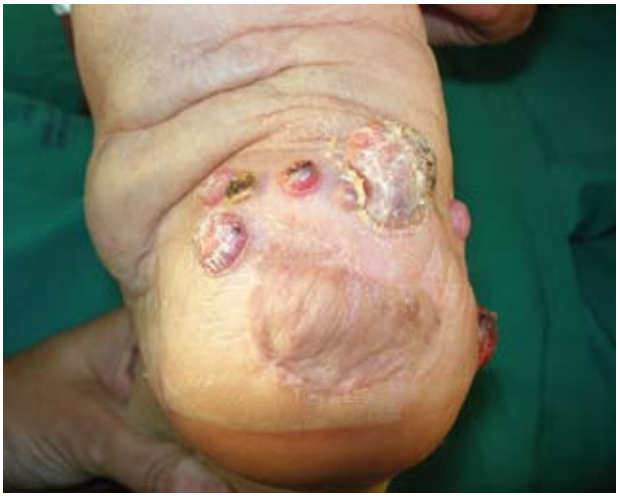

Figure 1. Satellite metastasis in a patient with primary melanoma on the heel. Regrowth of lesions within 5 cm of the excision of the primary tumor.

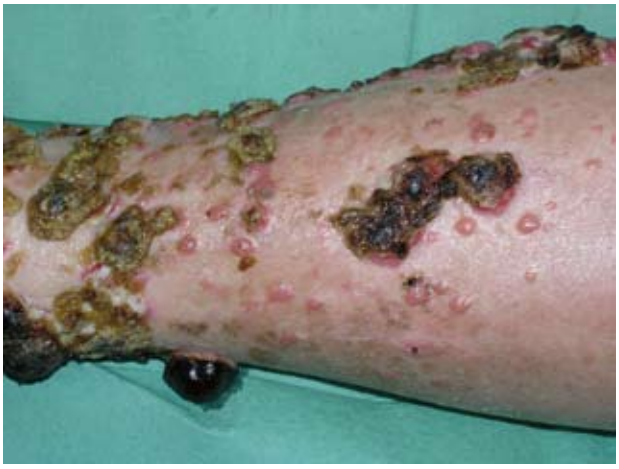

Figure 2. In-transit metastasis in a patient in whom the primary melanoma was located on the lower limb. Image supplied by Professor Carlos Ferrándiz Foraster, Hospital Germans Trias i Pujol, Badalona, Spain.

Table 2. Locally Advanced Melanoma

		NM	*AJCC 2002 TNM Stage*[2]	*Survival at 5 years*[2]
In-transit or satellite metastasis	Without lymph node involvement	N2c	Stage IIIB	No data reported in the study by Balch et al[2]
	With lymph node involvement	N3	Stage IIIC	27%
Tumor with Breslow depth >4 mm, and bulky tumors	Without ulceration	T4a	Stage IIB	67%
	Ulcerated	T4b	Stage IIC	45%

Abbreviation: AJCC, American Joint Committee on Cancer.

one hand and in-transit or satellite metastasis on the other.[2] The basis for this differentiation is that while local recurrence has not been shown to have any impact on patient survival, in-transit and satellite metastasis are both associated with increased mortality to a similar degree. The 2002 AJCC classification makes it clear that in-transit and satellite metastasis are comparable situations from the point of view of prognosis because they are both the result of lymphatic invasion by tumor cells. They are classified as N2c when there is no associated lymph node metastasis (stage IIIB) and N3 when accompanied by metastatic involvement of the corresponding lymph node region (stage IIIC) (Table 1).[2,3]

In addition to in-transit and satellite metastasis, the LAM classification also includes local primary or recurrent tumors corresponding to T4a-4b (Breslow depth >4 mm, with or without ulceration) and bulky tumors, but only when disease is localized and associated with a survival rate of under 50% at 5 years (Table 2).[2]

Our aim in this review was to focus on the management of locally advanced disease without distant metastasis, especially cases involving in-transit or satellite metastasis (TNM N2c and N3, stages IIIB and IIIC as defined by the 2002 AJCC classification).[2] Throughout this review, in-transit metastasis and satellite metastasis are treated as equivalent entities.

Incidence and Risk Factors for LAM

The incidence of in-transit and satellite metastasis in patients with melanoma has been evaluated in a number of studies. Of note is a recent prospective study of 1395 patients with melanoma by Pawlik et al[4] with a median follow-up of 4 years following excision of the primary tumor. Sentinel lymph node biopsy had been performed in all cases and the incidence of in-transit metastasis was 6.6%. When the authors of that study used a multivariate model to analyze the clinicopathologic factors that might predict in-transit disease, they found age, a lower limb location, a positive sentinel lymph node biopsy, and a Breslow depth greater than 2 mm to be independent predictors for in-transit metastasis (P<.001). With respect to the much-debated question of the existence of an association between the performance of sentinel lymph node biopsy and an increased incidence of in-transit metastasis (irrespective of the pathologic status of the node), Pawlik et al found no statistically significant relationship and suggested that sentinel node biopsy should not be considered a risk factor for in-transit metastasis.

They also reported an increased incidence (57%) of systemic metastasis in patients with in-transit disease and identified the following factors as predictors of distant metastasis in patients with LAM: a positive sentinel lymph node biopsy, subcutaneous rather than cutaneous in-transit deposits, a metastatic lesion with a diameter greater than 2 cm, and disease-free intervals of less than 1 year.[4]

Management of LAM

While the prognosis is similar for in-transit disease and advanced regional lymph node disease, the management of the former is generally more complicated. Lymph node metastases can be controlled by dissection of the appropriate nodes, a procedure that is also associated with a low incidence of recurrence in the node station.[5] By contrast, in-transit metastases generally require more complex treatment, are often refractory to treatment, and recur frequently.

In this review, we describe the diagnostic and therapeutic techniques currently available for patients with LAM (Figure 3). LAM is a condition that gives rise to a complex clinical picture and there are 2 essential factors that should be taken into consideration in all therapeutic decisions related to these patients. In the first place, the aim of almost all interventions will be palliative because none of the treatments used to manage LAM have been shown to improve survival. Secondly, the level of evidence supporting the use of these treatments is necessarily low to medium in all cases because of the difficulty of designing

randomized controlled studies involving patients with cancer. All treatment decisions must therefore necessarily be made on a case-by-case basis and should take into account the care setting in which the patient will be treated.

Decision-Making Algorithm (Figure 3)

Any treatment protocol or algorithm for patients with LAM must start by ascertaining whether disease is local or locoregional and by ruling out the presence of systemic metastasis (M0). When systemic metastasis is present (M1), the patient is a candidate for systemic treatment and there is no justification for an exclusively locoregional treatment approach. Once restaging has been completed and the suspicion of LAM confirmed, decisions will focus on evaluating resectability in order to assess the possibility of treating the metastasis surgically. Other treatment options, including isolated limb perfusion (ILP), are only considered when the lesion or lesions have been deemed unresectable or when surgery is not feasible for other reasons (Figure 3).

Restaging

The 2 imaging tools that have demonstrated the best validity in the detection of systemic metastasis in patients with LAM who develop in-transit and/or satellite metastasis (stage IIIB) are 2-fluorodeoxyglucose positron emission tomography (PET) and combined PET-computed tomography (PET-CT) imaging. Finkelstein et al,[6] who compared the sensitivity and specificity of PET-

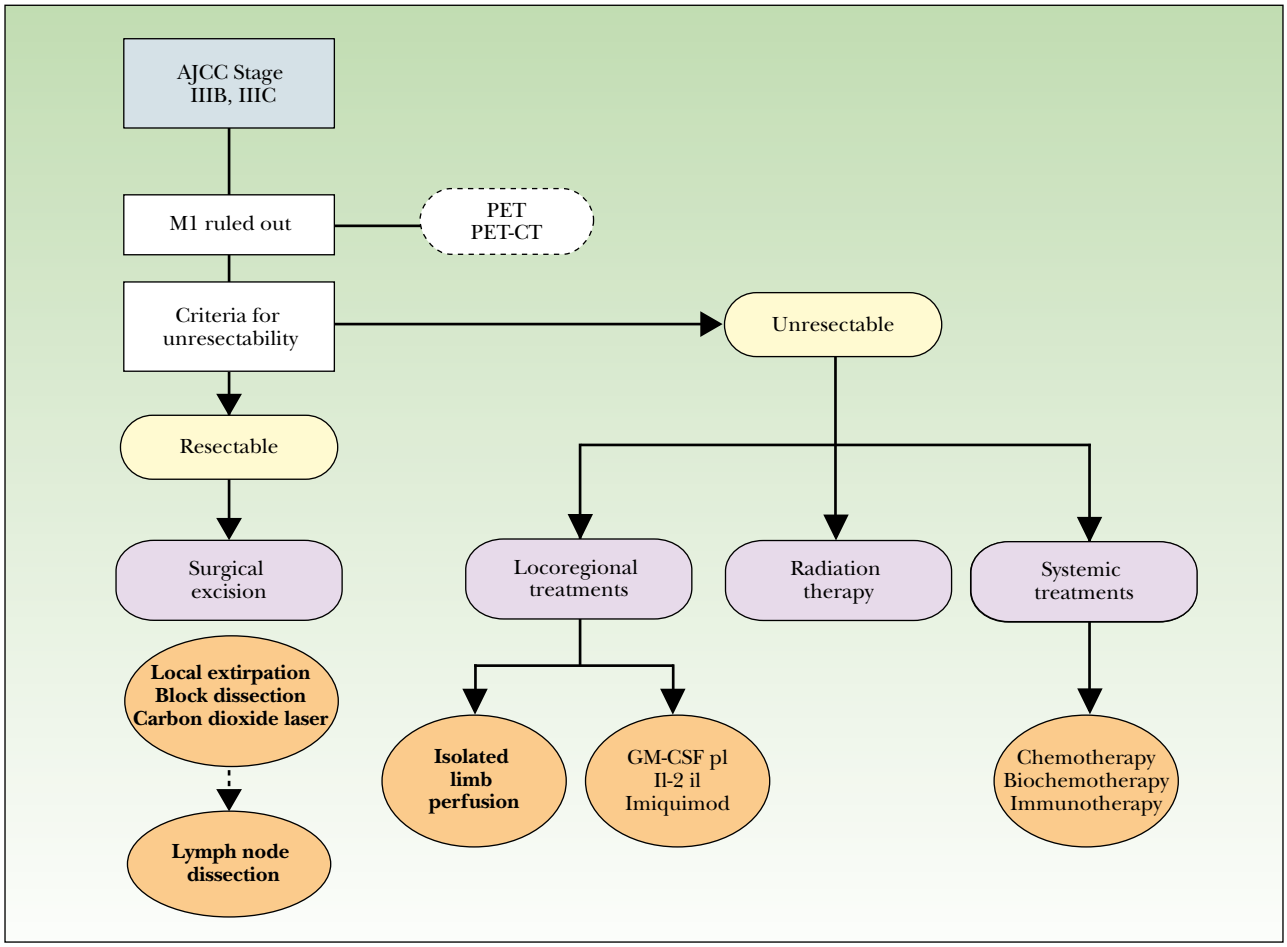

Figure 3. Initial algorithm for the management of locally advanced melanoma. AJCC indicates American Joint Committee on Cancer; IIIB, in-transit and/or satellite metastasis without lymph node involvement; IIIC, in-transit and/or satellite metastasis with lymph node involvement; GM-CSF pl, treatment with perilesional injection of granulocyte-macrophage colony-stimulating factor; Il-2 il, treatment with intralesional injection of interleukin 2; M1, TNM corresponding to the presence of distant metastasis; PET, positron emission tomography; PET-CT positron emission tomography combined with computed tomography images.

CT, PET, and other conventional imaging techniques (magnetic resonance imaging [MRI] and CT), reported a sensitivity and specificity for PET-CT of 92% and 94%, respectively, much higher values than those found for PET alone (sensitivity, 79%; specificity, 87%) or for the conventional imaging techniques (sensitivity, 76%; specificity, 87%). Although PET has detected metastases with a diameter of 3 mm in some studies,[7] the validity of PET-CT was highest for metastatic lesions larger than 10 mm.[8] In the case of locoregional disease, PET-CT can detect subcutaneous in-transit nodules that are clinically occult (Figure 4). This combined imaging technique has greater diagnostic validity than other imaging methods for investigating possible metastasis in patients with LAM because the CT provides useful information concerning the anatomical location of the high-uptake lesions demonstrated by PET. Moreover, restaging disease in patients with metastatic melanoma is an indication for PET-CT accepted by the health authorities in Spain.[9]

Information on current nodal status is also essential in any restaging of patients with in-transit metastasis. As mentioned above, the independent predictive factors for the development of in-transit or satellite metastases include a Breslow depth greater than 2 mm and a positive sentinel node biopsy. Consequently, most patients with in-transit and satellite metastases have previously undergone sentinel node biopsy and even regional lymph node dissection. In such cases, the study of lymph node status is limited to the clinical and imaging findings relating to the corresponding lymph node region. However, in a study by Pawlik et al,[4] 4.7% of patients with in-transit metastases had a primary melanoma with a Breslow depth under 1 mm. It would appear, therefore, that the occurrence of in-transit metastases in this group of patients cannot be attributed to the performance of a sentinel node biopsy during the treatment and staging of their primary disease.

In patients with lymph node involvement—whether clinically evident or detected by PET, CT, or ultrasound—fine needle aspiration is indicated to obtain the cytological information needed for eventual regional node dissection. There is no evidence supporting any survival benefit associated with lymph node dissection in patients with in-transit metastases and no lymph node involvement or in patients who have not previously undergone sentinel node biopsy or node dissection. Despite the lack of evidence, researchers in this field recommend that lymph node dissection be performed in all patients being treated for in-transit metastases. In this clinical situation, sentinel node biopsy is not indicated at this stage as it does not contribute any prognostic information beyond that already obtained from the patient's clinical condition (in-transit metastases, N2 → IIIB). In such cases, lymph node dissection can be performed during the surgical procedure undertaken to excise the metastases, during ILP or prior to other nonsurgical procedures.

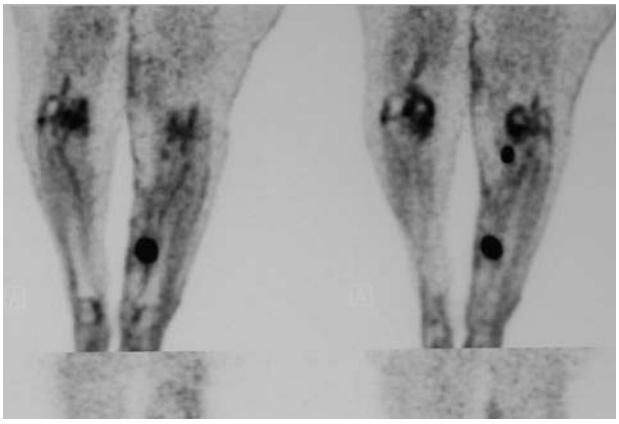

Figure 4. Positron emission tomography of a patient with in-transit metastasis in the lower limbs. In addition to the clinically palpable high-uptake lesion located on the middle and distal thirds of the leg, positron emission tomography detects a small and clinically occult nodule in the popliteal region.

In view of the lack of any direct evidence favoring sentinel node biopsy over prophylactic lymphadenectomy in this particular clinical situation, the decision on the most appropriate procedure should be taken on a case-by-case basis by a multidisciplinary melanoma team.

Resectability

As surgery is the first approach that should be considered in patients with in-transit or satellite metastases, the first essential task in this phase is to assess the resectability of the metastatic lesions.

The currently accepted clinical and radiologic criteria for nonresectable disease are shown in Table 3.[10] An exhaustive physical examination is required to identify the clinical criteria for nonresectable lesions; this should include deep palpation of the affected area, measurement of all tumors, and assessment of the mobility of lesions with respect to adjacent tissue, the motor function of the affected limb, and signs of neurologic and vascular involvement (Table 3). Radiologic criteria are identified by way of gadolinium-enhanced MRI or a CT scan when bone involvement is suspected. Infiltration of the neurovascular bundle demonstrated by MRI is a key criterion for unresectable disease (Table 3, Figure 5).

Surgical Treatment of Metastasis

While surgical resection is considered to be the first-line treatment for in-transit or satellite metastases in patients

Table 3. Clinical and Radiographic Criteria for Unresectable Lesions in Patients with Locally Advanced Melanoma[10]

Clinical Criteria	Vascular compromise	Peripheral edema, absence of pulse, decrease in temperature, cyanosis
	Neurological compromise	Neuropathic pain, weakness
	Bulky in-transit metastases	Diameter (>5-10 cm)
		Multiple lesions (>10-15 nodules)
	Periarticular location	
Radiographic Criteria	MRI	Neurovascular infiltration
		Muscle infiltration
	CT	Osseous infiltration

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

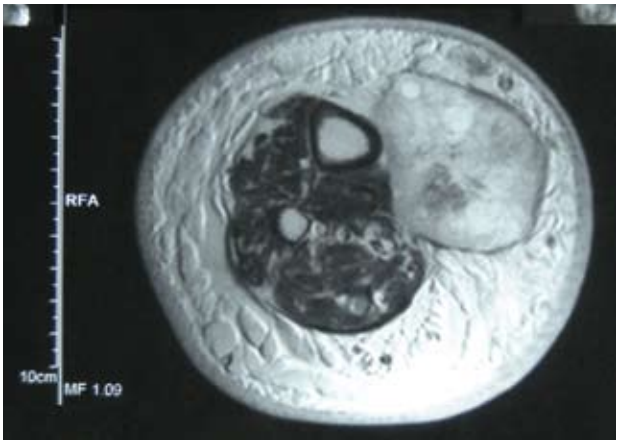

Figure 5. Gadolinium-enhanced magnetic resonance image of subcutaneous in-transit metastasis located in the tibial region. The lesion is considered unresectable because it is greater than 5 cm in diameter and it has infiltrated the posterior tibial neurovascular bundle and adjacent muscle.

with melanoma, there is no evidence that it improves prognosis in terms of overall survival. Metastasectomy should therefore be viewed in most cases as a palliative measure undertaken to improve the function of the affected limb and the patient's quality of life.

From the technical standpoint, conventional resection of in-transit and satellite metastases should be conservative, including clinically visible or palpable margins but not wide safety margins.[3] Unlike primary melanoma and local recurrence, in-transit and satellite metastasis usually consists of dermal lesions that are clearly differentiated from perilesional dermal and epidermal tissue and wide margin excision is not necessary because the lesions are clearly circumscribed. In patients with LAM, metastasectomy is associated with a lower incidence of local relapse than other treatment options, with a recurrence rate of under 10% at the same site as the extirpated metastasis. However, the rate of regional recurrence along the pathway to the corresponding lymph node station is similar to that of other treatments—between 50% and 90% depending on the series—an indication that resection has no influence on the development of regional recurrence.[11]

With respect to the closure of surgical defects, surgeons should opt, when possible, for direct closure, skin graft, or healing by second intention. Local flaps should be avoided because they further distort the regional anatomy and hinder early detection of local recurrence.

When multiple in-transit or satellite metastases are grouped together in a single region, they can be resected together in a procedure known as block dissection. When the in-transit metastases are located close to a lymph node region and are associated with regional node involvement, the regional lymph node chains can be included in the block dissection.[3] There is, however, no evidence supporting the appropriateness of this surgical approach; it should therefore be limited to block dissections that are neither excessively aggressive or mutilating for the patient.

Amputation of the affected limb is now considered overtreatment, and the procedure is, therefore, no longer performed. In fact, the few studies that deal with this intervention are now almost 20 years old, and survival among the patients who underwent amputation in these studies was less than 15% at 5 years. Amputation may, however, be indicated in certain exceptional cases, such as unresectable tumors with massive hemorrhage, rapid progression, vegetating masses, ulcerated lesions, loss of joint function, and in cases in which appropriate nonsurgical methods have failed or are not possible.[12,13] However, amputation is associated with complications (postoperative morbidity, functional deficit, phantom limb syndrome, etc.) that should be taken into consideration when any decision is being made about the appropriateness of a palliative surgical procedure.[12]

Metastasectomy by way of carbon dioxide laser ablation has been proposed as an appropriate alternative treatment for LAM. This proposal is based on the efficacy of this procedure demonstrated in some studies and its low morbidity compared to conventional surgical excision.[14] However, laser ablation has only been used to treat small superficial cutaneous lesions, and the local recurrence rate for metastases treated with carbon dioxide laser is close to 50% of the patients treated, with only a short recurrence-free interval of between 2 and 7 weeks.[15] Carbon dioxide laser metastasectomy may, therefore, be indicated only as an adjuvant therapy to complement other locoregional alternatives, such as ILP, radiation therapy, or even systemic chemotherapy. In this role, it could be used to manage the numerous small tumors that may persist after the chosen treatment.

Isolated Limb Perfusion

Among the locoregional treatment techniques used to treat patients with unresectable disease, ILP has been a focus of particular interest in recent years. It is not, however, a novel technique as it was described for the first time in an article published in 1959, which cited the treatment of melanoma on the extremities and the management of soft tissue tumors as its principal indications.[16]

ILP involves isolation of the affected limb (upper or lower) through the use of external pressure exerted by a tourniquet and the creation of a bypass circulatory circuit linked to an external perfusion pump by way of cannulation of the major vessels of the limb (Figure 6). Once the circulation of the limb has been isolated from the patient's systemic circulation system, a dose of the chemotherapeutic agent up to 10 times that prescribed in systemic chemotherapy regimens can be administered. The drug most often perfused is mephalan, which in the last 10 years has often been administered in combination with tumor necrosis factor or interferon. Drug is perfused under hyperthermic conditions to improve the release of the drug and to increase the vulnerability of the tumor cells. To safeguard against severe toxicity, it is essential to monitor both the blood temperature in the bypass circuit and the leakage of perfused chemotherapy into the systemic circulation system during the procedure.[17,18]

From a pathophysiologic standpoint, the advantage of ILP compared to other locoregional therapeutic procedures, including metastatic resection, is that it also targets tumor cells that may have infiltrated the lymphatic system but not yet become clinical lesions.

ILP is a lengthy and complex procedure performed under general anesthesia by a team of cardiovascular surgeons working within a multidisciplinary team that includes the dermatologist from the melanoma unit. The

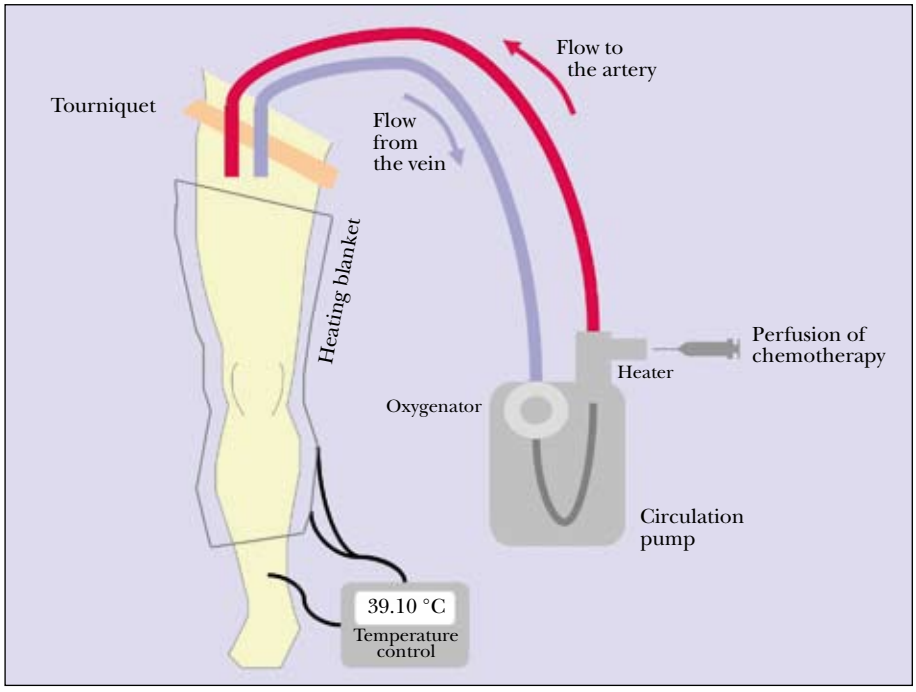

Figure 6. Diagram of the extracorporeal bypass circuit used in the isolated limb perfusion procedure.

patient's health and the locoregional physical conditions must be assessed to ascertain whether the candidate is suitable for such highly complex surgery. This assessment should take into consideration the patient's performance status, anesthesia risk (American Society of Anesthesiologists classification), and comorbidity, as well as the absence of peripheral vascular disease. Because of the complexity of the technique and scattered evidence available, this procedure is not practiced in most hospitals.

The studies in the literature on the use of ILP in the treatment of unresectable LAM have reported a median of 60% for complete response, 25% for partial response, and 6% for no response. Therapeutic response has even been maintained when ILP was repeated to treat successive postperfusion recurrences.[19,20] The prognosis for disease-free survival at 5 years in patients treated with ILP has varied between 16% and 53%, with a median disease-free interval of 16 months for the treated limb. Overall survival in patients treated with ILP has ranged from 19% to 50% at 5 years, with a median survival of 32 months. With respect to the most appropriate chemotherapy perfusion regimen, the few comparative studies in the literature have failed to demonstrate any significant differences between ILP with melphalan alone and a regimen of melphalan combined with tumor necrosis factor. Although ILP is associated with frequent mild local effects, severe and very severe regional toxicity—compartment syndrome and amputation—have only been reported in under 5% and 1% of the patients treated, respectively. The incidence of severe organ-specific systemic toxicity reported in the literature is less than 5%, the mortality rate reported is under 1%, and mortality varied depending on the techniques used. On the basis of these findings, we can conclude that ILP is a safe and effective option for the treatment of patients with unresectable LAM. It should, nonetheless, be remembered that, despite abundant evidence concerning this technique, the evidence level and grade of recommendation associated with these results is necessarily limited owing to the inevitable lack of controlled randomized trials comparing it with other treatment options.[21]

Intralesional and Perilesional Local Treatments

A number of studies have investigated the usefulness of various topical and intralesional treatments in patients with LAM in whom the therapeutic options described above are contraindicated or have failed.

However, the use of these alternative treatments is based on very limited evidence, and the efficacy of these approaches needs to be confirmed by clinical trials, or at least by larger descriptive series.

Imiquimod

Various regimens of topical 5% imiquimod in the treatment of cutaneous metastasis of melanoma have been studied with complete or partial response in most of the published cases (Table 4).[22-29] However, this data comes from noncomparative case series involving only small samples. Imiquimod has been used in combination with other therapeutic options in patients with LAM. One phase I/II study analyzed the response of a cohort of 13 patients with cutaneous metastasis and/or multiple subcutaneous metastases in whom topical 5% imiquimod was applied daily for 4 weeks followed by intralesional interleukin 2. Of the 182 lesions treated, the overall objective response obtained was 50%, and in 40% of these, response was complete.[30]

Given that the response of in-transit and satellite metastases has been unpredictable and that the regimens studied have varied considerably, controlled studies are needed to confirm the real value of topical imiquimod as an adjuvant treatment for cutaneous metastasis of melanoma, both as monotherapy and in combination with other treatment options.

Intralesional Interleukin 2

In a prospective series of patients with melanoma, interleukin 2 administered intralesionally by injection into each cutaneous or subcutaneous metastatic lesion 2 or 3 times a week during a variable period was associated with a complete response in 85% and a partial response in 6% of the lesions treated.[31] In that study, the treatment was well tolerated and the authors reported only mild to moderate side effects and concluded that intralesional injection was a safe and effective alternative treatment option in patients with LAM.

Perilesional Injection of Granulocyte-Macrophage Colony-Stimulating Factor

The ability of granulocyte-macrophage colony-stimulating factor to induce potent systemic antitumor immunity has led to the administration of this cytokine by perilesional injection in patients with cutaneous or subcutaneous metastatic melanoma. In a study of 7 patients, 70% showed a decrease in the total number of metastases, with a mean survival time of 33 months.[32] The perilesional injections were well tolerated, and the

Table 4. Topical Imiquimod 5% in the Treatment of Cutaneous Metastatic Melanoma

	Number of Patients	*Regimen*	*Response*
Steinmann[23]	1	3 times/wk × 18 wks	CR
Ugurel[24]	1	Once daily × 4 wks → alternate days × 8 wks. Occlusive therapy	CR
Bong[25]	3	Twice daily × 10-28 wks. Occlusive therapy	CR
Wolf[26]	2	3 times/wk × 16-32 wks	CR
Vereecken[27]	1	5 times/wk × 8 wks. Occlusive therapy	PR
Hesling[28]	1	Once daily × 16 wks	CR
Sigüenza[22]	1	5 times/wk × 4-12 wks	CR
Nagore[29]	2	5 times/wk × 8 wks	CR

Modified from Sigüenza et al[22]
Abbreviations: CR, complete response; PR, partial response.

only side effects were erythema at the injection sites and mild drowsiness.

Electrochemotherapy

Electrochemotherapy (chemotherapy with electroporation) is a treatment modality involving the administration of intralesional chemotherapy, usually bleomycin, while at the same time applying brief high-intensity pulsed electrical currents to the surface of the tumor. These electrical pulses increase cell membrane permeability thereby favoring the uptake of the chemotherapeutic agents into the neoplastic cell while avoiding the toxic effects of systemic chemotherapy. The use of electrochemotherapy in the local treatment of cutaneous metastasis of melanoma has been studied.[33,34] The authors of a controlled randomized study reported a therapeutic response in 72% of the patients treated with electrochemotherapy as compared to 32% of those treated with intralesional bleomycin administered without electroporation (*P*=.005).[34] Electrochemotherapy was well tolerated in all the patients and was administered in an outpatient setting. The results of another study demonstrated the absence of any systemic toxicity, although all the patients reported local discomfort during the procedure; local pain in 75% and muscle spasm with myoclonia in 25%.[33] Electrochemotherapy is, therefore, a safe and effective alternative palliative treatment, but one that is available only in very few specialized hospitals.[33,34]

Radiation Therapy

Traditionally, melanoma has been considered to be a tumor with a low sensitivity to radiation.[35] In recent years, however, researchers have discovered the beneficial effect of radiotherapy in the control of locoregional recurrence and symptomatic distant metastasis. In vitro studies have revealed that different melanoma cell lines have a wide spectrum of radiosensitivity, ranging from total resistance to radiation to complete sensitivity. Melanoma is now thought to be a tumor type with a wide range of radiosensitivity.[36] While the reason for this variability is poorly understood, it has been suggested that it may be due to the interaction of molecular and immune mechanisms on apoptosis in the final response of the tumor to the radiotherapy.

Another aspect of the current debate on this subject is the identification of the most appropriate dosing regimen for these patients. In an observational study of palliative radiation therapy, Overgaard et al[37] demonstrated the greater efficacy of high dose hypofractionated regimens (doses above 4 Gy administered in a smaller number of sessions), reporting complete response in 59% of patients as compared to in 33% with conventional regimens.[37] These studies included a high percentage of patients with cutaneous metastasis, including some with in-transit and/or satellite metastases. In the only randomized prospective study (RTOG 83-05) that compared a hypofractionated regimen (8 Gy in 4 fractions) with a conventional regimen (2.5 Gy in 20 fractions), the authors reported similar results for complete response rates (24% as compared to 23%), local control, and toxicity.[38] Thus, it is currently not possible to establish definitive recommendations concerning the best radiation therapy regimen in patients with locally advanced disease.

Nonrandomized and retrospective studies of the usefulness of adjuvant radiation therapy following surgical resection in patients with LAM have reported favorable results, with local recurrence occurring in only 4% to 11%

of high-risk cases.[39] The risk factors for further relapse and in-transit metastasis are rapidly developing in-transit metastases, Breslow depth of primary tumor >3-4 mm, microscopic or macroscopic persistence after surgery, and massive lymph node involvement. While, once again, there are no randomized prospective studies, the scant available scientific evidence does suggest that postoperative radiation therapy is a therapeutic modality worth considering with the aim of reducing local recurrence in specific cases of melanoma with adverse prognostic factors.

Chemotherapy and Other Systemic Treatments

Chemotherapy is a treatment option only used in patients with distant metastasis (stage IV in the 2002 AJCC staging system). In general, the efficacy of systemic treatment of metastatic melanoma (stage IV) is thought to be poor, with response rates of between 15% and 45%.[40,41] However, subgroups of patients with better response rates have been identified. These include patients with metastases affecting the skin and soft tissues, lymph node metastases, and patients with normal levels of lactate dehydrogenase.[42] A high proportion of patients with LAM meet these criteria.

Systemic chemotherapy may be indicated for the treatment of locoregional disease that has proved resistant to or not suitable for other therapies, However, it should be remembered that no specific studies have been carried out on the efficacy of systemic chemotherapy and/or biochemotherapy in patients with locally advanced disease. The results discussed below come from studies of patients with metastatic melanoma (M1), some of whom also had in-transit and/or satellite metastases.

Dacarbazine is the standard chemotherapeutic agent of choice in single-drug regimens. Although chemotherapy with dacarbazine has been shown to achieve the highest response rates, no associated survival benefit has been observed in patients with metastatic melanoma.[41,42] Temozolomide, an orally administered prodrug that shares an active metabolite with dacarbazine, achieved response and survival rates similar to dacarbazine in a randomized study of patients with metastatic melanoma.[43] Other drugs with activity in metastatic melanoma, such as fotemustine, paclitaxel, and carmustine, have likewise failed to achieve better results than dacarbazine.[42] With respect to polychemotherapy, the classic Dartmouth regimen (dacarbazine, cisplatin, carmustine, and tamoxifen), for many years considered the standard, has not demonstrated therapeutic benefits over monotherapy with dacarbazine in randomized studies.[44]

While regimens combining chemotherapy, immunotherapy, and biochemotherapy have demonstrated significant improvements in response rates and delayed recurrence, none of them have demonstrated improved overall survival rates in patients with systemic disease in randomized studies. The biochemotherapy regimen most often used, because of its lower toxicity, is concomitant administration of cisplatin-vinbastine-dacarbazine in association with interleukin 2 or interferon-α.[45] Randomized trials have failed to demonstrate any statistically significant differences in favor of biochemotherapy over conventional polychemotherapy.[46-48]

Conclusions

LAM is a clinical stage chiefly defined by the presence of in-transit or satellite metastases. It is characterized not only by a poor prognosis but also by clearly compromised functional capacity and quality of life.

After reviewing the currently available treatments for this clinical stage (Figure 7), we concluded that conventional surgical resection of the metastases—surgical metastasectomy—remains the first-line treatment option. In cases of unresectable disease localized in the limbs, ILP is the therapeutic intervention with the best response rate even when used to treat postperfusion relapses. If ILP is contraindicated or not available or the patient repeatedly refuses to undergo the procedure, radiation therapy, chemotherapy, and biochemotherapy should be considered. All these options can be combined with the intralesional and perilesional local treatments described (Figure 7). Owing to the complexity of the management of LAM, it is likely that a patient will be treated with several of the available therapies at different times during the course of the disease.

The treatment of patients with LAM should be based on up-to-date information about the different therapeutic options available and decisions should be made on a case-by-case basis taking into consideration the availability of each of these techniques and the experience of the health care team in charge of the treatment.

Conflict of Interest
The authors declare no conflicts of interest.

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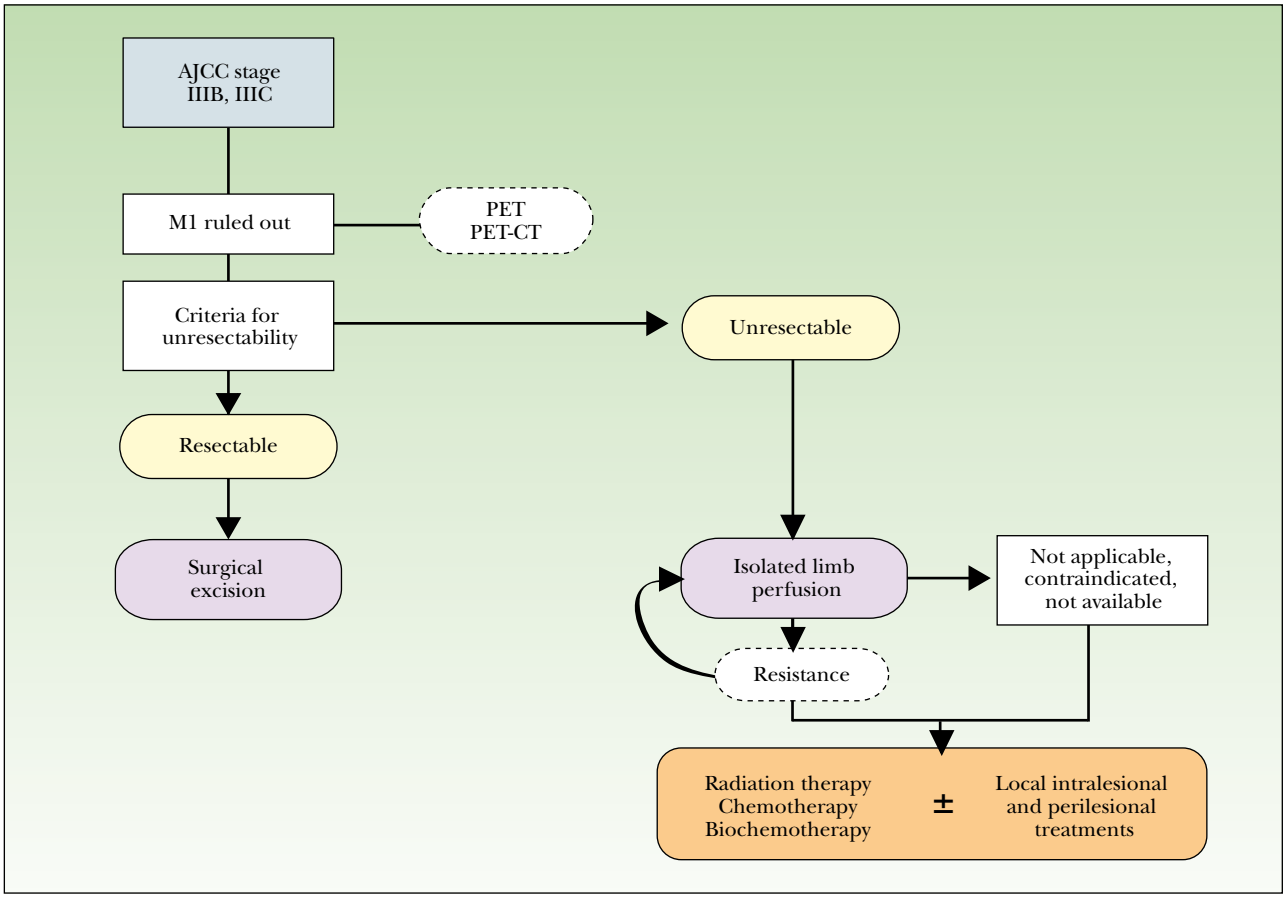

Figure 7. Proposed algorithm for the management of locally advanced melanoma. AJCC indicates American Joint Committee on Cancer; IIIB, in-transit and/or satellite metastasis without lymph node involvement; IIIC, in-transit and/or satellite metastasis with lymph node involvement; M1, TNM corresponding to the presence of distant metastasis; PET, positron emission tomography; PET-CT positron emission tomography combined with computed tomography images.

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