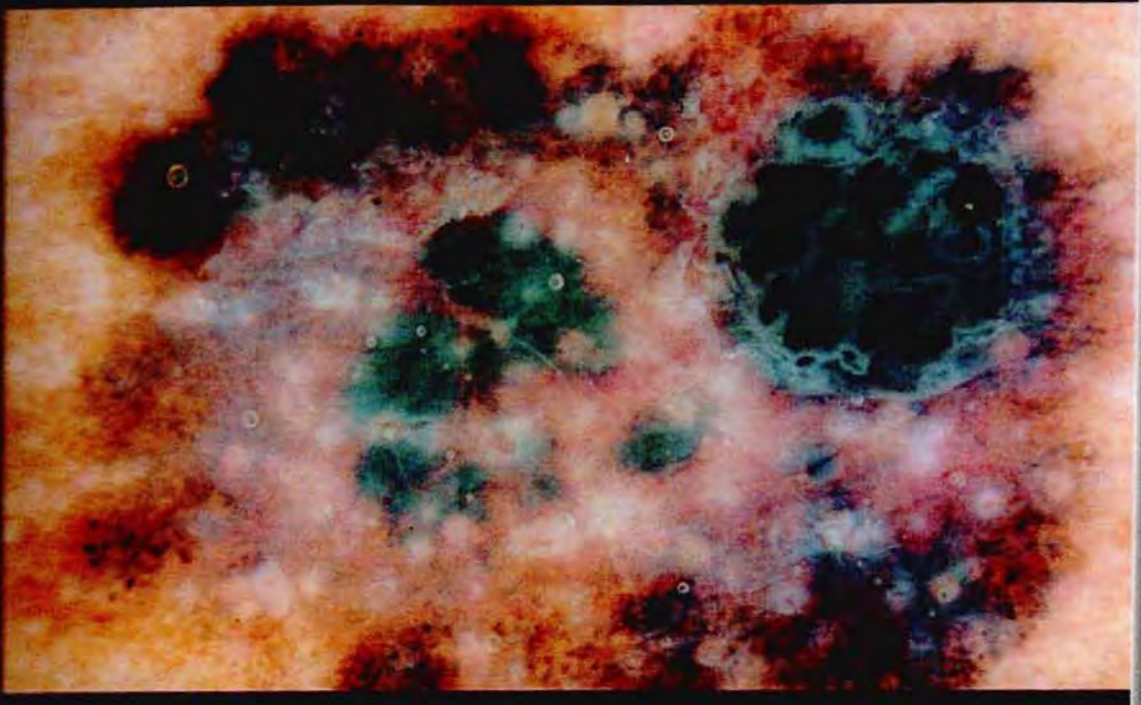
CUTANEOUS MELANOMA

A POCKET GUIDE FOR DIAGNOSIS AND MANAGEMENT



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SUBCHAPTER

5.2

Treatment of Stage III Melanoma

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Cutaneous melanoma at stage III expresses a locoregional spread of disease that may be characterized by lymph node metastases and/or in-transit metastases (IT-mets).

1 TREATMENT OF LYMPH NODE METASTASES

1.1 Lymph Node Metastases

- Metastases to regional lymph nodes represent the most important prognostic factor in melanoma patients and generally occur in 20% of cases [1,2]

- Sentinel node biopsy (SNB) allows to early identify patients with occult disease who may benefit from an immediate lymph node dissection, in order to improve disease-free survival (DFS) and melanoma-specific survival (MSS) [3–11].
  The gold standard of treatment for a node-positive disease is the complete dissection of the lymph node basin involved. It is defined as follows:
  - Completion lymph node dissection (CLND): When it is performed after a positive SNB, in order to complete the removal of the remaining non–sentinel nodes (SNs)
  - Therapeutic lymph node dissection (TLND): When it is performed after a clinical or radiological detection of metastatic nodes, confirmed after a histological examination
- However, numerous controversial issues on this topic do exist:
  The management of melanoma nodal metastases, detected after a positive SNB, with a CLND is still debated (benefits vs. the side effects).
  Findings supporting a routine CLND are as follows:
  Some investigations did not identify relevant subpopulations of patients having a low risk of further metastatic non-SNs [12,13].
  Histological analysis of non-SNs is typically less accurate as compared to that of SNs, so that the detection of metastatic cells in non-SNs could be underestimated; this may impact on patient outcome, since the detection of metastatic non-SNs is associated with an unfavorable prognosis [14].
  The Multicenter Selective Lymphadenectomy Trial (MSLT-I) indicated that SN-positive patients in the SNB arm who underwent early CLND had less morbidity than patients in the observation arm who underwent delayed TLND at the time of nodal recurrence [15]. Moreover, SN-positive patients who underwent early CLND had higher survival rates than those with delayed TLND at the time of metastatic nodal recurrence, particularly for primary melanoma of intermediate thickness [11,16].
  The most important side effects deriving from a CLND (including edema, lymphorrhea, etc.) are associated with the superficial inguinal–crural dissection rather than the deep iliac–obturatory dissection. In addition, this procedure shows a higher morbidity when delayed until a clinical or radiological evidence of disease nodal relapse occurs. The increased morbidity recorded for a delayed CLND suggests to adopt this procedure in cases of positive SNB rather than in those of macroscopic nodal disease.

Findings not supporting a routine CLND are as follows:
Not all patients with positive SNs develop clinical regional recurrence; in some cases the metastatic deposit in the SN represents the initial expression of the spread of disease, while in others the SNB may have removed the only metastatic focus. Thus, routine CLND in all SN-positive cases could lead to overtreatment for a subgroup of patients, while another subset will achieve a real benefit.
Results showing that CLND could improve survival as compared to a clinic and radiological observation after the detection of positive SNs are lacking; the hypothesis that the clinical nodal observation associated with a regular ultrasonography could be an acceptable procedure for patients with positive SNs is currently under prospective investigation in the randomized MSLT-II [17], but answering this question will require many years of follow-up.
A recent study found no benefit of complete lymph node dissection compared with that of observation in patients with melanoma and micrometastases in the sentinel lymph node. Therefore, complete lymphadenectomy should not be recommended in patients with melanoma with micrometastasis, at least in those with single cells or micrometastases of 1 mm diameter or less.

The optimal extent of the groin lymph node dissection for melanoma patients with positive SNB is another debated issue.
No agreement exists with regard to the surgical removal of pelvic (iliac–obturatory) lymph nodes.
Given the reported morbidity, including wound infection, seroma, flap necrosis, and lymph edema up to 80%, some surgeons consider the benefit–risk ratio unfavorable for patients, and thus limit the completion lymphadenectomy to the inguinal–crural nodal basin.
Conversely, other surgeons consider the incidence of pelvic lymph node metastases a relevant risk, sufficient to perform the pelvic completion lymphadenectomy, too. Such an aggressive approach may also be driven by the low benefits deriving from the approved codified adjuvant treatments, particularly from the use of interferon (IFN)-alpha [18].
In addition, a multicentric study showed that pelvic lymph nodes are frequently positive after an iliac–obturatory dissection.
Since the pelvic lymph node metastases were associated with a worse prognosis, pelvic lymph nodes should always be considered [19].

Another key question open to discussion concerns the prognostic value of metastatic deposit in SN.

The SN tumor burden is considered a significant prognostic factor for patient survival [20] [5-year overall survival (OS) rate of 100% in patients with single cell metastatic involvement of the SN, and 5-year distant metastasis-free survival of 91%, in line with the rates found in the SN-negative patient group].

Submicrometastasis (<0.1 mm) involvement of SN or isolated cluster of melanoma cells (>10) could biologically be considered differently from larger micrometastatic disease, and patients who showed this micrometastatic involvement in their regional nodes could be spared the morbidity of a CLND without compromising their survival chances.

Subsequent analyses [21–23] investigated different prognostic factors, particularly among cases with nodal metastatic deposit <0.1 mm, and showed that, when it was located in the subcapsular area, patients may be overtreated by a CLND, since their survival rates were similar to those of SN-negative patients.

- Up to date, the joint ASCO–SSO guidelines recommend as standard of care a CLND for all patients with positive SN [24,25].

1.2 Surgical Approach to Regional Lymph Node Basins

The cervical, axillar, and inguinal–iliac regional nodal basins are those generally involved by metastatic disease and candidate to surgery. Less frequently, the epitrochlear and popliteal basins are interested by metastatic spread.

1.2.1 Cervical Lymph Node Dissection (Fig. 5.2.1)

- The cervical node basin receives metastatic cells from primary head, neck, and upper trunk cancers.
- The surgical approach to patients with positive lymph nodes in this region is generally a modified neck dissection that includes the II, III, IV, and V levels, preserving the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle.
- A concomitant superficial parotidectomy is usually performed in case of primary melanomas on the frontal scalp or temporal regions with a lymphatic spread to the parotid.
- The importance of the number of removed nodes in this kind of dissection has to be underlined; a cervical lymph node dissection including 4 or more levels should remove at least 20 lymph nodes [19].
- A radical neck dissection must be performed in case of evidence of

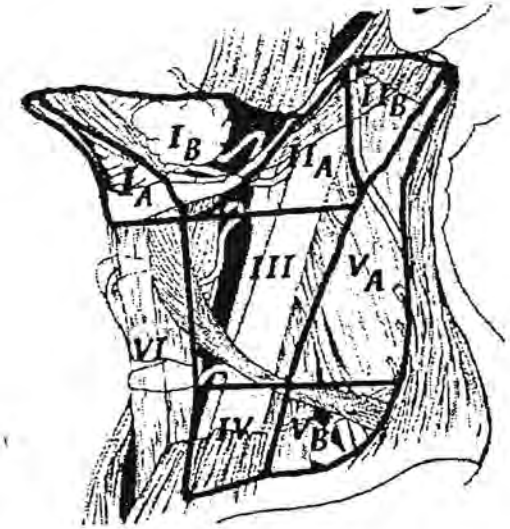
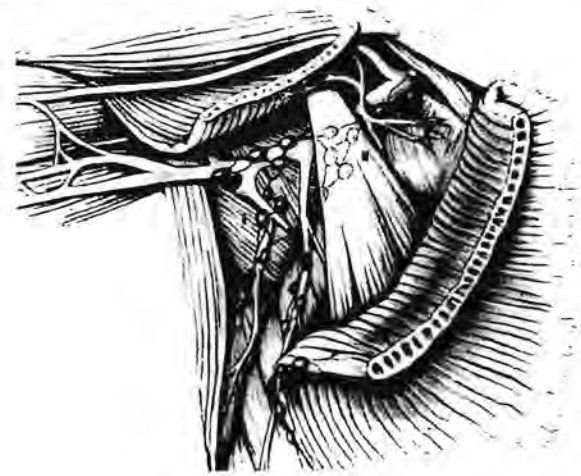


FIGURE 5.2.1 **Neck dissection.**

1.2.2 Axillary Lymph Node Dissection (Fig. 5.2.2)

- A complete axillary lymphadenectomy must include the removal of I, II, and III nodal levels in association with the minor pectoralis muscle.
- Also for this area the optimal number of excised lymph nodes is at least 20 [19].
- The evidence that only 18%–20% of these patients have further metastatic nodes at the CLND opened a discussion on the dissection of the axillary level III nodes.



- However, to date the standard recommendations remain a complete dissection including the axillary III nodal levels.

1.2.3 Inguinal–Crural (Superficial) and Iliac–Obturatory (Deep) Lymph Node Dissection (Fig. 5.2.3)

- Patients with inguinal nodal metastatic disease should undergo either superficial (inguinal–crural) dissection or deep (iliac–obturatory) dissection.
- This procedure must include the removal of the Cloquet node that is localized within the pelvis posteriorly and medially to the external iliac vein. The femoral nerve, running along the medial portion of the sartorius muscle, should be preserved while the saphenous vein is ligated at the level of the saphenofemoral junction and the femoral artery and vein are skeletonized.
- Iliac-obturatory lymph node dissection via a lateral abdominal extraperitoneal approach. The ureter is identified and preserved, while the epigastric vessels are ligated and the external iliac vessels are visualized and skeletonized up to the bifurcation of the common iliac vessels. The obturator nerve is identified and preserved and

FIGURE 5.2.3 Groin iliac–obturatory dissection.

finally the sartorius muscle is disengaged and rotated to cover and protect the femoral vessel.

- In this kind of dissection, the optimal number of removed lymph nodes could range between 15 and 25 [19].
- However, some surgeons perform only a superficial dissection in patients for whom there is an evidence of an inguinal microscopic nodal disease (SN-positive), although this procedure is not recommended due to the frequent detection of further positive pelvic nodes after the iliac–obturatory dissection [19].

1.2.4 Lymph Node Dissection of Minor Basins

- The presence of metastatic nodal disease can be detected after a SNB or a clinical/radiological exam also in minor nodal basins, such as the popliteal and epitrochlear ones.
- In similar cases, the therapeutic indication consists in the removal of all the lymph nodes lying in those areas.

2 ADJUVANT THERAPY

Metastases to the regional lymph nodes are the most common first clinical manifestation of disease spread after the excision of the primary tumor or for unknown primary melanoma [26]. Systemic adjuvant therapy has been investigated over the past decades in stage III melanoma patients with high risk of relapse, due to the poor effectiveness of surgical treatment alone.

2.1 Interferon

- To date, IFN is the only approved agent for an adjuvant therapy of stage III melanoma in patients who had already undergone surgery and with high risk of recurrence.
- In particular, IFN alfa-2b was approved in Europe and the United States, the pegylated (Peg) form of IFN alfa-2b in the United States and Switzerland, and the IFN alfa-2a in Europe. The mechanism of action of IFN in melanoma appears to be mainly immunomodulatory, although it also has an antiproliferative activity [27–29].
- Many dose regimens have been tested over the years and metaanalyses of phase III trials demonstrated that IFN has a consistent effect on recurrence-free survival (RFS) and DFS, but none or very low effect on OS [30–35]. These findings suggest that only a few subsets of patients are sensitive to IFN.
- These trials stratified patients by SN staging and by the presence or absence of ulceration in the primary tumor.

Both stage and ulceration emerged as prognostic factors; in fact, patients with nodal micrometastases and nonulcerated primary tumors had a better prognosis than those with clinically detected node metastases and ulceration in the primary lesion [1,2].

There is no definitive evidence regarding the optimal dose and duration of therapy with this agent. The overall clinical evidence should be shared with melanoma patients with an intermediate–high risk of relapse after surgery and a discussion on the advantages and disadvantages of different regimens, including potential side effects, should support the decision of using IFN as an adjuvant agent.

2.2 The MAGE Protein Family

- Several immunotherapy strategies have recently shown that immune manipulation can mediate regression of malignancies. The discovery of tumor antigens and of T lymphocytes directed against them has provided the basis for antigen-specific immunotherapy [36].
- In the past decade, several vaccination strategies have been designed for different treatments.
- The MAGE-A3 gene is expressed during embryogenesis and in a great variety of tumors [37]. It is presented to specific T cells by HLA molecules at the cell surface as a tumor-specific antigen [38], while it is not expressed in normal adult tissues, except testis and placenta [39]. Thus, this represented a selective target for tumor-specific active immunotherapy.
- Pilot studies [40,41] showed that immunotherapy with recombinant MAGE-A3 protein had antitumor activity in patients with metastatic melanoma, with a good tolerability.

  However, the preliminary evidence from a recent randomized trial showed that this therapeutic approach did not improve patient survival.

2.3 BRAF and NRAS Inhibitors

- The constitutive hyperactivation of the RAS/RAF/MEK/ERK pathway has been identified as the regulator of cell proliferation, invasion, and survival of melanocytic cells [42–46].
- The frequency of BRAF mutations varies between 40 and 70% in cutaneous melanoma [43,44,47], while NRAS mutations are present in 15%–30% of cutaneous melanomas [48,49].
- Many clinical trials are still testing the effectiveness and safety of these molecules in melanoma patients with intermediate/advanced disease. The first agent to be studied was vemurafenib. After the results of

clinical trials, this molecule was approved for treatment of metastatic melanoma [50]. Another BRAF inhibitor used for adjuvant treatment of stage III melanoma at high risk of recurrence is dabrafenib, approved as a single agent in the treatment of metastatic disease with BRAF V600E mutation [51–55]. The combination dabrafenib–trametinib was used as adjuvant therapy in stage III melanoma patients with BRAF V600E or K mutation. The combination of these targeted agents produced additive effects, but resistances occurred in most patients, with a short period of tumor control [56].

2.4 Anti–CTLA-4

- Longer responses in time seem to depend on immunologic control and are rarely obtained with chemotherapy or targeted therapies alone. This was first demonstrated by the effectiveness of anti–CTLA-4 molecules, resulting in the approval of ipilimumab, a monoclonal antibody against CTLA-4, for patients with advanced melanoma [57,58].
- The results of a recent randomized controlled trial evaluating the impact of adjuvant ipilimumab versus placebo in patients with advanced stage III melanoma indicated a significant impact on RFS (median RFS was 17 months in the placebo arm vs. 26 months in the treatment arm).
- As compared to targeted agents in BRAF-mutated melanomas, response rates with ipilimumab were slightly lower (i.e., −10/−15%), but had longer durability (i.e., about 1.5–2 years) in melanoma mutated and nonmutated patients [57,58]. Recent results confirmed that immunotherapy with ipilimumab is associated with 2- to 5-year survival in about 20% of previously treated patients and in over 30% of naive ones [59].
- Adverse events were quite frequent, often with grade 3–4, and were generally immune-related. Most adverse events involved the gastrointestinal, hepatic, and endocrine systems, and most of them were managed and resolved.

2.5 Anti–PD-1/PD-L1

- The programmed death (PD)-1 receptor represents another key immune receptor expressed by activated T cells [60,61].

  The efficacy of the anti–PD-1 molecules nivolumab and pembrolizumab appears better than that of ipilimumab; response rates were higher, ranging from 30% to 50%. The durability of response is similar or longer than that induced by ipilimumab, and the toxicity profile is also much more favorable [62–64].

- High expression of PD-L1 on tumor cells is associated with a worse prognosis and survival in several kinds of cancers such as renal cell, pancreatic, hepatocellular, and ovarian carcinomas [65–68]. Recent data from a phase III trial showed better results in terms of effectiveness of pembrolizumab versus that of ipilimumab. The estimated 6-month progression-free survival (PFS) rates were 47.3% for pembrolizumab administered every 2 weeks, 46.4% for pembrolizumab administered every 3 weeks, and 26.5% for ipilimumab. The corresponding 12-month survival rates were 74.1, 68.4, and 58.2% [69].

In conclusion, the prognosis for patients with melanoma has improved radically over the past few years. The therapeutic approaches in use, as well as the availability of new molecules for adjuvant treatments in patients with stage III melanoma with high risk of recurrence after surgery, are becoming even more promising.

3 TREATMENT OF IN-TRANSIT METASTASES

3.1 In-Transit Metastases

- Five to 8% of melanoma patients will develop IT-mets.
- These lesions are tumor embolic expressions within the dermal and subdermal lymphatics and can occur between the site of the primary tumor and the draining regional lymph nodal basin.
- IT-mets often anticipate the appearance of systemic disease and are associated with 5-year survival rates of 69 and 52%, respectively, depending on the concomitant absence or presence of lymph node metastases [1].
- Various treatment options exist according to the presentation and can range from a single or a few lesions to several and/or bulky lesions (surgical resection of a limited disease is the curative approach, but treatment can be more difficult when the interval between new lesions is short, when numerous and bulky metastases are present and multiple treatment modalities have already been performed without results).

The currently available techniques to treat regional IT-mets include:

1. Isolated limb perfusion and isolated limb infusion (Fig. 5.2.4):
   When melanoma IT-mets are confined to the extremities, the isolation of the affected limb from the systemic circulation represents an opportunity for such a therapeutic approach. Isolation can be achieved by surgical access to the artery and vein on iliac, femoral, popliteal, axillary, or brachial level. The artery and vein are clamped and cannulated after which the catheters can be connected to a heart–lung machine to get an oxygenated circuit. To further isolate the limb, a tourniquet is placed proximal to the site of perfusion.

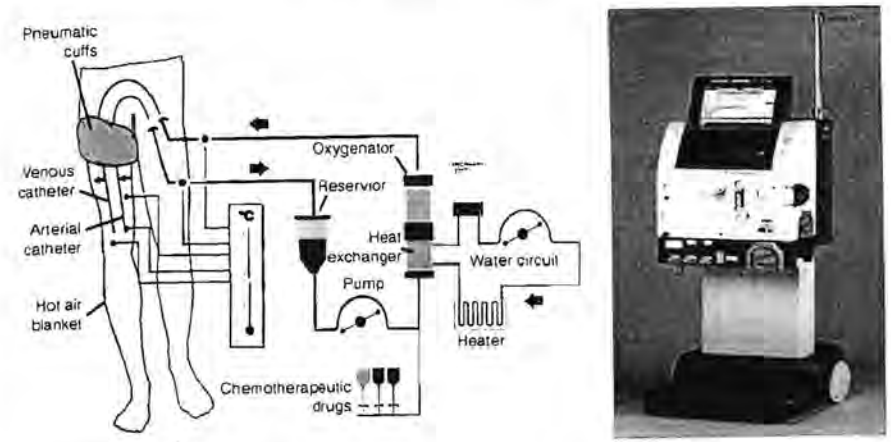


FIGURE 5.2.4 **Regional perfusion.**

3.2 Isolated Limb Perfusion

- It achieves a 20-fold concentration of chemotherapeutic drugs when compared with systemic therapy [70–72].
- Melphalan (L-phenylalanine mustard) has been the standard drug used in ILP because of its efficacy and toxicity profile [73].
- Standard dosages: 10 mg/L for lower limbs and 13 mg/L for upper limbs.
- The major risk related to ILP is the potential leakage of the effective agents to the systemic circulation; therefore a careful leakage monitoring is mandatory.
- Since the introduction of ILP, some variables, such as temperature, drugs, and procedure indications have been analyzed to improve tumor response.
- The temperature of the skin has to be warmed during perfusion to prevent vasoconstriction in the dermal and epidermal tissues: especially in superficial IT-mets, application of a warm water mattress can improve local drug delivery (the uptake of the drug by IT-mets in vivo is twice as high at 39.5°C than at 37°C [74], and hyperthermia improves the uptake in tumor cells, especially at temperatures greater than 41°C [75,76]). However, tissue temperatures of 41.5–43°C during ILP can yield high response rates [77], but the local toxicity of these

procedures can lead to severe complications [78]. *Mild hyperthermia for ILP is employed as a safer compromise between effectiveness of response and risk of high toxicity.*

Tumor necrosis factor-alpha (TNF-α) was introduced in association with melphalan to improve the action of ILP [79]. TNF has a dual mechanism of action: the direct cytotoxic effect on high-dose TNF to tumor cells [80] and the effect that induces a hemorrhagic necrosis on tumor cells [81]. While the systemic employment of this cytokine must be carefully managed because of its important side effects [82], *in the ILP the advantage of the TNF antitumor activity, in the absence of systemic effects, is increased in hyperthermic conditions with the addition of alkylating agents* [83–85] (the dose of TNF of 1 mg for the arm and 2 mg for the leg is as effective as the higher doses) [86–89].

3.3 Isolated Limb Infusion

It was described by Thompson et al. as a simplified alternative to ILP [90]. Percutaneous arterial and venous catheters are placed in the affected extremity and a tourniquet is placed proximal to the catheter tips to allow isolation of the limb from the systemic circulation.

High dose of a cytotoxic combination of melphalan and actinomycin D is generally used; drugs are infused into a hyperthermic, limb via the arterial catheter and blood is withdrawn from the venous catheter to be reinfused into the arterial side. Drug circulation time is 20–30 min under mild hyperthermic conditions of 38–39°C. ILI is a quicker and safer procedure with response rates similar to those of ILP [91].

- Despite ILP and ILI achieving excellent responses in melanoma IT-mets, the aggressive biological behavior of melanoma determines frequent local recurrent disease in the limbs.
- Reported recurrence rates after perfusion are approximately 50%. Management of residual disease or of disease recurrence following ILP or ILI may include local treatment (by excision) of the remaining or recurrent lesions or ECT as an effective alternative technique to control local disease.
- ILP and ILI can be repeated in selected patients, with results comparable to those obtained using the same techniques at first approach [92,93].
- In consideration of the likelihood of extraregional spread of metastatic cells, patients with IT-mets from melanoma have generally a poor prognosis.
- The duration of survival after these locoregional events seems to be related to the effectiveness of the responses achieved by ILP or ILI; a complete response after these treatments was associated with a [illegible] survival of 52 and 44 months, respectively [94,95].

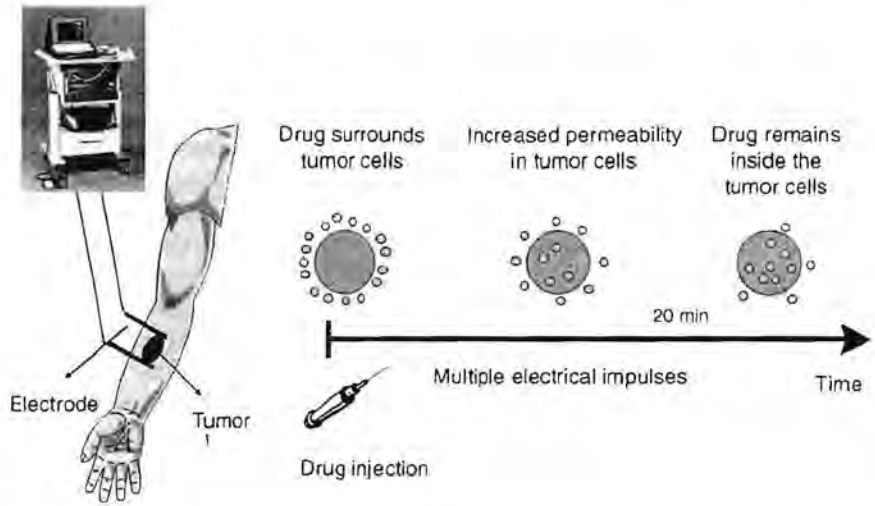


FIGURE 5.2.5 Electrochemotherapy (ECT).

- Consequently, a therapeutic approach with these techniques may be considered for subgroups of patients associated with a more favorable tumor biological behavior.

3.4 Electrochemotherapy (Fig. 5.2.5)

- It is an effective therapeutic option for treating melanoma cutaneous and subcutaneous metastases to achieve local tumor control and to preserve the patient's quality of life [96–108].
- The chemotherapeutic agent currently employed is bleomycin (15,000 units/m^2 i.v. in a bolus followed, within 8 min after intravenous injection, by the application of brief electric pulses to each tumor nodule).
- The main eligibility criteria are as follows:
  - Melanoma stage IIIB–C or IV (M1a) [1]
  - Lesions generally not deeper than 3 cm
  - No anticancer treatment 4 weeks before or 8 weeks after ECT treatment
  - Age ≥18 years
  - Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- The main exclusion criteria include:
  - Allergy to bleomycin
  - Severe concomitant disease
  - Life expectancy less than 3 months

Active infections
Cardiac pacemaker

- Electric current is delivered by means of a 2- to 3-cm long needle electrode, according to lesion size. The electrodes are connected to a pulse generator that produces high voltages (up to 1000 V), but delivered as a compressed train of eight pulses at the frequency of 5000 Hz and 100 μs duration, and are well tolerated by patients.
- ECT could be repeated every 8–12 weeks according to local response, the appearance of new lesions, and patients' compliance to treatment.
- ECT induces a reduction in blood flow within the treated area for up to 24 h, thus leading to tumor hypoxia that causes tumor cell destruction [109,110].
- ECT-induced tumor necrosis stimulates the release of tumor antigens, leading to a local inflammatory and immune reaction [111].

ECT represents an effective treatment option for intermediate–advanced stage melanoma patients with cutaneous and subcutaneous metastatic lesions.

3.5 Locoregional Treatments and Systemic Targeted Therapies

- Patients submitted to radical lymph node dissection, to ILP, ILI, or ECT, despite the excellent locoregional results, still have low survival rates. Moreover, these treatments are often associated with relevant side effects.
- In those cases where (poor) prognosis is generally determined by the disease biology, their employment is debated.
- The perspectives have significantly changed after the introduction of BRAF/NRAS/MEK inhibitors, anticytotoxic T-lymphocyte–associated (CTLA) protein-4 antibodies, and PD-1 pathway inhibitors.
- Most patients for whom these new molecules are employed have a stage IV disease, but an increasing number of trials are focusing on patients with unresectable stage III disease; in similar cases, the combination of two different drug delivery methods (systemic and isolated circuit) may represent a logical approach.

In conclusion, patients with extensive unresectable IT-mets, associated with an unfavorable survival, should be considered for an integrated therapeutic approach including ILP, ILI, or ECT plus targeted systemic agents.

3.6 Medical Therapy

- In stage III disease, in cases with many IT-mets or satellite metastases, or in cases of relapse notwithstanding repeated surgery, and when the latter is no longer feasible, there is the need for innovative treatment

options that may prevent or retard progression from stage III to stage IV (where recently approved systemic treatment options may be adequately employed).

- Intratumoral application of drugs is an appealing therapeutic concept, as high concentrations can be achieved within the tumor with lower systemic toxicity.
- Several cytokines have been used for intratumoral therapy with varying results [112–115].

IL-2 intratumoral treatment led to high rate of complete responses and, furthermore, showed an unexpectedly high 5-year OS rate of 61% for stage IIIB/C patients and 38% for stage IV patients [116,117].
Used as an intratumoral agent, TNF-α showed local antitumor activity [118].

- L19IL2 and L19TNF are clinical-stage immunocytokines, recombinant human fusion proteins comprising the cytokines IL-2 or TNF, fused to the monoclonal L19 antibody.
- The L19 antibody is a fully human antibody, capable of preferential localization around tumor blood vessels while sparing normal tissues [119,120]. L19, derived from a phage display library of human antibody fragments in the single-chain Fv (scFv) format, recognizes the alternatively spliced extra domain B (EDB) of fibronectin (FN), one of the best characterized markers of angiogenesis [119,121–124].
- L19IL2 is a recombinant fusion protein composed of two portions: L19 and IL-2.

L19IL2 has been already studied in advanced solid tumors (renal cell carcinoma [125] and pancreatic cancer).
Two studies aimed at assessing the antitumoral activity of systemic L19IL2 administration in combination with DTIC in patients with advanced metastatic melanoma have been carried out, as well as two other clinical trials aimed at assessing the intratumoral effect of L19IL2 either alone or in combination with L19TNF-α in patients suffering from stage III/IV M1a melanoma. These studies confirmed that L19IL2 can be safely and regularly administered to patients with metastatic melanoma.
The intralesional treatment of melanoma metastases with L19IL2 (up to 10 MioIU/week for 4 consecutive weeks) in stage III patients resulted in objective responses in about 50% of the lesions [126].
The treatment was generally well tolerated. Toxicities were usually mild, of short duration, and limited to inflammatory injection site reaction (local swelling and erythema) in most of treated patients.

- L19TNF is a recombinant fusion protein composed of two portions: L19 and TNF-α.
  This product has been studied in two different clinical trials:
  A phase I/II monotherapy study in patients with advanced solid tumors. The main conclusion from this study was that L19TNF can be administered to patients with advanced progressive solid tumors in an outpatient setting up to doses of 13 μg/kg. The observed toxicity profile was mild and reversible [127].
  A phase I trial in combination with melphalan in the ILP setting for the treatment of patients with metastatic melanoma lesions of the leg, who were candidates for amputation. Five patients were treated with 325 μg and 10 patients with 650 μg of L19TNF. The observed side effects of the L19TNF ILP procedure mainly consisted of reversible and manageable toxicities. Objective responses were observed in the majority of lesions (including some complete responses) while disease progressed outside the perfused limb, as expected. Some examples are shown in Fig. 5.2.4. According to the results of this study, L19TNF can be administered in combination with melphalan and mild hyperthermia, at a dose of 650 μg, in patients with inoperable melanoma lesions of one leg [128].
- Recently, phase III trials have been designed to demonstrate the efficacy of intratumoral administration of L19IL2 + L19TNF followed by surgery in patients suffering from stage IIIB and IIIC metastatic melanoma, as compared to that of surgery alone, in improving RFS.
  Weekly intratumoral administration of a mixture of 10 MioIU L19IL2 in combination with 312 μg of L19TNF for 4 consecutive weeks into injectable cutaneous/subcutaneous metastases is well tolerated, with few and generally mild recorded adverse events, and is associated with a high proportion of objective responses. Taken together, the benefits of intratumorally administered L19IL2 + L19TNF followed by surgery in terms of local tumor control and improvement of relapse-free survival and OS far outweigh the potential risks that are associated with such a treatment.

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SUBCHAPTER

5.3

The Treatment of Stage IV Metastatic Melanoma

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1 PATIENT CHARACTERISTICS, DISEASE EVALUATION, AND TREATMENT OPTIONS

There are some parameters that may correctly drive our evaluation on the best treatment for the patient we are dealing with (Table 5.3.1).

- Clinical scenario examples:
  If low tumor burden (e.g., one or two localized mets), low progression pattern, and good PS:
  - Local therapies (surgery)