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Review

Management of Cutaneous Melanoma M0: State of the Art and Trends

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This article reviews the epidemiology, diagnosis and treatment of cutaneous melanoma, including the most recent developments. The combination of positive family history, fair complexion, number of nevi, exposure to sun and/or chromosomal alterations seem to be implicated in the pathogenesis of cutaneous melanoma. Melanomas can be classified according to their growth patterns, and tumour microstaging is of straightforward predictive value for survival and risk of metastasis, although new factors are also being investigated. As yet, surgical excision is the only effective treatment available for primary tumours, resection margins varying according to tumour thickness. Elective node dissection is, however, no longer advocated for melanomas thinner than 1.5 mm, and there is disagreement as to its role for thicker lesions. In contrast, selective node dissection at the time of definitive surgery is becoming more widely accepted, with regional node dissection being restricted to positive cases. Therapeutic dissection is required for lymph node involvement, the most common pattern of recurrence from melanoma, which affects nearly 30% of all patients. Complete remission rates from isolated limb perfusion, which has been employed in patients with multiple recurrences or in-transit metastases, range from 40 to 90%, depending on drugs and techniques used in different series; the best responses so far have been obtained with tumour necrosis factor in combination with melphalan. Patients with thick lesions (> 4 mm) or lymph node metastases have a high risk of micrometastases that would warrant adjuvant therapy. The only agent found to affect survival is interferon alpha-2.

Key words: review, melanoma, cutaneous melanoma, epidemiology, diagnosis, treatment
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INTRODUCTION

THROUGHOUT THE world, cutaneous melanoma is increasing in Caucasians more rapidly than other solid tumours. Moreover, it is expected that by the year 2000 one in 90 people will be at risk of developing a melanoma [1]. From a biological viewpoint, patterns of genetic predisposition are emerging. A clear association has been found between melanoma and ultraviolet exposure, and there is convincing evidence of its interaction with host immunological response. These observations have prompted scientists to stress the importance of its early diagnosis and to propose new therapeutical approaches. Genetic predisposition is now under investigation at a molecular level, since specific chromosomal mutations occur in patients with a family history of melanoma [2–8]. Educational programmes have been designed to modify sun exposure habits, particularly in children [9]. The apparently good results of early diagnosis campaigns, which publicise the clinical features of melanoma, should, however, be confirmed by large international trials, although to date, the overall impression is that these campaigns may lead to presentation of thinner melanomas [10].

Together with the widely accepted prognostic factors for survival (Breslow's thickness and Clark's level), new parameters indicating tumour aggressiveness or lack of host immunological reaction warrant further studies to confirm their predictive value [11–13]. New investigational approaches for the clinical examination of patients include the search for subclinical metastatic melanoma in apparently negative lymph nodes using both imaging techniques (ultrasound and PET scanning) and surgical procedures ('sentinel' node biopsy) [14]. Further therapeutical advances are expected

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from clinical trials on elective node dissection, isolation limb perfusion with new drugs, and the use of interferon alpha and vaccination as adjuvant therapy.

Melanoma, however, is still considered quite a rare tumour, and patients are not always given appropriate treatment for it. Guidelines for the management of cutaneous melanoma are, therefore, still needed in order to make surgeons and other physicians more aware of the diagnostic and therapeutical problems involved, and encourage them to cooperate in the accrual of patients for ongoing studies.

In this article, we have reviewed the literature and compared original data from our 20-years experience with cutaneous melanoma with that reported by other authors throughout the world.

EPIDEMIOLOGY AND AETIOLOGY

Cutaneous melanoma appears closely related to ethnic factors, its incidence ranging from 0.2 per 10^5 per year, in Asian and Oriental peoples, to 40 per 10^5 per year in Queensland, Australia, and seems primarily to occur in white-collar, well-educated, urban workers, equally affecting men and women, although the latter reportedly have a better survival rate. Its site is gender-linked, most melanomas developing on the trunk in men and the extremities in women [15–18]. Birth cohort studies carried out in several countries show that mortality trends for cutaneous melanoma have stabilised in younger adults (< 50 years), despite a continuous increase in incidence, probably due to improvements in early detection [15, 19–21]. Risks and protective factors probably play a major role in determining the genetic alterations that seem to be involved in its aetiology.

Family history

5–10% of melanoma patients report at least one relative with melanoma, and this observation has been corroborated by the discovery of the familial dyplastic naevus syndrome [22–24]. Moreover, having had one primary melanoma is a clear risk factor (3–5%) for developing a second and subsequent primary melanoma, risk being much higher than that in the general population. Among patients with familial melanoma, the risk of developing multiple primaries is extremely high, especially if they have multiple atypical naevi [25].

Complexion

The typical melanoma patient is of fair complexion, and tends to burn rather than tan, even after brief exposure to the sun. The risk of developing cutaneous melanoma in redheads is almost 3-fold that in the general population, whilst in blonds it is 60% higher, and in subjects with darker hair with a fair complexion it is 2-fold higher. Increased risk of melanoma is therefore definitely associated with fair or red hair, blue eyes and light and/or sunburn-prone skin [15].

Naevi

Large case–control studies have shown that the most important risk factor for developing melanoma is the number of melanocytic naevi [22, 25–27]. A 3-fold increased risk was found in patients with more than 20 naevi [16].

Sunlight exposure

Migration studies suggest that the risk of melanoma is related to sun exposure at the place of residence in early life [28]. However, the relationship between intermittent sun exposure (recreational) and melanoma is controversial and latitude dependent, while chronic sun exposure (occupational) appears to reduce the risk of melanoma [15, 27, 29, 30]. Moreover, the regular use of sunscreen lotions seems to play no protective role against melanoma, probably because they delay or avoid sunburns, enhancing the exposure time to unfiltered radiation [31]. In fact, UVB exposure seems to play an important role as both an initiator and promoter of melanoma, inducing c-jun and c-fos transcription and an immunosuppressive effect [32–35]. Sunlamps and sunbeds are associated with a moderately increased risk of melanoma [15, 28, 36], and no protective effect seems to be attributable to artificial tanning.

Occupational factors

Nearly 35% of all melanomas, most affecting non-Caucasians, may not be due to overexposure to sun, the increased risk being related to working in the electronic, petrochemical, printing and rubber industries [37].

Protective factors

There are signs that serum alpha-tocopherol, beta-carotene and, recently, subcutaneous tissue arachidonic fatty acid levels, have protective effects [38].

Genetic implications

Traditionally, three chromosomes have been classically involved in the search for melanoma genes: short arms of chromosomes 1 and 9, and the long arm of chromosome 6. In 1989 it was shown that a gene on chromosome 1 was linked to hereditary melanoma [2], whilst chromosome 9 seems to play an important and potentially initiating role in familial melanomas, due to *p21* tumour suppressor gene alteration [3–5]. In fact, a proposed multistep model conceives the deactivation of 9p21 as the initial aetiological event from normal melanocytes to precancerous moles. From there on, mutations on chromosomes 1 and 6 should boost tumour progression and metastases. Moreover, linkage analysis kindred studies on multiple cutaneous melanoma have shown the presence of a locus for familial melanoma in the 9p13–p21 region [3], a locus that also seems to be involved in sporadic tumours. One of the target proteins in this process seems to be p16, a cyclin-kinase inhibitor [6–8], that in normal conditions inhibits phosphorylation of Rb and delays G1-S transition, giving rise to abnormal cell proliferation.

DIAGNOSIS

Clinical features

Cutaneous melanomas, which may be located anywhere on the skin, are variegated, have an irregular raised surface, an irregular border with indentations and ulceration of the surface epithelium [39–42]. They also typically change in size, configuration and/or colour. In early lesions (diameter ≤ 5 mm, flat or slightly raised), the clinical diagnosis can be significantly improved by epiluminescence microscopy, a non-invasive *in vivo* technique [43–45]. Melanomas can be classified according to their growth patterns, which are superficial spread, nodular, acral lentiginous and lentigo maligna [39, 46, 47].

Histological features

Primary cutaneous melanoma may develop in a biphasic or monophasic growth pattern [45, 48–51]. The former is

characterised by a radial growth phase, in which melanocytes proliferate in the epidermis [46, 48, 50, 52] and a subsequent neoplastic infiltration of the dermis and subcutaneous tissue, designated as vertical growth phase [49, 50, 53]. Monophasic malignant melanoma, which presents a pure vertical growth phase, is also known as nodular melanoma [46, 48–50]. It, nevertheless, may be the result of direct tumour progression from the radial growth phase [49, 54].

Histopathological criteria for the diagnosis of melanoma are architectural and cytological atypia. Asymmetry of the general architecture, poorly defined margins, loss of naevic growth pattern, upward spread of melanocytes, lack of maturation in the dermal component and atypical cell populations are the most important abnormalities suggesting melanoma [55]. The histological classification of cutaneous melanoma is reported in Table 1. Markers of melanocytes can be used to confirm the histological diagnosis; S-100 protein [56–58] and HMB-45 [59, 60] can be detected in paraffin-embedded specimens by specific antibodies [55]. S-100 is expressed by more than 90% of melanomas, but also by several other tumours and normal tissues; HMB-45, which is more specific for melanocytic cells [59, 61], is not always detected in metastatic melanomas.

Primary tumour microstaging is an integral part of the clinical management of cutaneous melanoma. Of all the clinical and histopathological parameters studied over the past 10 years, tumour thickness, measured according to Breslow, has the greatest predictive value for survival and metastasis [62, 63]. However, other variables may significantly influence the survival of melanoma patients: the anatomic level of invasion, evaluated according to Clark [46, 64, 65], mitotic rate [66–69] and ulceration [69–71]. Variables of unproven prognostic significance are phase of tumour growth [53, 72], histogenetic type [49, 71], host response [70, 73–75], regression [53, 76, 77] and vascular invasion [71, 72].

Recently investigated new factors warrant further studies to confirm their predictive value: the most important are angiogenesis, in thin [78] and regressing [11] lesions, HLA-DQB1*0301 and PCNA (proliferating cell nuclear antigen). The HLA-DQB1*0301 allele has been linked to an increased risk of developing cutaneous melanoma. Moreover, when this allele was present in melanoma patients, overall they presented thicker lesions and were more likely to have advanced disease (stage III–IV) [12]. We found that PCNA was more effective than Breslow's thickness in predicting loco-regional and distant recurrences in patients with primary cutaneous melanoma [13]. Recently, PCR has been employed for the detection of circulating melanoma cells in the peripheral blood of melanoma patients. Though its value for this purpose is still under investigation, there appears to be a strong correlation between the incidence of positive PCR findings and the risk of metastases [79].

Table 1. *Histological classification of malignant melanoma*

Superficial spreading melanoma
Lentigo maligna
Lentigo maligna melanoma
Nodular melanoma
Melanoma with unclassified epidermal component
Acral-lentiginous melanoma
Mucosal-lentiginous melanoma
Desmoplastic melanoma
Neurotropic melanoma
Malignant blue naevus
Melanoma in congenital melanocytic naevi
Minimal deviation melanoma
Clear cell sarcoma
Malignant melanocytic schwannoma

Source: Heenan PJ, Elder DE, Sobin LH. *Histological Typing of Skin Tumors*. Berlin, Springer, 1996, 4.

STAGING

Accurate staging is the cornerstone of prognostic evaluation and therapeutical approach for melanoma patients. For this, four systems have so far been employed worldwide. The original is a three-stage system that assigns stage I for localised disease, stage II for loco-regional metastases and stage III for distant metastases. The MD Anderson system involves four stages, including local recurrence into stage II, shifting loco-regional and distant disease to stages III and IV, respectively. Neither of these include tumour thickness as a prognostic discriminant, and the vast majority of patients are assigned to stage I. The AJCC four-stage system first introduced microstaging of primary melanoma (Breslow's thickness and Clark's level) as important prognostic determinants for patients with clinically localised disease, subdividing stage I from stage II according to tumour thickness [80]. The TNM system [81] also classifies the tumour according to its thickness and level of invasion, presence of nodal or 'in-transit' metastases and distant metastases (Table 2). With this system, patients are stratified within homogeneous prognostic groups.

The search for loco-regional or distant metastases is still a challenging issue in patients with cutaneous melanoma. Apart from accurate physical examination, only chest x-rays are used routinely for staging. Lymphoscintigraphy can be useful in defining the lymphatic basin for head and neck or trunk melanomas. More expensive and/or invasive exams are undertaken only if there is clinical suspicion of metastases.

Recently introduced ultrasound scanning of the axillary and inguinal lymph nodes is very useful in detecting lymph node metastases in intermediate to high risk melanoma patients. In our series of 85 patients, sensitivity ranged from 88.9 to 100%, specificity was 83.3% and diagnostic accuracy was 85.3%, with a positive predictive value of around 50% and a negative predictive value of nearly 100% [82]. These findings warrant the routine use of ultrasound for the

Table 2. *UICC–TNM classification of cutaneous melanoma*

	Breslow (mm)	Clark's level	
pT1	≤ 0.75	II	
pT2	> 0.75–1.5	III	
pT3	> 1.5–4.0	IV	
pT4	> 4.0/satellites	V	
N1	Regional ≤ 3 cm		
N2	Regional > 3 cm and/or in-transit metastases		
M0	No evidence of metastases		
M1	Distant metastases		
Stage grouping (TNM)			
I	pT1	N0	M0
	pT2		
II	pT3	N0	M0
	pT4	N0	M0
III	Any pT	N1/N2	M0
IV	Any pT	Any N	M1

pre-operative staging and follow-up of patients with cutaneous melanoma. PET seems to be a new promising approach for the detection of lymph nodes metastases [14].

TREATMENT

The only effective treatment available for patients with primary tumour and/or lymph node metastasis from skin melanoma is surgical excision, while isolated hyperthermic antiblastic limb perfusion is more effective against locally recurrent tumours (in transit metastasis). So far, among many approaches of adjuvant therapy, only the administration of high-dose interferon alpha-2 has been found to improve effectively the survival of operable high-risk patients.

Surgery

Primary tumour. The treatment of primary melanoma can be divided into three main elements: biopsy, margins of excision, and reconstruction of the defect.

Biopsy. Excision biopsy is the recommended initial treatment for melanoma when the diagnosis is doubtful and the lesion is small. Under local anaesthesia, a visual clear margin of at least 2 mm should be included, with a few millimetres of subcutaneous fat and the specimen promptly sent for standard examination on paraffin-embedded sections. Frozen sections may play a role in the evaluation of surgical margins when melanomas with poorly defined margins are excised (i.e. lentigo maligna, amelanotic, desmoplastic and mucosal melanoma) or during Mohs micrographic surgery [83, 84]. A margin of 10 mm is desirable if direct closure is easily obtainable, since this treatment may be definitive if the pathologist confirms the diagnosis of thin melanoma. Incisional or punch biopsy may be undertaken for large lesions (i.e. congenital giant naevi and large lentigo maligna) or subungual melanoma. This procedure has no adverse effect on the prognosis if it is followed by radical surgery within 4–6 weeks [85].

Margins of excision. If melanoma *in situ* is completely excised (primary biopsy reveals a free margin greater than 2 mm), no local recurrence should occur, and it should have no impact on patient's survival. However, where possible a 5 mm margin should be obtained. Thin (≤ 0.76 mm) and intermediate (0.76–1.5 mm) melanoma requires an excision with a minimum margin of 1 cm. A margin greater than 2 cm is not justified for this type of lesion. For thick melanoma (≥ 1.5 mm), re-excision of the wound with a minimum margin of 2 cm is recommended. A maximum margin of 3 cm may be justified for tumours thicker than 4 mm, since the risk of local recurrence is minimal outside this area. The excision should reach deep subcutaneous tissue but should not include the underlying fascia because excision or preservation of the fascia seems to have no effect on the prognosis and the cosmetic result is generally superior when a skin graft is used to cover the defect [86, 87]. The surgical approach to primary cutaneous melanoma is supported by a recent prospective randomised trial by the WHO Melanoma Group [88]. Another multicentric randomised study is now underway to determine whether a 1 cm margin is sufficient for thick melanomas [89]. Particular situations require particular approaches. For example, melanoma on the face must be excised with narrower margins, because surrounding structures (i.e. eyelids, nostrils and mouth) may be affected by the closure or subsequent scarring [90]; if fingers or toes are the primary site, amputation is recommended. In particular, authors have long emphasised disarticulation at the base of the finger or the toe for a subungual melanoma. Recently, more distal function-preserving amputations have been suggested for these cases [91]. Likewise, mastectomy is no longer recommended for the treatment of breast melanoma since no statistically significant differences have been shown for local control and prognosis after local skin excision [92]. Extended excisional margins (up to 3 cm) are advisable for desmoplastic and neurotropic melanomas, which are usually associated with a higher recurrence rate [16].

Reconstruction of the defect. When the margin is 1 cm or less, direct closure after an elliptic excision is possible in most cases. Larger defects may necessitate reconstruction using a free graft or a skin flap. The former may be a split-thickness skin graft, taken from the thigh or the upper arm (not the same limb if the primary is located in it) and generally used to cover the site of the excision in the extremities and the trunk; otherwise a full-thickness skin graft may be taken from behind the ear or from the supraclavicular region to obtain better aesthetic and functional results on the face or hands. Free skin grafts have been recommended, as they make it easier to check for local recurrences or metastases. The latter, which can be achieved using various techniques, usually provides cosmetically and functionally superior results and faster postoperative healing, and is cost-effective. Recent results, show that skin flaps should always be considered when a superior cosmetic result is required, and thick coverage is advantageous [93].

Special considerations

Elective node dissection. It is widely believed that elective node dissection is contra-indicated for melanomas thinner than 1.5 mm, unless a regular follow-up cannot be guaranteed. The clinical approach for patients with intermediate thickness melanoma (1.5–4 mm) is even more problematic. Some authors continue to advocate elective lymph node dissection, at least for subgroups of patients (melanomas of the extremities in men, head and neck or trunk tumours in both sexes) with an estimated risk of microscopic metastases for distant sites that is lower than the risk of metastases to regional lymph nodes [16]. However, controlled prospective clinical trials have not yet demonstrated that elective node dissection has a statistically significant effect on survival [94, 95], although these studies were criticised for an important methodological bias, mainly due to unknown stratification criteria at the time when the studies were performed [96]. New prospective multicentric trials have been undertaken by international groups (WHO Melanoma Programme for trunk melanomas thicker than 1.5 mm, and National Cancer Institute Intergroup Melanoma Commitee for intermediate-thick cutaneous melanomas of the whole body), which should definitively clarify the role of elective node dissection in melanoma care.

Selective lymphadenectomy. As an alternative to elective node dissection in intermediate–high risk melanoma patients, a new procedure has been proposed [97]: the lymphatic route(s) draining the area of the melanoma is/are detected by lymphoscintigraphy and marked on the skin on the basis of the scintigram. Then, at definitive surgery, an intradermal injection (0.5–1 cm^3) of blue dye (patent blue V or isosulphan) is made around the primary site (or the biopsy scar) and the first sentinel node(s) to stain blue is/are excised and sent to the pathologist for frozen section to detect any

micrometastasis. If the findings are positive, a standard curative dissection is performed; if negative the biopsy wound is closed without further surgery and a strict follow-up is planned. Studies completed so far and our experience with 31 thick melanomas show that this technique is very reliable (Table 3) [98, 99]. As this allows the identification of early lymph node involvement, it might improve benefit from adjuvant therapy. However, the value of lymph node dissection based on the finding of a positive sentinel node has yet to be demonstrated. Controlled clinical trials conducted by the WHO Melanoma Programme and a number of large American centres are now in progress to investigate this point.

Local recurrence and in-transit metastasis. From a biological standpoint, local recurrences and in-transit metastases from melanoma are indistinguishable. Anatomically they present as a single or multiple nodules either within the epidermis, the dermis, subcutaneous tissue or in combination, and are generally the result of development of melanoma cells being trapped in the lymphatics. The definition of both clinical situations is conventional since disease within 2–5 cm of the scar from a melanoma previously excised (often inadequately) is considered local recurrence, and recurrent nodules beyond this limit and the regional node basin are considered in-transit metastasis. Currently, the incidence of local recurrence and in-transit metastases from cutaneous melanoma are very low, at 3.2% and 2%, respectively [16, 100]. Surgery can play a role in their management, excision with a wide margin being appropriate for a single isolated loco-regional recurrence, especially if the primary has favourable prognostic features with a consequently low risk of further multiple recurrence. Patients with multiple recurrent nodules are good candidates for isolated limb perfusion or radiotherapy [101]. Recently, multiple laser beam excisions have also been advocated for extensive disease [102]. Palliative surgery (even amputation) may prevent or relieve symptoms in patients with large recurrent nodules in cases in which the above therapeutic options are ineffective. Whatever the therapy undertaken, patients with local and/or regional melanoma recurrence have a poor prognosis: most of them will develop distant metastasis, and their 10-year survival is around 20% [100, 103]. They should, therefore, be considered eligible for experimental adjuvant treatments and referred to experienced centres.

Lymph node metastasis. Almost one-third of patients with cutaneous melanoma develop lymph node metastasis during their life-time [104], this being the most common recurrence pattern after primary surgery [105]. A clinical suspicion of lymph node metastasis should be confirmed by fine-needle aspiration cytology, if available, or open biopsy. Excision of metastatic nodes (therapeutic dissection), the only effective treatment for cure or local disease control, differs according to each major lymph node basin being treated.

Cervical. For patients with limited metastasis, most surgeons prefer modified to radical neck dissection without sacrificing the sternomastoid muscle, the spinal accessory nerve and the jugular vein if these structures are not directly involved by tumour, with undoubtedly better cosmetic and functional results. Turkula and Woods state that as long as it is complete, this procedure does not appear to affect recurrence adversely [106]. It must, however, be borne in mind that as melanomas in the frontotemporal region of the scalp, forehead and periorbital areas can metastasise to the lymph nodes within the parotid gland, dissection should include superficial parotidectomy. Radical neck dissection is recommended when massive nodal metastasis is clinically evident.

Axillary. This dissection must include all three levels up to the apex of the axilla. As the supra-axillary fat pad can harbour metastatic disease, it should be removed in continuity with all tissue overlying the inferior surface of the axillary vein, whereas thoracodorsal and long thoracic nerves should be spared unless the tumour directly invades them. It is often helpful to strip down the insertion of the pectoralis minor muscle for adequate exposure of the third-level nodes to ensure complete resection of the most medial and apical lymph nodes.

Inguinal. With superficial groin dissection, all tissue within the femoral triangle overlying the vessels should be removed *en bloc* together with the node bearing tissue superior to the inguinal ligament but superficial to the external oblique muscle aponeurosis. When the inguinal nodes are involved, a deep pelvic dissection of the iliac and obturator nodes is associated as a standard procedure, since 25–50% metastasize [107, 108].

It has not yet been established whether or not a lymph node dissection should be performed in continuity with resection of a primary melanoma, especially where distal limb melanomas are concerned. The 'in continuity' procedure seems to prevent in-transit metastasis (incidence of 2% versus 14%) and severe lymphoedema [109, 110], while whether it results in any increase in survival is controversial [111, 112].

Seroma, pain and skin slough are the most frequent short-term complications (7–27%) from lymph node dissection irrespective of the site of metastasis, while the most common long-term complications are pain and functional deficit (6–7%) after neck dissections, functional deficit (9%) after axillary node dissection and leg oedema (26%) after groin dissections [113].

The reported local recurrence rate after therapeutic lymph node dissection, which is around 20%, seems to be influenced by the number of positive nodes, being 14% in patients with 1–3 nodes and 53% in those with more than four nodes involved [114, 115]. The efficacy of adjuvant radiotherapy in preventing local recurrence after therapeutic node dissection has not yet been well established, although a few studies have

Table 3. 'Sentinel node' biopsy in stage I melanoma patients

Author	Ref	No. of patients	No. of anatomical sites explored	Identified sentinel node (%)	Positive sentinel node (%)	Positive non-sentinel node (%)
Morton	[97]	223	237	82	20	1
Reintgen	[98]	42	—	100	19	0
Thompson	[99]	118	135	87	21	1.9
Rossi	*	31	33	94	29	6

*Unpublished data.

Table 4. Results of regional perfusion with traditional cytostatics in stage IIIA, IIIAB melanoma patients

Authors (year)	Ref	No. of pts	Cytostatics	5-year survival (%) IIIA	IIIAB	Loc. rec. rate (%)
Krementz (1985)	[126]	182	L-PAM	35	31	
Shiu (1986)	[127]	18	Nit. Must.	50	38	
Stehlin (1988)	[128]	117	L-PAM	70	36	
Hoekstra (1989)	[129]	110	L-PAM	67	40	38
Krementz (1994)	[130]	1139	L-PAM, Nit. Must.	35	23	
Cavaliere (1994)	[131]	327	L-PAM, DTIC, IFN, Cis-Pt, Ara-C	54–46	21–33	49–36
Fletcher (1994)	[132]	21	Cis-Pt	47		36
Rossi	†	49	Cis-Pt, L-PAM	41		38

*Median follow-up = 28 months. †Unpublished data.
Cis-Pt, Cisplatin; Nit. Must, nitrogen mustard; L-PAM, Melphalan; DTIC, dacarbazine; IFN, interferon; Ara-C, cytosine arabinoside.

shown a significant improvement in local control in patients who received irradiation, without evidence of increased morbidity [16]

Currently, survival at 5 and 10 years in these patients is 50 and 30%, respectively [116, 117]. Multivariate analysis identified gender, thickness and ulceration of the primary tumour, the number and types of nodes positive at histology, the length of time to nodal recurrence, and relapse in the same lymph node group following dissection, as prognostic factors with an independent influence on the time to survival [114, 118–123].

Isolated limb perfusion

Isolated limb perfusion was set up 25 years ago by Creech and Krementz with the rationale of delivering high drug doses to an area affected by an advanced tumour while minimising systemic toxicity [124]. Later, it was suggested that the temperature of the perfusate should be raised, since Cavaliere and associates demonstrated that cancer cells show selective heat sensitivity [125]. Thus far, perfusion has been administered to melanoma patients as palliation or cure for in-transit metastasis and as adjuvant treatment for patients with a high risk of melanomas of the limbs.

The value of perfusion has not yet been clearly demonstrated. Regimens have varied, different drugs (melphalan, nitrogen mustard, imidazole carboxamide, actinomycin-D, cisplatin, cytarabine, thiotepa, tumour necrosis factor), dosages, temperature and duration being used. Moreover, various surgical procedures have been performed in association with perfusion, and the staging system currently generally used (MD Anderson) is not detailed enough to allow any comparison of results. Tables 4 and 5 show the results of some important studies with curative perfusion in patients with metastatic in-transit melanoma of the limbs [126–137]. Complete remission rates range from 40 to 90%. The efficacy of Melphalan perfusion alone seems to be influenced by the number of lesions, tumour temperature ($\geq 41.5°C$), type of schedule (single versus multiple), the absence of regional node involvement and leg versus other tumour sites [138, 139]. The impact of perfusion on patient survival is linked to the percentage of patients with disease confined only to the perfused limb. According to the review by Jaques and associates, which considers long-term results after major amputation for advanced melanoma of the extremity, approximately one-third of all patients achieving a durable complete remission following perfusion should be cured [140]. Long-lasting complete response rate is the only significant endpoint for perfusion with curative intent. However, as yet no study is available on patients with measurable disease with a follow-up long enough to allow any reliable conclusion regarding the long-term complete response rate following perfusion. Klaase and associates reported an overall 3-year limb recurrence-free interval of 38%, and the prognostic factors found to be associated with this interval were one as opposed to more than one lesion, complete remission and female gender. In the same report, the 3-year survival rate after complete remission was 60% [138]. Amputation and death due to perfusion are rare, occurring in 1–2% and 0.5% of cases, respectively [141]. More frequently, lymphoedema (28%) and muscular atrophy or fibrosis (11%)

Table 5. Results of isolation perfusion with TNF and L-PAM in IIIA, IIIAB melanoma patients

Authors (year)	Ref	No. of pts	TNF dosage	Response (%) CR	PR	Relapse (%) Regional	Systemic	Survival (%)	Median follow-up (months)
Lienard (1994)	[133]	53	3–4 mg + IFN-gamma	90	10	39.6	45.2	NED 56 DOD 44	28
Vaglini (1994)	[134]	12	2–4 mg + IFN-gamma	58		50	42	NED 40 LWD 35	10
Vaglini (1994)	[134]	10	0.5–1.5 mg	70	30	20		NED75 LWD 25	3
Hill (1993)	[135]	4	0.125–0.5 mg	100	30		1	NED 75 DOD 25	20
Fraker (1996)	[136]	36	4–6 mg + IFN-gamma	76–36	16–64	52.6–25		NED 44 DOD 6	12
Di Filippo (1996)	[137]	15	1–2.4 mg	67	33	20	13	NED 86 DOD 14	12

NED, alive with no evidence of disease; DOD, dead of disease; LWD, alive with disease.

cause long-term limb morbidity [142]. Recently, an increasing systemic toxicity (pulmonary, renal and liver) has been observed due to a high percentage of leakage of tumour necrosis factor-alpha during perfusion [133]. Although it may have severe systemic effects, isolated perfusion with tumour necrosis factor and melphalan in association with interferon is, at present, the most promising therapeutical approach under exploration. Studies are underway to establish the optimal drug dosage, the role of interferon and melphalan within the association and, finally, to ascertain whether this approach improves the overall response rate and, if so, whether this means it improves overall disease-free survival.

In their update of their study on limb perfusion with TNF, melphalan and rIFN-gamma, Lienard and associates recently found that rIFN-gamma only affected subcutaneous metastases [143]. Advances in experimental work with new drugs, biological response modifiers and carriers may result in a wider and more effective application of isolated perfusion.

Regarding the use of adjuvant perfusion in patients with high-risk melanoma without in-transit metastasis, the EORTC–WHO randomised trial has completed patient accrual; so far, its findings appear to rule out any survival advantage in the perfusion group [144].

Adjuvant systemic therapy

As the estimate risk of micrometastases in patients with pT4 (> 4 mm) melanoma or lymph node metastasis is 70–80%, there is an evident need for an effective adjuvant systemic therapy [16]. Numerous chemotherapeutic, biological and hormonal agents have been suggested to improve the prognosis of these patients.

Chemotherapy. Although no significant advantage has been observed in the overall survival rate of arms treated with adjuvant systemic conventional chemotherapy, given alone or in combination with non-specific immunotherapy, entry criteria in these studies were widely heterogeneous and different staging systems have been used as well as non-optimal chemotherapeutic agents, thus precluding any definitive conclusion [145]. Unfortunately, randomised studies have failed to demonstrate a statistically significant benefit from high-dose chemotherapy followed by autologous bone marrow transplantation [146]. Based on recent studies, reporting that platinum-based regimens are beneficial in patients with metastasis, new adjuvant large prospective trials with chemotherapy, sometimes combined with immunological or hormonal agents, are under investigation in Europe and the U.S.A.

Interferon. Adjuvant applications of interferon alpha-2 or gamma in high-risk melanoma patients have been tested since 1984, and now six large randomised trials are either underway or have been completed. A significant prolongation of relapse-free survival and overall survival has recently been reported by Kirkwood and associates at a median follow-up of 6.9 years (37% for patients receiving a high-dose regimen of interferon alpha-2 versus 26% for the group observed in ECOG trial E1684) [147]. Low-dose regimens have been tested by ECOG (trial E1690) and the WHO Melanoma Programme (trial 16) for two and three years, respectively. Although both studies demonstrated some favourable impact on the survival in subgroups of patients, an interim analysis of the WHO studies has shown no effect on stage III melanoma patients [148]. Recently, a randomised trial on interferon-gamma conducted by SWOG was closed because of possible adverse effects in the arm treated with interferon [149].

Vaccines and levamisole. As yet, no survival benefit has been demonstrated in randomised trials in vaccinated patients, although various approaches to melanoma vaccination have been used [150–153]. A survival advantage has been demonstrated only for subgroups of patients who develop a specific immunological reaction [153]. After adjuvant administration of a new partially purified vaccine, surgically resected stage III (AJCC) melanoma patients have an overall survival 50% longer than comparable historical controls [154]. A randomised trial is underway to verify these results. Only one out of five randomised trials conducted in high-risk melanoma patients with adjuvant levamisole, combined with or without BCG or chemotherapy, has demonstrated a significant improvement in survival after surgery [155–161].

A new boost for immunotherapy came from the discovery of highly specific tumour antigens, and the possibility of generating cytolytic T-lymphocytes (CTL) against them. These discoveries are promising because they may enable the formulation of highly specific vaccines and a highly specific autologous CTL [162, 163].

Other modalities. Pooled data from two separate multicentric randomised studies have shown a significant improvement in the survival rate of patients treated with adjuvant *Corynebacterium parvum* when compared with those treated postoperatively with BCG [164]. Likewise, the postoperative administration of megestrol acetate appears to provide a survival advantage for patients with respect to the control arm [165].

CONCLUSIONS

Although the incidence of cutaneous melanoma is increasing rapidly in Western countries, it is still considered a rare tumour, and for patients with suspected disease, effective means for diagnosis are often not used. Nor are patients with a diagnosis necessarily given appropriate treatment. Moreover, therapeutic options are seldom used in clinical trials with a view to solving many clinical problems related to the management of cutaneous melanoma.

Diagnostic delays often occur despite improvements in early detection, due to educational campaigns and new diagnostic procedures (e.g. epiluminescence microscopy). The patient's clinical examination is seldom cost-effective, highly sophisticated examinations often being performed without there being a clinical suspicion of metastases. Other techniques, such as lymphoscintigraphy and ultrasound scanning, are employed less often, although they have low costs and are useful for staging and follow-up. In some cases, surgical treatment is inadequate (too narrow excision of the primary or incomplete lymph node dissection) or excessive (unnecessary excision of the underlying fascia or elective lymphadenectomy), and many surgeons are unaware of new techniques such as sentinel node biopsy. Moreover, patients with in-transit metastasis of the extremities are not always considered for isolated limb perfusion, and therefore accrual of patients is insufficient for clinical trials in search of effective adjuvant systemic therapy.

Considerable advances could be made in the management of cutaneous melanoma through the dissemination of guidelines for the diagnosis and treatment of melanoma, and through setting-up referral centres within pre-established

geographic areas, where special methods of treatment should be provided and clinical research undertaken.

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