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Malignant melanoma

Filippo de Braud [a,*], David Khayat [b], Bin B.R. Kroon [c], Riccardo Valdagni [d], Paolo Bruzzi [e], Natale Cascinelli [f]

[a] *START Project, European Institute of Oncology, Milan, Italy*
[b] *Hopital Pitié-Salpetrière, Paris, France*
[c] *The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[d] *Clinica S. Pio X, Milan, Italy*
[e] *Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy*
[f] *Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy*

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* Corresponding author. Tel.: +39-02-23903352; fax: +39-02-23903353.
E-mail address: start@cancerworld.org (F. de Braud).

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Abstract

In the European Community cutaneous melanoma accounts for 1 and 1.8% of cancers occurring in men and women, respectively. The incidence rate is increasing faster than that of any other tumour. Sun exposure, patient's phenotype, family history, and history of a previous melanoma are the major risk factors. The change over a period of months is the main sign of a skin lesion turned into a melanoma. The ABCDE scheme for early detection of melanoma is commonly accepted. A new staging classification will be published in the next AJCC/UICC Cancer Staging System Manual in 2002. The clinical course of melanoma is determined by its dissemination and depends on thickness, ulceration, localisation, gender and histology of the primary tumour. Tumour stage at diagnosis remains the major prognostic factor. Surgery is the standard treatment option for operable local–regional disease. Sentinel node biopsy represents a promising experimental approach in the clinical detection and early treatment of occult lymph node involvement. For metastatic inoperable patients systemic chemotherapy can be attempted, while radiation therapy has to be considered as palliative treatment. No studies concerning frequency of follow-up are currently available, but common procedures may be performed.

Keywords: Cutaneous melanoma; Genetics; Clinical detection; Mortality rate

1. General information

1.1. Incidence

1.1.1. General data

The incidence of cutaneous melanoma in the European Community (EC) is 1 and 1.8% of tumours occurring in men and women respectively. Overall there are 17 000 new diagnoses and 5000 deaths from melanoma in the EC every year. The incidence of melanoma continues to rise faster than that of any other malignancy: it increased 15-fold in the last 50 years—a rate of increase of approximately 3–7% per year. In Western Europe approximately 80 per 1 million inhabitants are affected annually. There is a slight female preponderance (54%) [1].

1.1.2. Age and race

The average age of a person with melanoma is 45 years, relatively young for a cancer patient. Melanoma is extremely rare prior to puberty; thereafter the incidence increases with age until the 5th decade.

In non-whites melanoma is rare and mostly confined to unpigmented sites such as subungual regions, the palms of the hand or soles of the feet. However, the mortality rate in non-white patients is higher.

1.2. Aetiological and risk factors

Sun exposure, the patient's phenotype, family history, genetics and history of a previous melanoma are factors associated with a higher probability of developing melanoma.

1.2.1. Familial melanoma

Familial melanoma is seen in about 5–10% of cases. There is evidence that it is genetically heterogeneous, since loci for familial melanoma susceptibility have been identified on the chromosome arms 1p and 9p by means of homozygous deletion studies. The genetic abnormalities involve tumour suppressor genes encoding for cyclin-dependent kinase inhibitors, as well promoters (Section 2.1.2).

1.2.2. Precursors

- Xeroderma pigmentosum
- Lentigo maligna (melanosis precancerosa of Dubreuilh)

Giant congenital nevus (>19 cm) is reported to be associated with an increased risk of melanoma up to 4.9–6% for a person of 60 years old, however it is uncertain if it can be considered as a direct precursor.

1.2.3. Risk factors

- Alterations in an existing nevus
- Adult age (older than 15 years)
- White race
- Prior melanoma
- Family history positive for melanoma
- Immuno-suppression
- Fair complexion, freckles and red or blond hair
- History of excessive sunburn (e.g. 'tanning' holidays, solarium use)
- Nevus with architectural disorder (formerly: dysplastic nevus–cell nevus)
- Large number of (non-dysplastic) nevi.

Table 1
ABCDE signs

A	Lesion asymmetry
B	Border irregularity
C	Colour variegation
D	Diameter > 6 mm
E	Enlargement

Individuals with many 'dysplastic' (and non-dysplastic) nevi (3 more than 5 mm or 50 more than 2 mm) and with family history of melanoma are at higher risk of developing a melanoma, which may not necessarily arise in the dysplastic lesion but can also occur on normal skin.

1.2.4. Sun and ultraviolet exposure

The risk of melanoma correlates more with intense sun exposure and sunburn than with the total lifetime sun exposure [2,3].

Animal studies and population-based studies point to ultraviolet B-radiation emitted by the sun as a major exogenous causative factor [4–6]. Evidence also exists that melanoma patients are greater users of artificial ultraviolet sources than the general population [7]. The correlation between ultraviolet B-radiation and melanoma incidence, however, is not straight forward, since melanoma does not show a preference for skin parts exposed to sunlight unlike other cutaneous malignancies. A multistep model of carcinogenesis, in which other factors also play a role, is likely [8,9]. By contrast with the long-held belief, increased use of sunscreens does not protect against the development of melanoma, but may actually increase the risk of acquiring the disease. A case-controlled study of 856 patients showed that sunscreen use increased the risk by 50–130% [10].

1.3. Screening and case finding

1.3.1. What is meant by prevention?

Melanoma represents an important public health problem in terms of morbidity and mortality. Efforts therefore, should be undertaken aiming at both primary prevention (risk reduction) and secondary prevention (early detection, which is critical to improve the clinical outcome of this disease).

1.3.2. Primary prevention

Ongoing public education is the major tool in achieving primary prevention of melanoma. It is recommended on a type R basis that public education especially targets individuals at increased risk (Section 1.2.2). These individuals should be taught to be alert to the warning signs of melanoma (ABCDE signs, Table 1), and should be strongly encouraged to reduce exposure to (intermittent) ultraviolet B-radiation, including sunlamps and sunbeds.

1.3.3. Secondary prevention (early detection)

Although secondary prevention (early detection) in the form of screening [11] seems attractive in this easily recognisable and—at least in the early stages—simply treatable disease, randomized trials of screening versus no screening are lacking. Recently a population-based case-controlled study [12] of 1199 Caucasians resident in the US has shown that skin self-examination was associated with a reduced incidence of melanoma and may reduce the risk of advanced disease. A report of mass screening of the general population from the American Academy of Dermatologist revealed that most of the melanomas detected were localised, with median thickness of 0.3 mm, and that nearly half of the patients with a detected melanoma would not have seen a physician spontaneously [13]. Nevertheless the evidence of an advantage for surveillance and screening programmes is stronger in high-risk populations, where a number of studies have confirmed that primary melanomas were diagnosed at a stage where they were smaller and thinner [14].

So screening is suitable for individual clinical use on a type R basis and it is recommended on a type C basis [14] for individuals at higher risk. High-risk individuals should be identified and encouraged to perform skin self-examination as a screening and preventive measure.

1.4. Referral

1.4.1. Specialised institutions

Referral of melanoma patients to specialised institutions is generally not recommended. However, for patients who meet the eligibility criteria for prospective trials as defined by the following conditions, this option should be discussed:

a) Operable primary melanoma studies on excision margins or sentinel node biopsy.
b) Individuals at high-risk of primary melanoma and patients with lymph node metastases when an adjuvant treatment has to be considered.
c) Patients with distant spread: who may be suitable for studies to elucidate the role of chemotherapeutic agents and/or biological response modifiers.

Referral to specialised centres has to be recommended for patients who, after resection of the primary lesion, need sentinel node biopsy, have to undergo lymphnode dissection of the neck or groin, or need operations that require special expertise. The same applies to the procedure of isolated regional perfusion of the limbs. In the palliative setting referral has to be considered in cases where radiotherapy has to be given or when resection of metastases from sites such as lung or brain has to be performed.

1.5. Recent reviews and books

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2. Pathology and biology

2.1. Biological data

Melanomas are malignant tumours deriving from the transformation and proliferation of melanocytes which normally reside in the basal cell layer of the epidermis. Primary cutaneous melanoma can arise on a precursor lesion (i.e. lentigo maligna, dysplastic nevus and congenital nevus) or directly on normal skin [15].

Melanoma cells are characterised by relative growth autonomy in culture. So an autocrine mechanism of growth stimulation has been suggested, which functions through the secretion of endogenous peptide growth factors such as basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF), TGF-b or interleukin-1 (IL-1) [16].

2.1.1. Tumour growth

Tumour growth can be biphasic or monophasic [15]. The biphasic pattern consists of a horizontal or radial initial growth phase (intra-epidermal) followed by a subsequent vertical growth phase corresponding to the infiltration of the dermis and hypodermis. Those melanomas having such biphasic growth pattern are the so-called superficial spreading melanoma (SSM) and the lentigo maligna melanoma (LMM). Very often, acral lentiginous melanoma also has such a biphasic growth pattern. The monophasic growth pattern of melanoma

consists of tumours having a pure vertical growth which includes mainly the so-called nodular melanoma (NM). The vertical growth phase can include the desmoplastic variant and minimal-deviation variant.

2.1.2. Genetic abnormalities

There is evidence that familial melanoma is genetically heterogeneous [17], and loci for familial melanoma susceptibility have been identified on the chromosome arms 1p and 9p by means of studies for homozygous deletions. Multiple genetic events have been related to the pathogenesis of melanoma [18].

Indeed there are families of proteins inhibiting CDK: $p16^{INK4a}$ and its homologues and the families of CIP and KIP proteins.

While the linkage with a gene on chromosome 9 is clear, the role of chromosome 1 is still uncertain. Certain 9p21 markers are deleted in more than half of the melanoma lines studied. The gene named multiple tumour suppressor 1 (CDKN2A/MTS1) encoding $p16^{INK4a}$—a low-molecular weight protein of 148 residues and a previously identified inhibitor of cyclin-dependent protein kinases (CDKs)—has been localised to the p21 region of human chromosome 9 and found to be within the critical deleted region.

It consists of 3 coding exons: exon 1 containing 125 bp, exon 2 containing 307 bp and exon 3 just 12 bp. Homozygous deletions of the 9p21 region were found in 56% of melanoma tumour lines tested (84 melanoma cell lines were studied). The $p16^{INK4a}$ locus overlaps an alternating reading frame (ARF) of p14 and familial mutation of the entire cistronic unit $p16^{INK4a}/p14^{ARF}$ has been reported.

It was shown that there are three genes homologous to $p16^{INK4a}$: p15 ^{INK4b}(CDKN2B/MTS2) on 9p21; $p18^{INK4c}$ on 1p32; $p19^{INK4d}$ on 19p13. Based on DNA sequence and deletion analysis, a minimum of 75% of melanoma lines contained mutant MTS1 or had lost the gene from both homologues. Mutations of the $p16^{INK4a}$ coding region and adjoining splice junction sequences were identified in 33/36 melanoma cases in 9 families, whereas 2 were detected in normal controls and are not disease-related. Analysis of these mutations showed that 92% of melanoma cases, 30% of dysplastic nevus cases, and 15% of unaffected individuals carried one of the mutations. Of the 48 individuals identified as carrying a p16 mutation only 15 (31%) did not have melanoma. The nonsense mutation (Arg50Ter), splice donor site mutation (IVS2+1 [G–T]), and 3 of the melanoma-specific missense mutations (Val118Asp, Gly93Trp, and Arg79Pro) are highly correlated with melanoma in these families, and were not found in control analyses. With some exceptions, the distribution of disease-specific mutations in several families is consistent with p16 being a familial melanoma gene in 9p21 [19,20].

2.2. Precancerous lesions

Despite the still present controversy regarding the nature of the lesions potentially associated with melanoma, their identification is very important in order to understand the biology of this disease and to identify individuals at risk [21].

2.2.1. Lentigo maligna

Lentigo maligna is the precursor lesion of LMM (Section 2.3.3). Pleiomorphic melanocytes are spread along the dermo-epidermal junction. The epidermis is often atrophic as such lesions usually occur in elderly people or sun-damaged skin.

2.2.2. Dysplastic nevus

One of their most characteristic features of dysplastic nevus is the presence of lentiginous melanocytic hyperplasia, with cytologic atypia of the nevomelanocytes. These cells, lying along the dermo-epidermal junction, are very often surrounded by collagenous changes, lymphocytic infiltrates and prominent vascularity.

Individuals with many 'dysplastic' (and non-dysplastic) nevi may be at higher risk of developing a melanoma, which does not necessarily arise in the dysplastic lesion but can also appear on normal skin. The incidence of melanoma in a dysplastic nevus is 1:3000 per year. So dysplastic nevi should not be considered as precursors of melanoma, but they are markers that allow identification of individuals at increased risk for melanoma.

2.2.3. Congenital nevus

Congenital nevus can be clinically diagnosed just by size because virtually all nevi greater than 2–3 cm are congenital. Smaller congenital nevi are reliably diagnosed by their history. Nevertheless there are some histological findings that suggest a congenital origin, such as the presence of nevus cells in a single cell array in the lower reticular dermis and subcutaneous fat or in nests in sebaceous glands, hair follicles, eccrine ducts and hair papillae. The estimated risk of melanoma associated with lesions smaller than 10 cm is still controversial.

2.3. Histological types

Melanomas are conveniently categorised by growth pattern. Four major types can be distinguished: SSM (65%), NM (25%), LMM (5%) and acral lentiginous melanoma (5%). SSM, LMM, acral lentiginous melanoma are classified as radial 'growth phase patterns' and NM as 'pure vertical growth phase melanoma'. Other variants of vertical growth phase of melanoma are desmoplastic melanoma and minimal-deviation melanoma [21].

2.3.1. ICD-O classification

The following histotypes are considered 'typical' melanomas. The ICD-O (International Classification of Diseases for Oncology) morphology code is provided in brackets [22].

[M-8720/3]	NOS
[M-8744/3]	acral lentiginous, malignant
[M-8730/3]	amelanotic
[M-8722/3]	balloon cell
[M-8745/3]	desmoplastic, malignant
[M-8771/3]	epithelioid cell
[M-8770/3]	epithelioid and spindle cell, mixed
[M-8720/2]	in situ
[M-8770/0]	juvenile
[M-8742/3]	lentigo maligna
[M-8720/3]	malignant, NOS
[M-8761/3]	malignant, in giant pigmented nevus
[M-8742/3]	malignant, in Hutchinson's melanotic freckle
[M-8740/3]	malignant, in junctional nevus
[M-8741/3]	malignant, in precancerous melanosis
[M-8745/3]	malignant, neurotropic
[M-9044/3]	malignant, of soft parts
[M-8723/3]	malignant, regressing
[M-8721/3]	nodular
[M-8772/3]	spindle cell, NOS
[M-8773/3]	spindle cell, type A
[M-8774/3]	spindle cell, type B
[M-8743/3]	superficial spreading

2.3.2. Superficial spreading melanoma

SSM is the most frequent histological type of melanoma. It is mostly characterised by a prominent intra-epidermal proliferation, usually in single array. This initial phase of the tumour growth may last for months or years, the malignant cells invading either solely the epidermis (in situ or Clark's level I) or more frequently the superficial part of the dermis (level II). However, in the radial phase of the tumour, malignant cells in the dermis are found only as small clusters or even as single isolated tumour cells. The prognosis (Section 5.3.1) at this stage is still very good. In the latter phase of the tumour growth, malignant melanocytes start invading the deeper part of the dermis (level, III, IV and V).

2.3.3. Lentigo maligna melanoma

LMM is a much less common type of melanoma. It corresponds to a degenerated lentigo maligna. The vertical growth phase is usually composed of spindle-like cells which often invade the reticular dermis surrounded by fibrotic stroma (dermoplastic) or may form fascicles displaying neural features and infiltrate the perineural structures of the skin.

2.3.4. Acral lentiginous melanoma

Acral lentiginous melanoma occurs on the palms of the hands or soles of the feet. In these locations both SSM and NM can be found.

2.3.5. Nodular melanoma

NMs represent about one-third of the melanomas diagnosed every year in the Caucasian population. NM is a tumour which right from the initial phase, starts its progression vertically, invading the deeper layers of the skin. Usually, few or no intra-epidermal components surrounding the nodule are seen.

Polypoid melanoma is a variant of NM, histologically characterised by an accumulation of melanoma cells in a large volume above the skin surface. The increase in the tumour volume encourages dislodgement of melanoma cells that are carried to the superficial lymphatic vessels, resulting in a poor prognosis.

2.4. Accuracy and reliability of pathological diagnosis

2.4.1. The pathological report

It is recommended on a type C basis that pathological reports should include the patient's age, sex, the anatomical location of the melanoma and the size of the resected area. It is also recommended that signs of regression, if any, and mitotic rate are reported.

The pathological report of a melanoma, in order to define the patient's risk and the appropriateness of his follow-up and/or treatment, should always include: histologic type, presence of ulceration, presence of infiltrative lymphocytes, regression, microsatellite lesions, radicality (margins), microstaging (maximum vertical tumour thickness according to Breslow and level of invasion according to Clark).

2.4.2. Histopathologic examination

Histopathologic examination of a suspected melanoma should always be performed by pathologists who have specific experience in melanoma and who are trained to recognise differential diagnoses such as Spitz nevus, pigmented spindle cell nevus, dysplastic nevus, halo nevus, combined nevus, recurrent nevus and cellular blue nevus. Immuno-histochemical techniques are helpful. Other diagnoses, such as carcinomas, can be excluded by the absence of reaction to certain specific antigens (cytokeratin, vimentin, leucocyte common antigen) and the diagnosis of melanoma can be supported by the positivity of two reactions: HMB45 and S-100 protein, the former being the more specific to melanoma.

2.5. Microstaging (The Clark and Breslow microstaging)

2.5.1. The Clark microstaging

The Clark microstaging is based on the depth of infiltration of the melanoma into the skin [23]. The various levels of tumour penetration include level I, which means in situ melanoma, not infiltrating through the basal cell layer; level II, infiltration into the papillary dermis; level III, infiltration as far as, but not into the reticular dermis; level IV, infiltration into the reticular dermis; and level V, infiltration into the subcutaneous tissue.

2.5.2. The Breslow microstaging

The Breslow microstaging method measures the actual thickness of the tumour using an ocular micrometer [24]. The measuring of the Breslow thickness requires a number of precautions to be taken by the surgeon and the pathologist regarding excision, primary handling of the specimen, and excision and cutting of representative sections. Measurement of Breslow thickness is highly accurate: intra- and inter-observer variability are low. Several studies have demonstrated that tumour thickness is a more reliable prognostic parameter than Clark's microstaging.

Recently [25] ulceration has been proved as the most relevant prognostic factor for lesions thicker than 1 mm, while Clark's levels IV and V are still relevant only for lesions of less than 1 mm.

2.6. Particular histological types

2.6.1. Desmoplastic melanoma

Desmoplastic melanoma is a rare type of melanoma which may be associated with lentigo maligna and is localised to sun-exposed sites, especially the face, where 41% of cases occur. Variants of this tumour include neural-transforming melanoma and neurotropic melanoma. This tumour is notorious for its tendency to infiltrate adventitia of blood vessels and spread by perineural invasion and for its very high rates of local recurrence; approximately 50% (ranging from 25 to 82%). Therefore a careful examination of the margins of the specimens is mandatory.

2.6.2. Malignant blue nevus

Malignant blue nevus lesions arise mainly on the scalp and may be associated with a pre-existing cellular blue nevus. It is very rare, in fact only 11 well-documented cases have been reported, so metastatic melanoma should always be ruled out.

2.6.3. Mucous membranes, iris and clear cell sarcoma

Melanoma may occur in any anatomical location of the body where melanocytic cells could be present. This explains the possibility, though very rare, of developing such tumours in sites such as the mucous membranes (oral cavity, nasopharynx, anal canal, vagina and urethra), the choroid and the iris in the eye or clear cell sarcoma. These tumours raise specific problems in terms of diagnosis and treatment and they will be the focus of specific chapters.

3. Diagnosis

3.1. Signs and symptoms

The principal sign of a skin lesion proven to be a melanoma is some change over a period of months. A shorter period (days or weeks) is usually more related to inflammatory conditions. The main initially observed changes of an increase in size and colour changes occur in about 70% of patients [26]. Increase in height, itching and ulceration or bleeding usually occur in more advanced lesions [27].

When melanomas grow thicker, ulceration can occur and bleeding is an ominous sign. Itching may be a subjective complaint. Around the lesion a reddish discoloration may be seen, while in case of SSM there sometimes is an unpigmented halo.

The ABCDE concept of early recognition, introduced in the sixties, is widely disseminated and is recommended.

A lesion asymmetry
B border irregularity
C colour variegation
D diameter >6 mm
E enlargement

Through the application of the ABCDE guidelines, thinner, lower-risk melanomas can be identified.

3.1.1. Superficial spreading melanoma

SSM usually appears as a deeply pigmented area in a junctional nevus. It is generally flat at first and develops an asymmetric irregular surface as it enlarges. Patches of regression resulting in an amelanotic area are frequently seen. Later on it becomes an asymmetrically raised patch with a sculpted edge, irregularly pigmented with colours varying from paleish-blue and pink to a mottled brown–black variegation, sometimes completely black. It may be growing slowly over a number of years.

3.1.2. Nodular melanoma

NM presents as a nodule with sharply demarcated borders on the skin, often shiny with a slightly infiltrated base. The colour, generally darker and more uniform than that of SSM, may vary from black to unpigmented. These lesions are characterised by a relatively rapid vertical growth phase. Compared to

SSM, NMs are more common in men, occur more often on the trunk and head and neck region, arise more often de novo, and are biologically more aggressive, particularly those that have a stalk or are polypoid.

3.1.3. Lentigo maligna melanoma

LMM develops in 5% of lentigo maligna lesions (melanosis praecancerosa of Dubreuilh or Hutchinson's melanotic freckle). This type of lesion is typically located in sun-exposed areas such as the face and forearms in an elderly person. This tumour is estimated to comprise 15% of all the head and neck melanomas. It begins as a tan macule with irregular edges [28]. Later on the colour becomes darker, the lesion grows larger and the appearance changes to brown–black variegation. After a horizontal not-invasive growth phase of up to 20 years, vertical growth may develop, clinically presenting as a pigmented nodule: the LMM. A recent study estimated a 2.2% lifetime risk of invasive melanoma for lentigo maligna patients whose life expectancy is 11 years, or a 4.7% lifetime risk with a life expectancy of 33 years [29]. Long-term follow-up studies of lentigo maligna patients are as yet lacking.

3.1.4. Acral lentiginous melanoma

Acral lentiginous melanoma can be found on the non-hairy skin of the acra (palm, sole, nailbed). The clinical picture may be variable due to the thick skin at these sites and diagnostic (patients' and doctors') delay, which is a common phenomenon in these lesions. Acral lentiginous melanomas occur rarely in whites, but comprise 35% of the melanomas that develop in black races, Hispanics, or Asians.

3.2. Diagnostic strategy

A thorough physical examination must be performed when a patient presents with a lesion arousing suspicions of melanoma. The skin and subcutaneous tissue around the primary lesion and between it and the regional nodal basin have to be examined for satellite and in-transit metastases. The regional nodal basin must be evaluated. The skin of the entire body must be examined for concurrent primary melanomas as they occur in 1% of cases. Physical examination must be performed by an expert physician or dermatologist [30].

Dermoscopy (epiluminescence microscopy) is a diagnostic technique that can be used to examine in vivo skin lesions with 10- to 20-fold enlargement. This type of instrument employs oil applied to the surface of the lesion (making the dermis more transparent), a glass plate pressed against the oil (to enhance the in vivo evaluation of structures at the dermo-epidermal junction), a light source and magnification. The clinician is able to see structures not discernible to the naked eye. The in vivo diagnostic accuracy of discriminating between benign versus malignant pigmented lesions may be increased with this technique. It has been estimated that epiluminescence increases diagnostic accuracy for smaller, clinically borderline lesions by about 20%. More recently, digital imaging systems with and without epiluminescence have been studied to determine whether, and to what extent, these devices may augment and/or automate diagnosis [31,32]. Nevertheless, dermoscopy is recommended to be utilised only by experienced physicians.

An excisional biopsy is the standard option on a type C basis as it is the appropriate diagnostic procedure for a skin lesion suspected of being a melanoma, provided it is anatomically, functionally, and cosmetically feasible [8].

Punch biopsy, incisional or shave biopsy, excochleation, whether or not followed by electrocoagulation or cryotherapy, are discouraged. Reliable histology requires examination of the whole lesion. The diagnostic procedure should not be mutilating in the functional or cosmetic sense. Fine needle aspiration for a cytological diagnosis of a primary lesion is unreliable and is not recommended on a type C basis [8].

3.3. Pathological diagnosis

3.3.1. Biopsy

An excisional biopsy is the standard option on a type C basis as the appropriate diagnostic procedure for a skin lesion suspected of being a melanoma, provided it is anatomically, functionally, and cosmetically feasible [8].

Punch biopsy, incisional or shave biopsy, excochleation, whether or not followed by electrocoagulation or cryotherapy, are discouraged. Reliable histology requires examination of the whole lesion. The diagnostic procedure should not be mutilating in the functional or cosmetic sense. Fine needle aspiration for a cytological diagnosis of a primary lesion is unreliable and is not recommended on a type C basis [8].

Accurate measurement of melanoma thickness, at the moment the most important prognostic parameter, is only possible when the entire lesion is excised. Partial specimens bear the risk of not being representative. Moreover, microstaging (Section 2.5) may be hampered due to the risk of tangential embedding of the specimen. Apart from Breslow thickness, accurate assessment of other histological features may also be hindered by partial biopsy, such as the histogenetic type of melanoma, the presence or absence of ulceration and the Clark level of invasion.

Measurement of the Breslow thickness and the Clark level by frozen section examination is unreliable [33] and is not recommended on a type C basis.

3.3.2. Margin for diagnostic excision

As a resection margin for the diagnostic excision, a distance of 2 mm from the border of the lesion and into the subcutaneous tissue is recommended. Undermining of the surgical resection edges should be avoided, because if the excision is not radical, an extra wide re-excision might be necessary. The orientation of the biopsy wound should be planned with the definitive excision in mind. Preference is given to anaesthesia at a distance from the tumour ('field block'). Local anaesthesia directly around the lesion is discouraged.

3.3.3. Incisional diagnostic biopsy

When an excisional biopsy is not feasible, for example when the lesion is very large and/or is so anatomically situated that total excision would be mutilating or disfiguring, especially in the head and neck region, incisional diagnostic biopsy is unavoidable. In these cases a representative biopsy at a peripheral suspicious site of the lesion is advocated. If the lesion proves to be a melanoma, the entire growth can be excised by subsequent radical surgery, which then still allows proper microstaging for prognosis [33].

The advantages of excisional biopsy are obvious. First only total excision will establish a satisfactory diagnosis in certain instances. Is the lesion a melanoma or not? A variety of naevocytic lesions may pose diagnostic problems, especially if only part of the lesion is taken for histopathological examination. Moreover, many melanomas show histological evidence of a pre-existing nevus. If an incisional biopsy has been erroneously taken from such a pre-existing nevus part, an incorrect diagnosis will be given. Second, only excisional biopsy will enable proper microstaging and prognosis.

4. Staging

4.1. Staging classification

4.1.1. Staging system

The formerly used staging system for melanoma was a simple classification scheme dividing patients into three categories: stage I for localised disease, stage II for regional metastatic disease and stage III for distant metastases.

However, because 80% of newly diagnosed melanoma patients now present with stage I, a new four-stage system of classification to divide patients more evenly has been recommended by the American Joint Committee on Cancer (AJCC), and Union Internationale Contre le Cancer (UICC) [34]. Such a classification has been recently modified further and it will become official with the publication of the next edition of the AJCC Cancer Staging Manual in 2002 [35].

New staging will include thickness and ulceration, determine the T-classification, the number of metastatic lymph nodes and the delineation of occult vs. palpable nodal metastases, the N-classification and the site of distant metastases and the presence of elevated serum LDH in the M-classification.

4.1.2. AJCC new staging system

Primary tumour		
T1	tumour $\leqslant 1.0$ mm thick	A: without ulceration and Clark's level II/III B: with ulceration or Clark's level IV/V
T2	tumour 1.01–2.0 mm thick	A: without ulceration B: with ulceration
T3	tumour 2.01–4.00 mm thick	A: without ulceration B: with ulceration
T4	tumour >4.00 mm thick	A: without ulceration B: with ulceration
Regional lymph nodes		
N1	1 node	A: micrometastasis B: macrometastasis
N2	2–3 nodes	A: micrometastasis B: macrometastasis C: in-transit metastases/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes or matted nodes or in-transit metastases satellite(s) with metastatic nodes	

Distant metastasis		
M1a	distant skin, subcutaneous or nodal metastases	LDH = Normal
M1b	lung metastases	LDH = Normal
M1c	visceral metastases. Any distant metastases	LDH = Elevated

Stages	Clinical staging	Pathologic staging
0	Tis N0 M0	Tis N0 M0
IA	T1a N0 M0	T1a N0 M0
IB	T1b N0 M0	T1b N0 M0
	T2a N0 M0	T2a N0 M0
IIA	T2b N0 M0	T2b N0 M0
	T3a N0 M0	T3a N0 M0
IIB	T3b N0 M0	T3b N0 M0
	T4a N0 M0	T4a N0 M0
IIC	T4b N0 M0	T4b N0 M0
III	Any T N1 M0	
	N2	
	N3	
IIIA		T1-4a N1-2a M0
IIIB		T1-4b N1-2a M0
		T1-4a N1-2b M0
		T1-4a/b N2c M0
IIIC		T1-4b N1-2b M0
		T1-4b N2b M0
		Any T N3 M0
IV		Any T, any N, M1

4.1.3. Changes in melanoma staging comparing previous (1997) and new (2002) versions

Factor	Old system	New system	Comments
Level of invasion	Primary determinant of T staging	Used only for defining T1 melanomas	Correlation only significant for thin lesions
Thickness	Second prognostic factor of T staging, thresholds of 0.75, 1.50, 4.0 mm	Primary determinant of T staging; thresholds of 1.0, 2.0, 4.0 mm	Correlation of metastatic risk is a continuous variable
Ulceration	Not included	Included as a second determinant of T and N staging category	Signifies a locally advanced lesion; dominant prognostic factor for grouping stage I, II and III
Satellite metastases	In T category	In N category	Merged with in-transit lesions
Thick melanomas, >4.0 mm	In stage IIIA	In stage IIC	Stage III defined as regional metastasis
Dimensions of nodal metastases	Primary determinant of N staging	Not used	No evidence of significant prognostic correlation
No. of nodal metastases	Not included	Primary determinant of N staging	Thresholds of 1 v 2–3 v 4 metastatic nodes
Metastatic tumour burden	Not included	Included as second determinant of N staging	Clinically occult (microscopic) v clinically apparent (macroscopic) burden of nodal metastases
Lung metastases	Merged with all other visceral metastases	Separate category as M1b	Has a somewhat better prognosis than other visceral metastases

Table (*Continued*)

Factor	Old system	New system	Comments
Clinical v pathologic staging	Did not account for sentinel node technology	Sentinel node results incorporated into definition of pathologic staging	Large variability in outcome between clinical and pathologic staging

4.1.4. M.D. Anderson system

To compare results obtained in regional isolated perfusion, use is made of the M.D. Anderson staging system, focusing especially on local-regional recurrent disease.

IA	Primary intact
IB	Primary excised
IIA*	Local recurrence in contact with scar/skin graft
IIB*	Satellites $\leqslant 3$ cm from primary/skin graft
IIIA	Satellites/in-transit metastases > 3 cm from primary/skin graft
IIIB	Regional lymph node metastases
IIIAB	Satellites/in-transit metastases with regional lymph node metastases
IV	Distant metastasis

*The original M.D. Anderson staging system is adopted according to Klaase [36] by splitting up stage II into stage IIA and IIB.

4.2. Staging procedures

4.2.1. Physical examination

A thorough physical examination must be performed when a patient presents with a lesion arousing suspicions of melanoma. The skin and subcutaneous tissue around the primary lesion and between it and the regional nodal basin have to be examined for satellite and in-transit metastases. The regional nodal basin must be evaluated. The skin of the entire body must be examined for concurrent primary melanomas as they occur in 1% of cases.

4.2.2. Radiographic and/or laboratory studies

In superficial lesions, radiographic and/or laboratory studies are not needed, although chest radiography, liver ultrasound and serum lactodehydrogenase are frequently obtained. Preoperative CT or MRI to screen for lymph node metastases is still investigational in patients with melanoma in the head and neck area [37]. The same applies to ultrasonography, both for assessment of the primary tumour and for detection of lymph node metastases [38,39]. Fine needle aspiration for a cytological diagnosis under ultrasound guidance of lymph nodes is still investigational. As a diagnostic strategy, radio-immunoscanning is not recommended.

4.2.3. Pathological staging (microstaging)

Pathological staging is important to determine prognosis and treatment. Two methods of microstaging are used worldwide.

The Clark microstaging [23] is based on the depth of infiltration of the melanoma into the skin.

The various levels of tumour penetration include: level I, in situ melanoma, not infiltrating through the basal cell layer; level II, infiltration into the papillary dermis; level III, infiltration as far as, but not into the reticular dermis; level IV, infiltration into the reticular dermis; and level V, infiltration into the subcutaneous tissue.

The Breslow microstaging [24] method measures the actual thickness of the tumour using an ocular micrometer. Measurement of the Breslow thickness requires a number of precautions to be taken by the surgeon and the pathologist regarding excision, primarily handling of the specimen, and excision and cutting of representative sections. The measurement of Breslow thickness is highly accurate: intra- and inter-observer variability are low. Several studies have demonstrated that tumour thickness is a more reliable prognostic parameter than Clark's microstaging.

4.2.4. Sentinel node biopsy

An important development in the last decade regarding the clinical detection and early treatment of occult lymph node involvement is the intra-operative biopsy of the sentinel node, the nearest draining lymph node to the primary melanoma. These lymph nodes can be identified by preoperative lymphoscintigraphy and intra-operative tracing using a coloured dye and a hand held gamma-detection probe. The radiopharmaceutical and the dye are injected intradermally around the excisional biopsy wound of the primary melanoma. Micrometastases in the sentinel nodes are discovered in about 20% of cases, when this sentinel node biopsy is performed in melanomas thicker than 1 mm. Formal lymphnode dissection should follow. In experienced hands a high accuracy rate can be achieved by this lymphatic mapping and sentinel node biopsy, but this approach is still considered investigational, since the biological significance of involved sentinel nodes is unknown. As a matter of fact, the group of patients with positive sentinel node is not homogeneous [40]. A randomised study to determine whether lymphatic

mapping and sentinel node biopsy improves regional tumour control and survival is in progress. Sentinel lymph node status has emerged as the most important prognostic factor in clinical stage I and II patients and is a useful selection criterion for entry of patients to randomized trials on adjuvant treatments [41–46].

5. Prognosis

5.1. General considerations

5.1.1. Natural history

The clinical course of melanoma is determined by its dissemination and depends on type, thickness, localisation, growth rate and histology of the primary tumour. Locally melanoma grows wider in diameter and especially thicker resulting in ulcerating lesions. The pattern of dissemination is unpredictable with periods of rapid growth, while spontaneous regression may also occur. Local–regional dissemination takes place in the form of satellites and in-transit metastases and metastases to lymph nodes.

5.1.2. Satellites and in-transit metastases

Satellites and in-transit metastases are typical of melanoma and develop between the site of the primary tumour and regional lymph nodes in the lymphatics of skin and subcutaneous tissue. They may become very numerous and sometimes remain confined to the region for a long time. Within 3 cm from the primary tumour they are called satellites. Satellites and in-transit metastases are seen in about 2 and 3% of patients respectively and are rarely less than 2 mm thick. They can be responsible for the tendency of thicker melanomas to show local recurrence.

5.1.3. Lymph node metastasis

Lymph node metastasis occurs in about 20% of melanoma patients and frequently precedes haematogenic metastasis. In 5% of cases overt metastatic nodes are present at the time of initial diagnosis. Lymph node metastases are mostly confined within the glandular capsule. Growth through the capsule and particularly spread in lymphatics are unfavourable prognostic features.

5.1.4. Distant metastasis

Haematogenic dissemination of metastases occurs, unlike the usual pattern seen with epithelial tumours (liver and lung), relatively frequently in brain, intestinal tract and nonregional cutaneous and subcutaneous areas. Systemic dissemination of tumour occurs in 20% of patients at some time during the course of the disease. Cerebral metastasis and liver metastasis are a frequent cause of death. Metastasis without a known primary site (usually in lymph nodes) is encountered in about 5% of melanoma patients [47].

5.2. Prognostic factors

5.2.1. Clinical prognostic factors

To validate the new AJCC staging system the survival data of 17 600 melanoma patients were collected and analyzed [48]. Stage of disease at diagnosis is still the most important prognostic factor; the 10-year overall survival is 71% for patients with AJCC stages I and II disease and between 20 and 30% for stage III disease [49]. Other prognostic factors for primary melanoma include ulceration, tumour thickness, level of invasion, primary site (extremity melanomas responding better than axial lesions) and sex (females faring better than males). For lesions thinner than 1 mm, the level of invasion seems to be more predictive of survival than ulceration, whereas ulceration is clearly the most predictive additive parameter for lesions thicker than 1.0 mm [48].

In a large series [50] of stages I and II disease the most important prognostic factors were ulceration, tumour thickness, age, primary site, level of invasion and sex. Among these prognostic factors ulceration, tumour thickness, and age, are also claimed to be valid for stage III disease, however the number of node metastases is most significant [50].

5.2.2. Histological prognostic factors

At present it is generally accepted that the maximal tumour thickness according to Breslow is the best predictor of prognosis. The Breslow microstaging method measures the actual thickness of the tumour using an ocular micrometer. Measurement of the Breslow thickness requires a number of precautions to be taken by the surgeon and the pathologist regarding excision, primary handling of the specimen, and excision and cutting of representative sections. Measurement of Breslow thickness is highly accurate: intra- and inter-observer variability are low. Several studies have demonstrated that tumour thickness is a more reliable prognostic parameter than Clark's microstaging. There is an almost linear correlation between maximal tumour thickness and survival.

The second histological predictor of prognosis is the depth of infiltration of the tumour (Clark microstaging). The Clark microstaging is based on the depth of infiltration of the melanoma into the skin. The various levels of tumour penetration include level I, which means in situ melanoma, not infiltrating through the basal cell layer; level II, infiltration into the papillary dermis; level III, infiltration as far as, but not into the reticular dermis; level IV, infiltration into the reticular dermis; and level V, infiltration into the subcutaneous tissue. Clark levels I and II are associated with an

excellent prognosis, Clark level V (infiltration down into the subcutaneous fat) with a poor prognosis. In the intermediate group, level IIIs and IV, there is considerable variation, making Breslow thickness a superior diagnostic parameter. Recently [25] ulceration has been proved as the most relevant prognostic factor for lesions thicker than 1 mm, while Clark's levels IV and V are still relevant only for lesions of less than 1 mm.

Also histological type has been reported to have some prognostic influence, LMM having the best prognosis and NM the worst.

Particular histological types as desmoplastic melanoma (Section 5.4.1) and polypoid melanoma (Section 5.4.2) are reported below.

Other histological prognostic criteria are the number of mitoses, lymphatic infiltration (TIL cells), vascular invasion, the presence of micrometastasis and amelanosis.

5.3. Prognosis of operable disease

5.3.1. Life expectancy

After proper surgical treatment the 5-year life expectancy in Western Europe is presently above 80%, due to the awareness of the public of the implications of changes in moles, resulting in early diagnosis. Ten-year survival is in the range of 85–95% for melanomas not thicker than 1 mm, 80–60% for those between 1 and 2 mm, 60–50% for those between 2 and 4 mm, and 50–30% for those thicker than 4 mm, depending on the presence or absence of ulceration [48].

Local recurrences, satellites and in-transit metastases reduce the 5-year survival for melanoma to about 20% and lymph node metastases to about 30–50%, depending on the degree of nodal involvement (microscopically or macroscopically) and number of affected nodes [47,51–53].

5.4. Prognosis of particular histological types

5.4.1. Desmoplastic melanoma

Desmoplastic melanoma is a rare type of melanoma which may be associated with lentigo maligna and is localised to sun-exposed sites, especially the face, where 41% of cases occur. Variants of this tumour include neural-transforming melanoma and neurotropic melanoma. This tumour is notorious for its tendency to spread by perineural invasion and for its very high rates of local recurrence, approximately 50% (ranging from 25 to 82%). Extensive excision with a 2–3 cm margin, when feasible, is therefore recommended on a type C basis, followed by meticulous microscopic examination of the specimen margins for any evidence of perineural or perivascular invasion. A close follow-up policy should be adopted. The frightening aspect of these tumours is that, if present on the face, infiltration along nerves into the central nervous system may occur. Partial removal of bone in these cases may therefore also be necessary [54].

5.4.2. Polypoid melanoma

Polypoid melanoma is a variant of NM, histologically characterised by an accumulation of melanoma cells in a large volume above the skin surface. The increase in the tumour volume encourages dislodgement of melanoma cells that are carried to superficial lymphatic vessels, resulting in a poor prognosis [55].

5.5. Pregnancy, oral contraceptives, oestrogen replacement therapy and prognosis

According to the results of several large case comparative studies pregnancy does not alter the prognosis for women with melanoma whether the woman is pregnant at the time of diagnosis or becomes so after apparently successful treatment [56]. Nevertheless some of those reports have also shown that median thickness of melanomas diagnosed in pregnancy is higher than those found in non-pregnant women matched for site of melanoma. An explanation of this observation is the belief that melanocytic nevi enlarge or new nevi appear during pregnancy leading to a misdiagnosis of early melanoma. Although there are no large studies of this hypothesis, Pennoyer et al. [57] described only 6.2% change among nevi distribution and size in a small population of pregnant women. It is recommended on a type C basis that the advice to women who wish to embark on pregnancy after treatment for primary melanoma is based on the well-known prognostic criteria, among which thickness and stage of disease are the most important [58].

The influence of oral contraceptives, even for prolonged duration, on the incidence and outcome of melanoma appears, at present, to be minimal or absent [59]. The same holds true for oestrogen replacement therapy [60].

5.6. Advanced or metastatic disease

Survival from the time of metastasis in melanoma is usually limited. Five-year survival after regional lymph node metastasis is 20–50% [49] and 2-year survival after distant visceral metastasis is about 1–2% only. In the latter case, median survival ranges between 2 and 8 months according to the site and the number of metastases. The best survivals after haematogenic metastasis are usually achieved in the case of lymph nodes, subcutaneous or intradermal and lung metastases. However, the most significant differences are between visceral and non-visceral metastases [48]. The survival of patients with cerebral and/or liver metastasis rarely exceeds 6 to 8 months. The availability of active

chemo-immunotherapeutic or polychemotherapeutic regimens may have improved, although to a very limited extent, such a prognosis. Adopting some aggressive options, including the surgical removal of lung, (sub-)cutaneous, lymph node or cerebral metastasis, total brain irradiation, 'gamma knife' radiotherapy, polychemotherapy and chemo-immunotherapy, may lead to the possibility of a small but significant number of long-term survivors. The factors, influencing treatment response and therefore determining the legitimacy of such attitudes, are usually based on the performance status of the patients and the tumour burden as defined by the number of metastatic sites, the number and the size of metastases and the speed of the tumour growth [61].

6. Treatment

6.1. Treatment strategy at clinical diagnosis

6.1.1. General statements

Surgery is the standard option *on a type C basis* for localised primary melanoma. Margins of resection must be wider according to the depth of the lesion up to a maximum of 2 cm for lesions deeper than 2 mm. Lesions not thicker than 2 mm can be excised with a margin of 1 cm.

The trend towards narrower excision margins does not apply to desmoplastic melanoma (Section 5.4.1), a tumour generally located on the face and notorious for its tendency to recur locally.

LMM (Section 2.3.3) also needs different treatment tailoring because of the frequently large dimensions of the surrounding pre-invasive lentigo maligna component. The standard treatment *on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation with soft X-ray or 30–250 key orthovoltage using high dose per fraction. Nevertheless, the use of radiotherapy must be considered investigational.

For patients clinically node negative, elective node dissection (ELND) is still controversial and it is not recommended *on a type 1 level of evidence* [62,63]. Sentinel node biopsy is a promising experimental approach that is possibly the solution to this controversy [64,65].There is no evidence of any benefit from adjuvant chemotherapy.

Adjuvant Alpha Interferon (IFN-α) has given controversial results depending on the stage of disease, the dose and the subset of patients. Its use must be considered inappropriate on a type 1 level of evidence basis for patients with stage II melanoma [66] and investigational only in stage III disease on a *type 2 level of evidence*. The only benefit was seen from high dose IFN-α (20 MU/m2 i.v. daily × 5 of 7 days for 4 weeks followed by 10 MU/m2 three times a week for 48 weeks) in a subset of selected patients, but at the expense of significant toxicity, even if there are recent reports on survival advantages from high-dose IFN-α [66–69].

Sentinel node biopsy is an important selection criterion for the entry of patients to adjuvant trials. Only stage III patients, including those 'upstaged' from stage I and II patients by positive sentinel node biopsy, should be eligible.

Systemic chemotherapy is the treatment of choice for metastatic non-operable disease *on a type R basis*, but there is no regimen that could be claimed as standard.

Radiation therapy (RT) is effective in the palliative treatment of brain and bone lesions as well as nodal metastases and spinal cord compression [70–74]. The role of RT as adjuvant treatment after therapeutic lymph node dissection, and after surgical excision of brain metastases is considered suitable for individual clinical use in selected patients on a *type 3 level of evidence* [70–72,75–79].

6.2. In situ or non-invasive melanoma

6.2.1. Treatment strategy

For in situ or non-invasive melanoma, therapeutic excision with an extra margin of 0.5 cm is the standard treatment *on a type C basis*, because these tumours, notwithstanding their inability to metastasise, may recur locally due to horizontal growth.

6.2.2. Therapeutic excision

Excision down to the fascia is usually performed perpendicular to the surface [80]. It is standard treatment *on a type C basis* to leave the fascia intact. Primary closure of the defect is standard treatment *on a type C basis*. Therapeutic excisions, like diagnostic ones, can be done on an outpatient basis.

6.3. Stage I (AJCC) disease (I A: pT1a N0 M0; I B: pT1b, T2a N0 M0)

6.3.1. Treatment strategy

Surgery is the standard option *on a type C basis* for localised primary melanoma. Margins of resection must be wider according to the depth of the lesion up to a maximum of 2 cm for lesions deeper than 2 mm. Lesions not thicker than 2 mm can be excised with a margin of 1 cm. The trend towards narrower excision margins does not apply to desmoplastic melanoma (Section 5.4.1), a tumour generally located on the face and notorious for its tendency to recur locally.

LMM (Section 2.3.3) also needs different treatment tailoring because of the frequently large dimensions of

the surrounding pre-invasive lentigo maligna component. The standard treatment *on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation with soft X-ray or 30–250 key orthovoltage using high dose per fraction. Nevertheless, the use of radiotherapy must be considered investigational.

For patients clinically node negative, elective node dissection (ELND) (Section 6.3.3) is still controversial but it is not recommended *on a type 1 level of evidence* [62,63]. Sentinel node biopsy (Section 6.3.4) is a promising experimental approach, that will possibly provide the solution to this controversy.

6.3.2. Therapeutic excision of primary melanoma

There is a continuing trend towards narrower excision margins in primary melanoma. Based on recently published results of prospective randomised trials, a 1 cm excision margin now is the standard treatment *on a type 1 level of evidence* for melanomas not thicker than 2 mm [81].

The trend towards narrower excision margins does not apply to desmoplastic melanoma (Section 5.4.1), a tumour generally located on the face and notorious for its tendency to recur locally.

LMM also needs different treatment tailoring because of the frequently large dimensions of the surrounding pre-invasive lentigo maligna component (Section 2.3.3). The standard treatment *on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation using high dose per fraction but the use of radiotherapy must be considered investigational and applicable only on rare occasions such when the patient is medically inoperable or refuses surgery [70]. Nevertheless, the use of radiotherapy must be considered investigational.

To perform therapeutic excision the skin must be cut, according to the Breslow thickness, 1 or 2 cm from the visible margin of the primary melanoma or the wound of the excisional biopsy. Excision down to the fascia is usually performed perpendicular to the surface. It is standard treatment *on a type C basis* to leave the fascia intact [80], except when there is only a thin subcutaneous fat layer, especially in the case of a thick melanoma or when it is necessary not to 're-open' the previous excision scar (for instance when the biopsy proved not to be radical). If possible, primary closure of the defect is standard treatment *on a type C basis*. Undermining of the skin edges is a tempting possibility to facilitate this and is permitted, since the supposition that this jeopardises oncological principles is exaggerated. In the rare instances that primary closure is not possible the wound can be closed by a local skin flap, or by skin grafting. A donor site away from the region involved is generally preferred in order to make the skin graft.

The therapeutic excision, like the diagnostic one, can usually be done on an outpatient basis. Hospitalisation is needed when it is anticipated that the defect will need closing by a skin graft or by an extensive local skin flap.

Particular sites (Section 6.7) such as head and neck, fingers and toes as well as mucosal melanoma may require different treatment tailoring.

6.3.3. Elective lymph node dissection

Elective regional lymph node dissection is the removal of a lymph node area, in the absence of clinically suspect nodes, in the lymphatic drainage region of a tumour. The place of elective lymph node dissection in patients with melanomas between 1 and 4 mm thick has been controversial for many years, but recent evidence points in the direction that in this subgroup the side effects of the procedure outweigh possible survival benefit. According to a retrospective study of 4682 patients at Breslow depths of less than 0.76 mm and between 0.76 and 1.5 mm, the regional nodes and the nodal basin were positive in 0, and 5% of cases respectively [82]. No significant advantage in survival has been reported from prospective randomised trials [63,83–85] and the outcome of retrospective studies is contradictory. In one prospective study, however, advantage of ELND has been claimed for non-ulcerating limb melanomas with a thickness between 1 and 2 mm [63]. Because subgroup analysis, in principle, is considered to be statistically invalid, the treatment option *on a type 2 level of evidence* is not to perform elective lymph node dissection. If the wait-and-see option is decided upon, careful follow-up is recommended *on a type R basis* [12] to detect any nodal metastatic spread at the earliest possible stage. This has to be stressed the more since metastases of melanoma sometimes have an explosive growth. Besides regular follow-up visits, the patient therefore should be instructed to check the regional lymph node station personally, for example once a month.

6.3.4. The sentinel node biopsy

An important development in the last decade in the clinical detection and early treatment of occult lymph node involvement is the *investigational* method of intra-operative biopsy of the sentinel node, the nearest draining lymph node to the primary melanoma [43]. These lymph nodes can be identified by preoperative lymphoscintigraphy and intra-operative tracing using dye and a hand-held gamma-detection probe [42]. The radiopharmaceutical and the dye are injected intradermally around the excisional biopsy wound of the primary melanoma. Micrometastases in the sentinel

nodes are discovered in about 20% of cases, when this sentinel node biopsy is performed in melanomas thicker than 1 mm. Formal lymph node dissection should follow. In experienced hands a high accuracy rate can be achieved by this lymphatic mapping and sentinel node biopsy, but this approach is still considered investigational, since the biological significance of involved sentinel nodes is unknown. A randomised study to determine whether lymphatic mapping and sentinel node biopsy improves regional tumour control and survival is in progress. Sentinel lymph node status has emerged as the most important prognostic factor in clinical stage I and II patients, and is an important selection criterion for the entry of patients to adjuvant trials [41–46].

6.3.5. Postsurgical adjuvant treatment

There is *no evidence* of a role for systemic chemotherapy, immunotherapy or radiotherapy in the adjuvant setting for stage I melanoma [86]. This kind of approach is not recommended. Clinical stage I patients, who are 'upstaged' by sentinel node biopsy to stage III, are elegible for entry to adjuvant trials testing the value of IFN, vaccines etc.

The role of radiation therapy after surgical procedures is currently undergoing reappraisal. Post-operative irradiation can be administered as suitable for individual clinical use *on a type R basis* in order to maximise local control when micro- or macro-scopic residual disease is left in situ and a reintervention is not feasible for medical reasons, for unacceptable morbidity, or for cosmetic limitations.

6.4. Stage II (AJCC) disease (II A: pT2b,T3a N0 M0; II B: pT3b,T4a N0 M0; IIC: T4a N0 M0)

6.4.1. Treatment strategy

Surgery is the *standard option on a type C basis* for localised primary melanoma. For melanomas 2–4 mm thick, a 2 cm resection margin is the standard treatment *on a type 1 level of evidence* [87].

The trend towards narrower excision margins does not apply to desmoplastic melanoma (Section 5.4.1), a tumour generally located on the face and notorious for its tendency to recur locally.

LMM (Section 2.3.3) also needs different treatment tailoring because of the frequently large dimensions of the surrounding pre-invasive lentigo maligna component. The standard treatment *on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation using high dose per fraction but the use of radiotherapy must be considered investigational and applicable only on rare occasions such as when patients are medically inoperable or refuse surgery [70]. For patients clinically node negative, elective node dissection (ELND) (Section 6.4.3) is still controversial but it is not recommended *on a type 1 level of evidence* [62,63]. Sentinel node biopsy (Section 6.4.4) is a promising experimental approach, that will possibly provide the solution to this controversy. There is no clear evidence of any benefit from adjuvant chemotherapy (Section 6.4.5) or post-operative irradiation (Section 6.4.6). The latter has some evidence of benefit in head and neck (Section 6.7.4).

Adjuvant IFN-α has been proven as effective in increasing the disease free interval and improving survival in only one randomized study [66], despite an advantage for disease free survival being reported by four other randomised studies [66,88–90] The effectivity of IFN-α, reported in the ECOG 1964 study with high dose treatment, however, was not reproduced in the subsequent Intergroup study. In stage II melanoma adjuvant treatment with IFN-α, therefore, must be considered inappropriate on a type 1 level of evidence basis.

Clinical stage II patients, who are 'upstaged' by sentinel node biopsy to stage III, are eligible for entry to adjuvant trials testing the value of IFN, vaccines etc.

6.4.2. Therapeutic excision of primary melanoma

For melanomas 2–4 mm thick, a 2 cm excision margin is the standard treatment *on a type 1 level of evidence* [87]. There is no information from randomised trials concerning patients with melanomas thicker than 4 mm. However, since it is likely that haematogenic micrometastases already exist in the majority of these patients, the width of the local resection margin is less relevant. Excision with a 2 cm margin may therefore prove to be an adequate procedure in these patients as well. This assumption has recently been substantiated through a retrospective study [91].

The trend towards narrower excision margins does not apply to desmoplastic melanoma, a tumour generally located on the face and notorious for its tendency to recur locally (Section 5.4.1).

LMM also needs different treatment tailoring because of the frequently large dimensions of the surrounding pre-invasive lentigo maligna component (Section 2.3.3). The standard treatment *on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation using high dose per fraction but the use of radiotherapy must be considered investigational and applicable only on rare occasions such as when the patient is medically inoperable or refuses surgery [70]. Nevertheless, the use of radiotherapy must be considered investigational.

Particular sites (Section 6.7) as head and neck, fingers and toes as well as mucosal melanoma may require different treatment tailoring.

In order to perform a therapeutic excision the skin must be cut, according to the Breslow thickness, 1 or 2 cm from the visible margin of the primary melanoma or the wound of the excisional biopsy. Excision down to the fascia is usually performed perpendicular to the surface. It is standard treatment *on a type C basis* to leave the fascia intact [80] except when there is only a thin subcutaneous fat layer, especially in the case of a thick melanoma or when it is necessary not to 're-open' the previous excision scar (for instance when the biopsy proved not to be radical). If possible, primary closure of the defect is standard treatment *on a type C basis*. Undermining of the skin edges is a tempting possibility to facilitate this and is permitted, since the supposition that this jeopardises oncological principles is exaggerated. In the rare instances that primary closure is not possible the wound can be closed with a local skin flap, or by skin grafting. A donor site away from the region involved is generally preferred in order to make the skin graft.

The therapeutic excision, like the diagnostic one, can usually be done on an outpatient basis. Hospitalisation is needed when it is anticipated that the defect will need closing by a skin graft or by an extensive local skin flap.

6.4.3. Elective lymph node dissection

Elective regional lymph node dissection is the removal of a lymph node area in the lymphatic drainage region of a tumour in the absence of clinically suspect nodes. The place of elective lymph node dissection in patients with melanomas between 1 and 4 mm thick has been controversial for many years, but recent evidence points in the direction that in this subgroup the side effects of the procedure outweigh possible survival benefit.

At Breslow depths of 1.5–2.5 mm, 2.5–4.0 mm, and greater than 4 mm, the regional nodal basin was positive in, 16, 24, and 36% of cases, respectively [82]. No significant advantage in survival has been reported from prospective randomised trials [83–85] and the outcome of retrospective studies is contradictory. In one prospective study, however, an advantage of ELND has been claimed for patients with 1–2 mm non-ulcerating disease, when it is localised on limbs [63]. In another trial, conducted by the WHO in patients with melanoma of the trunk, a survival benefit was shown for patients whose involved lymph nodes were removed electively compared with those who underwent delayed lymph node dissection [65]. Because subgroup analysis, in principle, is considered to be statistically invalid, the treatment option is not to perform elective lymph node dissection *on a type 2 level of evidence*. If the wait-and-see option is decided upon, careful follow-up is recommended *on a type R basis* [12] to detect any nodal metastatic spread at the earliest possible stage. This has to be stressed the more since metastases of melanoma sometimes have an explosive growth. Besides regular follow-up visits, the patient therefore should be instructed to check the regional lymph node station personally, for example once a month.

6.4.4. The sentinel node biopsy

An important development in the last decade in the clinical detection and early treatment of occult lymph node involvement is the investigational method of intraoperative biopsy of the sentinel node, the nearest draining lymph node to the primary melanoma [43]. These lymph nodes can be identified by preoperative lymphoscintigraphy and intra-operative tracing using dye and a hand-held gamma-detection probe [42]. The radiopharmaceutical and the dye are injected intradermally around the excisional biopsy wound of the primary melanoma. Micrometastases in the sentinel nodes are discovered in about 20% of cases when this sentinel node biopsy is performed in melanomas thicker than 1 mm. Formal lymph node dissection should follow. In experienced hands a high accuracy rate can be achieved by this lymphatic mapping and sentinel node biopsy, but this approach is still considered investigational, since the biological significance of involved sentinel nodes is unknown. A randomised study to determine whether lymphatic mapping and sentinel node biopsy improves regional tumour control and survival is in progress. Sentinel lymph node status has emerged as the most important prognostic factor in clinical stage I and II patients [41–46,64], and is an important selection criterion for the entry of patients to adjuvant trials.

6.4.5. Postsurgical adjuvant treatment

There is no evidence for a role of chemotherapy in the adjuvant setting for stage II melanoma The role of alpha-Interferon (IFN-α) has been investigated in few randomised trials. Among them the only study reporting a survival advantage was the ECOG 1964 study of high dose α-2b IFN [66]; these results were not reproduced in the subsequent Intergroup study comparing high vs low dose IFN vs observation [92]. Furthermore about 50% of patients experienced toxicities with high dose IFN and this schedule is more expensive [66,69].

Adjuvant IFN-α has been proven as effective in increasing the disease-free survival (DFS), but not overall survival (OS) in at least four randomised studies [66,88–90].

A recent review of all randomized studies on adjuvant IFN-α either at low dose or intermediate or high dose concluded that according to the trials with mature data on DFS and OS there is no benefit for low-dose IFN-α and a possible advantage on DFS from high dose IFN-α but with relevant toxicity [93]. Even the reported

survival advantage from ECOG 1964 is apparently weakening with longer follow-up (data unpublished). Therefore, IFN-α must be considered inappropriate for improving survival in patients with clinical stage II disease. Patients who are 'upstaged' by sentinel node biopsy to stage III are eligible for entry to adjuvant trials, testing the value of IFN, vaccines, etc.

Adjuvant regional perfusion in primary melanoma is of no benefit. Results of the large EORTC/WHO trial on this subject are negative with regard to overall survival, despite a reduction of local recurrence in the treated limbs [94].

6.4.6. Irradiation

Irradiation of deep primary lesions after surgery is considered investigational or suitable for individual clinical use *on a type R basis* [70,72,79].

The role of radiation therapy after surgical procedures is currently undergoing reappraisal. Post-operative irradiation can be administered in order to maximise local control in the following clinical situations:

(a) when micro- or macro-scopic residual disease is left in situ and a reintervention is not feasible for medical reasons, for unacceptable morbidity, or for cosmetic limitations;

(b) in head and neck lesions where there is a high-risk of recurrence because of the depth of invasion, it is appropriate to treat the surgical bed and/or regional lymph-node areas [75].

For head and neck cases, where melanoma can be considered a separate entity with a different biological behaviour, elective, post-operative and adjuvant radiation may be employed [70,72,79]. Radiotherapy can be considered suitable for individual clinical use *on a type 3 level of evidence*. Different hypofractionated schedules such as 3 Gy × 18, 4.5 Gy × 10, 6 Gy × 5, 7-8 Gy × 3 (0-7-21 scheme) can be appropriate, depending on the extent of disease, site of lesions, and the risk of late side effects.

6.5. Stage III (AJCC) disease (Any T, N 1–3, M0)

6.5.1. Treatment strategy

Surgery is the *standard option on a type C basis* for localised primary melanoma. Margins of resection must be wider, according to the depth of the lesion, up to a maximum of 2 cm for lesions deeper than 2 mm. The trend towards narrower excision margins does not apply to desmoplastic melanoma (Section 5.4.1), a tumour generally located on the face and notorious for its tendency to recur locally. LMM (Section 2.3.3) also needs different treatment tailoring because of the frequently large dimensions of the surrounding pre-invasive lentigo maligna component. The *standard treatment on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation with soft X-ray or 30–250 key orthovoltage using high dose per fraction. Nevertheless, the use of radiotherapy must be considered investigational.

In the presence of involved regional lymph nodes, therapeutic lymph node dissection (Section 6.5.3) is the *standard treatment on a type C basis*; solitary lymph node removal is inappropriate.

There is *no evidence* for a role of chemotherapy in the adjuvant setting (Section 6.5.4) for stage III melanoma [86]. The role of Interferon alpha (IFN-α) has been investigated in few randomised trials [95,96] and the only proven benefit was obtained from high dose IFN-α (20 MU/m2 i.v. daily × 5 of 7 days for 4 weeks followed by 10 MU/m2 three times a week for 48 weeks) in a subset of selected patients, but at the expense of significant toxicity [66–68].

A recent review of all randomized studies on adjuvant IFN-α either at low dose or intermediate or high dose concluded that according to the trials with mature data on DFS and OS there is no benefit for low-dose IFN-α and a possible advantage on DFS from high dose IFN-α but with relevant toxicity [93]. Even the reported survival advantage from ECOG 1964 is apparently weakening with longer follow-up (data unpublished).

Therefore, in patient with stage III disease there *no evidence* for a role of low dose Interferon in the adjuvant setting *on a type 1 level of evidence* while HDIFN must be considered as suitable for individual clinical use *on a type 2 level of evidence*.

6.5.2. Therapeutic excision of primary melanoma

There is a continuing trend towards using narrower excision margins for primary melanoma. Based on recently published results of prospective randomised trials, a 1 cm excision margin now is the standard treatment *on a type 1 level of evidence* for melanomas not thicker than 2 mm [81]. A 2 cm margin is recommended for melanoma thicker than 2 mm *on a type C basis* [87].

There is no information from randomised trials concerning patients with melanomas thicker than 4 mm. However, since it is likely that haematogenic micrometastases already exist in the majority of these patients, the width of the local resection margin is less relevant. Excision with a 2 cm margin may therefore prove to be an adequate procedure in these patients as well. The trend towards narrower excision margins does not apply to desmoplastic melanoma, a tumour generally located on the face and notorious for its tendency to recur locally (Section 5.4.1).

LMM also needs different treatment tailoring because of the frequently large dimensions of the surrounding

pre-invasive lentigo maligna component (Section 2.3.3). The standard treatment *on a type R basis* is to excise the invasive part of this growth with margins according to its thickness, thereby ensuring that, if possible, the non-invasive lentigo maligna component is totally removed. These neoplasms can be well controlled by irradiation using high dose per fraction but the use of radiotherapy must be considered investigational and applicable only in rare occasions such as when the patient is medically inoperable or refuses surgery [70]. Nevertheless, the use of radiotherapy must be considered investigational.

In order to perform the therapeutic excision the skin must be cut, according to the Breslow thickness, 1 or 2 cm from the visible margin of the primary melanoma or the wound of the excisional biopsy. Excision down to the fascia is usually performed perpendicular to the surface. It is standard treatment *on a type C basis* to leave the fascia intact [80] except when there is only a thin subcutaneous fat layer, especially in the case of a thick melanoma or when it is necessary not to 're-open' the previous excision scar (for instance when the biopsy proved not to be radical). If possible, primary closure of the defect is standard treatment *on a type C basis*. Undermining of the skin edges is a tempting possibility to facilitate this and is permitted, since the supposition that this jeopardises oncological principles is exaggerated. In the rare instances that primary closure is not possible the wound can be closed with a local skin flap, or by skin grafting. A donor site away from the region involved is generally preferred to make the skin graft.

The therapeutic excision, like the diagnostic one, can usually be done on an outpatient basis. Hospitalisation is needed when it is anticipated that the defect will need closing with a skin graft or with an extensive local skin flap.

Particular sites (Section 6.7) as head and neck or fingers and toes as well as mucosal melanoma may require different treatment tailoring.

6.5.3. Therapeutic lymph node dissection

In the presence of involved regional lymph nodes, therapeutic lymph node dissection is the standard treatment *on a type C basis*; solitary lymph node removal is inappropriate. Clinically dubious findings can necessitate fine needle aspiration of the suspect lymph node. A negative outcome may justify a policy of waiting under strict follow-up conditions [97,98].

Even in the presence of distant metastases palliative resection of the involved lymph node area will often be carried out to avoid local complications such as ulceration, haemorrhage or neural invasion. It is suitable for individual clinical use *on a type R basis.*

When the primary melanoma has been located in the vicinity of the suspicious lymph node station, it is standard treatment *on a type R basis* to re-excise the scar of the primary melanoma in continuity (en-block) with the lymph node dissection.

In the groin, it is standard option to perform a femoro-inguinal (superficial groin) and iliacal-obturator (deep groin) dissection to the bifurcation of the iliac artery [99–101].

In the axilla the standard treatment *on a type C basis* is to perform a complete lymph node clearance. The minor pectoral muscle is excised en-block with the lymph node specimen, if necessary.

In the neck usually a complete therapeutic neck dissection is carried out as standard treatment option *on a type C basis*. This may be a radical neck dissection, sacrificing the sternocleidomastoid muscle, the internal jugular vein and the accessory nerve, or a modified radical dissection sparing one or more of these structures. The rationale for preservation of these structures is often arbitrary and indicated by the proximity of the lymph node metastases to one of these structures. In judging these two procedures, factors such as survival, regional tumour control and functional and cosmetic results should be considered. The parotid gland is situated in the lymph drainage area of a melanoma of the temple/forehead, ear and anterior scalp. Therefore, in these cases a superficial parotidectomy should be performed in continuity with the neck dissection. Involvement of the retroauricular and occipital lymph nodes requires removal of the lymph node-bearing tissue of the retroauricular and suboccipital region in continuity with the contents of the posterior triangle of the neck and internal jugular chain [98,102].

6.5.4. Postsurgical adjuvant treatment

There is *no evidence* for a role of chemotherapy in the adjuvant setting for stage III melanoma [86].

A recent review [93] of all randomized studies on adjuvant IFN-α either at low dose or intermediate or high dose concluded that according to the trials with mature data on DFS and OS there is no benefit for low-dose IFN-α [95,96] and a possible advantage from high dose IFN-α but with relevant toxicity. The only proven benefit was obtained with high dose IFN-α (20 MU/m2 i.v. daily × 5 of 7 days for 4 weeks followed by 10 MU/m2 three times a week for 48 weeks) in a subset of selected patients, but at the expense of significant toxicity [66–68].The positive results obtained with high dose IFN-α-2b from the ECOG 1964 study [66] were not reproduced in the subsequent Intergroup study (E1690) comparing high vs low dose IFN vs observation in 642 patients [92]. Recently a third study (Intergroup E 1694) in 880 patients proved a significant improvement in overall and relapse free survival from HDI as compared to a vaccine formulated from the GM2 ganglioside antigen [68]. However the short follow-up of this study (<2 years) does not allow a definitive conclusion. No definitive data are available from the EORTC 18952

study (on 1418 patients). Moreover, there was clinically relevant toxicity associated with high dose IFN [69], and even the reported survival advantage from ECOG 1964 is apparently weakening with longer follow-up (data unpublished).

So in patient with stage III disease there *no evidence* for a role of low dose Interferon in the adjuvant setting on a type 1 level of evidence while HDIFN must be considered suitable for individual clinical use on a type 2 level of evidence.

The positive results obtained with high dose IFN-α-2b from the ECOG study were not reproduced in the subsequent Intergroup study comparing high vs low dose IFN-α vs observation [92]. Furthermore clinically relevant toxicity occurred with high dose IFN [69].

Based on these data adjuvant IFN-αust be considered investigational. Further randomised studies are ongoing to evaluate intermediate doses of IFN-α and they still include a control arm, as in the EORTC study #18952.

Isolated regional perfusion may be investigational or suitable for individual clinical use *on a type 2 level of evidence* as an adjunct to excision to improve local-regional control in the presence of in-transit metastases [103,104].

6.5.5. Radiation therapy

Irradiation of deep primary lesions after surgery is considered investigational or suitable for individual clinical use *on a type R basis* [70,72,77]. The role of radiation therapy after surgical procedures is currently undergoing reappraisal. Post-operative irradiation can be administered in order to maximise local control in the following clinical situations:

(a) when micro- or macroscopic residual disease is left in situ and a reintervention is not feasible for medical reasons, for unacceptable morbidity, or for cosmetic limitations [70,72,77];

(b) in head and neck lesions where there is a high-risk of recurrence because of the depth of invasion, it is appropriate to treat the surgical bed and/or regional lymph-node areas [75,79];

(c) after a therapeutic lymph-node dissection in metastatic nodal disease when narrow margins, multiple nodes and/or extranodal spreading are present [76,78,105].

Post-operative radiation therapy following surgery for regional lymph node metastases has been investigated in two randomised trials using hypofractionation-7 fractions a week of 6 Gy or conventional fractionation-50 Gy in 25 fractions. No difference in overall survival or death from melanoma was noted, but reduced recurrence rate was obtained in the hypofractionated trial. This treatment can be considered suitable for individual clinical use *on a type 2 level of evidence* [76,78,106].

In head and neck, where melanoma can be considered a separate entity with different biological behaviour, elective, post-operative and adjuvant radiation may be applied. Radiotherapy can be considered *suitable for individual clinical use on a type 3 level of evidence*. Different hypofractionated schedules such as 3 Gy × 18, 4.5 Gy × 10, 6 Gy × 5, 7–8 Gy × 3 (0-7-21 scheme) can be appropriate, depending on the extent of disease, site of lesions, risk of late side effects, presence of regional nodes, etc. [70,72,75,79].

6.6. Stage IV (AJCC) disease (Any T, N2, M0 or any T any N M1)

6.6.1. Treatment strategy

It is *standard treatment on a type C basis* to excise local recurrences, satellites and in-transit metastases (Section 6.6.2) when feasible [107].Isolated regional perfusion may be investigational or suitable for individual clinical use *on a type 2 level of evidence* as an adjunct to excision to improve local-regional control [103,104,108].Metastatic disease (Section 6.6.3) is treated with systemic chemotherapy if it is not suitable for surgical palliation *on a type R basis*, but there is no regimen that could be claimed as standard.

Radiation therapy (Section 6.6.5) is effective in the palliative treatment of brain, bone and nodal lesions as well as spinal cord compression [70–74]. Its role as adjuvant treatment after therapeutic lymph node dissection or melanoma excision is considered suitable for individual clinical use in selected patients on a *type 3 level of* evidence [70,72,75–79].

6.6.2. Local recurrences, satellites and in-transit metastases

It is *standard treatment on a type C basis* to excise local recurrences, satellites and in-transit metastases when feasible [107].

Isolated regional perfusion may be investigational or suitable for individual clinical use *on a type 2 level of evidence* as an adjunct to excision to improve local-regional control [103,104,108].

The value of regional perfusion in patients with in-transit metastases or extensive tumour growth in an extremity, that cannot be resected completely, is generally accepted and is *suitable for individual clinical use on a type R basis*. In approximately 80% of such patients a complete remission can be achieved, which in a substantial percentage of patients (about 35%) is long standing (>3 years). By means of perfusion, amputation of the limb can usually be avoided [104,108,109].

This method consists of isolation of the blood circulation of the extremity and connection to an extra-corporeal circuit with oxygenation and temperature regulation. Subsequently the extremity is perfused with a high dose of a cytostatic drug, usually melphalan.

In an ongoing randomised study the value of the combination of melphalan with the biological response modifier recombinant tumour necrosis factor-a, is being evaluated [108].

Cryosurgery, electrocoagulation, laser treatment [110], radiotherapy combined with hyperthermia [72,111] and intralesional administration of BCG or dinitrochlorobenzene (DNCB) [112] also have a place in the palliative treatment of widespread local–regional disease.

6.6.3. Metastatic disease

The prognosis of patients with distant metastases is very poor, with a median survival varying from 2 to 8 months according to the anatomical site of the metastases and the number of metastases (Section 5.6). Surgery, when possible, should be recommended as suitable for individual clinical use any time the complete removal of all visible metastases is achievable. Unfortunately, this therapeutic approach is relatively inaccessible for most patients with metastatic disease.

6.6.4. Metastasectomy

In some patients with haematogenic metastases metastasectomy is suitable for individual clinical use *on a type R basis* [113]. This surgery frequently results in a quick and good palliation. The indication for metastasectomy is rather strong for solitary metastases, the more so since systemic cytostatic and/or immunotherapeutic schedules have yielded almost no efficacy so far. A proper indication for metastasectomy is haematogenic cutaneous and subcutaneous metastases. Surgical intervention also has to be considered for patients with complaints and/or complications from gastro-intestinal metastatic melanoma, such as chronic or acute blood loss, ileus (invagination) or perforation [114]. Excision of a solitary brain metastasis sometimes results in a good palliation. In cases of lung metastasis palliation is not the primary goal, however in solitary lung metastasis some prolongation of survival may be achieved.

6.6.4.1. Radiotherapy. Radiotherapy can be suitable for individual clinical use as a palliative treatment for spinal cord compression, brain metastases, nodal metastases, lung metastases, bone metastases, for brain metastases after surgery, and lastly, for pain control [70–72,115]. Radiobiological and clinical data no longer support the concept of radioresistance of melanoma [73,74,111,116]. Intrinsic radiosensitivity appears heterogeneous but within the range of values seen in the great majority of tumour cells lines. Melanoma exhibits high response rates to irradiation using different time–dose fractionation regimens. Melanoma cells have the ability to efficiently repair both sub-lethal and potentially lethal radiation damage [117–119].

Clinical data are consistent with the finding that high dose per fraction can achieve a higher complete response rate [118], but a randomised study comparing high dose (8 Gy × 4) or low dose per fraction (2.5 Gy × 20) regimens showed similar high response rates (range 23–72%; 2 years local control: 48–82%). Both fractionation schemes can be considered as standard options *on a type 2 level of evidence* [70,72,74].

Patient's life expectancy, patient's quality of life or the possible exhibition of late side effects can address the choice of radiation regimen: this can be regarded as suitable for individual clinical use *on a type R basis*.

6.6.4.2. Chemotherapy. Systemic chemotherapy treatment for melanoma has not demonstrated significant activity. The most efficient drugs are dacarbazine (DTIC), nitrosourea, cisplatinum (CDDP) and vinca-alkaloids. DTIC is considered the most active single agent, it gives a response rate of about 12–20%. Responses are rare in visceral sites and they are anecdotal in cerebral metastasis [120]. Temozolomide is a prodrug of DTIC which can be administered orally and has better distribution into the cerebrospinal fluid. It is a promising new agent because of the oral route of administration and it produces responses rates similar to those obtianed with DTIC (21% CR+PR in phase II studies) [121]. Fotemustine, not yet available worldwide, gives a response rate of about 24% in metastatic melanoma with around 20–25% responses in brain metastases. Its toxicity profile is usually very acceptable and includes mainly neutropenia and thrombopenia [122]. For all these drugs, complete response occurs in less than 10% of cases and the median duration of response is between 4 and 6 months.

Several two-, three- or four-drug regimens have been tested. The most common regimens used are CVD (CDDP, Vinblastine, DTIC) or the combination of CDDP and DTIC. All of them can achieve a response rate of about 30–45% with a median duration of response and complete response rates that are not significantly different from those achieved with fotemustine or dacarbazine alone [123].

Although it is preferable to include MM patients in phase III trials, the choice between mono- or poly-chemotherapy is made as suitable for individual clinical use on a *type R basis*, because there are no data supporting a survival advantage for treatment independent from other prognostic factors.

6.6.4.3. Chemotherapy plus tamoxifen. The use of tamoxifen is not be recommended *on* a *type 2 level of evidence* since most of the available data from randomised prospective studies showed no advantage of adding tamoxifen to the CBD regimen, to DTIC or to the combination of CDDP+DTIC in patients with disease resistant to CDDP [124–128].

6.6.4.4. Immunotherapy and chemo-immunotherapy. Immunotherapy is another option for such patients. Recombinant a-INF gives between 12 and 18% response rates with doses ranging between 3 and 18 million units subcutaneously three times a week. Responses in visceral sites are rare. Toxicities include mainly fatigue, myalgia, fever, leucopenia and thrombocytopenia. Recombinant Interleukin-2 as a single drug, gives 15–25% response rates with doses ranging between 9 and 18 million units, total dose or per square meter. It is given as bolus injection by the subcutaneous route, or, more usually, using continuous perfusion [129,130]. Toxicities include flu-like syndrome, fever, hypotension, vascular leak syndrome with oliguria, œdema, and neutrothrombocytopenia. High dose IL-2 produced a 7% complete response rate and 4% long-lasting CR [131].

Although the combination of Interleukin-2 and IFN-α has been shown to be synergistic *in vitro*, results in humans have been rather disappointing with response rates not exceeding 30% [132].

The combination of DTIC with IFN-α has been claimed as more effective than DTIC alone but the only little advantage is in terms of response rate without any advantage in survival [133].

The combination of rIL2 and DTIC+IFN or polychemotherapy did not demonstrate any significant benefit [134,135].

The combinations of IFN and or IL2 should not be recommended *on a type 2 level of evidence* in the palliative setting outside clinical studies[135]. This is also the case for the combination of cisplatinum and a-INF which initially was associated with a high response rate (above 50%), with 10–20% complete responses and some long-lasting unmaintained remissions. However, these results were not reproduced in more recent randomized studies [135,136].

6.6.4.5. Gene therapy and vaccines. Vaccines and gene therapy *should be* recommended as strictly investigational [137].

6.6.5. Bone metastases

Radiation therapy is standard treatment for symptomatic bone metastases *on a type C basis*. Palliative radiotherapy using either conventional or hypofractionated regimens is effective in 50–85% of patients, with total doses in the range of 20–36 Gy, dose per fraction of 3–6 Gy over 2–3 weeks [70,71,138].

6.6.6. Spinal cord compression

For spinal cord compression irradiation plus corticosteroids is the *standard treatment on a type R basis*. Radiotherapy can be used as sole decompressive modality or as an adjuvant to laminectomy. Palliation can be achieved in 44–85% of cases [70,72,127,138]. Irradiation regimens should be selected on the basis of patient long-term or short-term prognosis, and on spinal cord tolerance which limits the utilisation of high dose per fraction schedules (30 Gy at 2–3 Gy per day in 2–3 weeks).

6.6.7. Cerebral metastases

Cerebral metastases have a poor prognosis with a median survival from diagnosis of 2–5 months. Radiotherapy can provide effective, temporary palliation. Solitary brain metastases should be treated with surgical resection plus post-operative irradiation, that is standard treatment *on a type 3 level of evidence* [71];[139]. Combination therapy appears to be superior to each treatment modality alone. Radiosurgery, avoiding surgical and anaesthetic risks, can be appropriate for solitary small lesions: this can be regarded as investigational or suitable for individual clinical use *on a type 3 level of evidence* [140].

In cases of multiple metastases or residual disease after surgery, palliative radiotherapy is standard treatment *on a type R basis* [70–72,141]. Whole brain irradiation has been suggested for patients with multiple lesions at doses of 30 Gy over 2 weeks or 20 Gy over 2 weeks, the dose should be selected on the basis of prognosis, the presence of other sites of metastases, and performance status.

6.7. Treatment of particular sites

6.7.1. Melanomas of hand and foot

The tendency to use narrower excision margins is of utmost importance in the treatment of melanomas of the hand and foot. However, even with 1 or 2 cm margins, mutilation often cannot be avoided. Here, surgeons have to use their best judgement, weighing function and cosmetic appearance against the possible increased risk of local recurrence, when wishing to use an even narrower excision margin than indicated. Skin grafting in this area is seldom indicated.

6.7.2. Melanomas of the fingers and toes

For melanomas of the fingers and toes, amputation is usually considered the best treatment option. The amputation level for subungual melanoma of the toes can be taken at the metatarsophalangeal joint and for subungual melanoma of the fingers at the proximal interphalangeal joint. In cases of thin subungual melanomas, a more distal amputation level must be considered. For subungual melanoma of the thumb, amputation distal to the metacarpophalangeal joint is standard treatment *on a type R basis*, if possible, in order to preserve some function of the thumb stump.

6.7.3. Mucosal melanoma

Melanoma of the mucosa is an uncommon neoplasm accounting for about 4% of all melanomas and is

characterised by a poor prognosis. Head and neck, anorectal and urogenital regions are the most frequently involved sites [142,143].

Post-operative and palliative irradiation for anorectal and urogenital melanoma can be recommended as suitable for individual clinical use *on a type R basis.*

Mucosal melanoma of the head and neck most frequently involves the oral cavity, nasal cavity and paranasal sinuses. When surgery is not feasible, radical radiation can be considered as standard option *on a type C basis* giving complete response and durable local control rates in the range of 50–75% [70,77,144].

Few data are available on the use of irradiation in the post-operative setting; however, it can be considered as optional treatment *on a type R basis* [145].

Inclusion of the CNS in the treatment field obviously represents a limiting factor in the utilisation of high dose per fraction regimens.

6.7.4. Head and neck melanoma

Less than 20% of patients develop melanoma in the head and neck area. Such individuals are considered as having a worse prognosis but there are no clear data to support this conclusion. Scalp melanoma probably has a poor prognosis because it is thicker at diagnosis.

Surgeons have to use their best judgement, weighing function and cosmetic appearance against the possible increased risk of local recurrence when performing an even narrower excision than is usually indicated. There are no data supporting the hypothesis of an increase in local recurrences when narrower margins were utilised in this area. Skin grafting in the head and neck area, especially in the face, is seldom indicated.

For treatment of some types and stages of head and neck melanoma, post-operative and adjuvant radiation may be appropriate [70,72,75,97]. Radiotherapy can be considered *suitable for individual clinical use on a type 3 level of evidence.* Different hypofractionated schedules such as 3 Gy × 18, 4.5 Gy × 10, 6 Gy × 5, 7–8 Gy × 3 (0-7-21 scheme) can be employed, depending on the extent of disease, site of lesions, risk of late side effects, presence of regional nodes, etc. [75,79].

7. Late effects and sequelae

7.1. Treatment related late effects and sequelae

Disfiguring wounds and scars are the most frequent late effects of surgical treatment of melanoma. Plastic surgery may be necessary for wound repair.

7.2. Second tumours

There are controversial data concerning second primary tumours among patients with melanoma. There is a higher incidence of tumours among patients treated for melanoma and a higher risk of a second primary melanoma, lymphomas, non-melanoma skin cancers, brain and nervous system cancers according to various reports. Age, sex and time from diagnosis of melanoma have been reported to be influential factors.

8. Follow-up

8.1. General aims

The post-operative follow-up of melanoma patients is the same irrespective of the tumour site. The major goal of follow-up is the detection of local–regional recurrences and nodal recurrence, because distant metastatic disease is largely incurable and elaborate laboratory and imaging studies have not proven to be useful. The value of the (potential) tumour marker in the blood, the S-100 protein, is under investigation. It has been reported that this marker can be used to detect melanoma recurrences before they become apparent [146].

Patients are required to perform self-examination of the skin and of regional lymph nodes. There are no studies concerning the frequency of follow-up visits.

In a large study of 602 patients with thin melanoma (<0.75 mm) only 24 recurrences (4%) were recorded and among them there were only 5 (1%) operable recurrences within 5 years [147].

8.2. Suggested protocols

A common procedure for follow-up is to review the history and perform a physical examination three/four times a year in the first 2 or 3 years. Thereafter this proceedure should be followed every 6 months for a total period between 5 and 10 years. In asymptomatic patients, laboratory and radiological studies to detect metastatic disease are not justified outside clinical trials.

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Biographies

Filippo de Braud is Clinical Editor of START. He is Director of Clinical Pharmacology and New Drugs Development Unit at the European Institute of Oncology – Milan, Italy.

David Khayat is Head of the Department of Medical Oncology at Hopital Pitié-Salpetrière – Paris, France. He is also a University teacher and member of different

International Committees and of the Editorial Boards of important cancer journals.

Riccardo Valdagni is Director of the Radiation Oncology Department at Casa di Cura San Pio X in Milan. He is also psychotherapist at Ruolo Terapeutico – Centro Psicanalitico in Milan.

Bin Kroon is Professor of Surgery and Head of the Department of Surgery at The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital – Amsterdam, The Netherlands.

Paolo Bruzzi is Head of the Unit of Clinical Epidemiology and Trials at the National Cancer Research Institute – Genoa, Italy.

Natale Cascinelli is Scientific Director of the National Cancer Institute of Milan, Italy – and the President of the WHO Melanoma Program.

START METHODOLOGY

START is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the **START** project. The **START** Editorial team is glad to receive comments on this (please, address them to the START Secretariat). The background has been detailed in *Ann Oncol 1999; 10: 769-774.*

TYPE of OPTION

START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis,

- ***STANDARD ("standard", "recommended" [or "not recommended"])***

This can be considered a conventional choice for the average patient.

- ***INDIVIDUALIZED ("suitable for individual clinical use")***

This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.

- ***INVESTIGATIONAL ONLY ("investigational")***

This is something which, in principle, can be offered to the patient only within a clinical study.

TYPE of BASIS for available options

START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.

- ***"TYPE C basis" (General consensus)***

There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed

- ***"TYPE 1 evidence" (Randomised trial(s) available, strong evidence)***

Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.

- ***"TYPE 2 evidence" (Randomised trial(s) available, weak evidence)***

One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.

- ***"TYPE 3 evidence" (External controlled comparisons available)***

Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.

- ***"TYPE R basis" (Rational inference)***

Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).