News

Consensus on the Management of Melanoma of the Skin in the Netherlands

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On behalf of the Dutch Melanoma Working Party

In 1990, the Dutch Melanoma Working Party, in cooperation with the National Organization for Quality Assurance in Hospitals, organised the second consensus conference on the mangement of melanoma of the skin. The following guidelines were approved: The margin of a therapeutical excision should be 1 cm for melanomas not thicker than 1.0 mm, 2 cm for a thickness of 1.1–2.0 mm, 3 cm for a thickness of 2.1–3.0 mm. No consensus was reached for tumours thicker than 3.0 mm. The conclusion of the histopathological report should state the histological type of melanoma, the thickness, the level of invasion, the presence of ulceration, regression, microsatellitosis and completeness of removal. In melanomas between 1.5 mm and 4 mm, elective lymph node dissection may be considered, but its value has not been proven. Clinically suspicious regional lymph nodes require a therapeutical lymph node dissection, solitary lymph node removal is inappropriate. Prophylactic (adjuvant) regional perfusion in primary melanoma should only be performed in the context of a clinical trial. Regional perfusion is the treatment of choice for satellitosis and/or in-transit metastases of the extremities without evidence of distant metastases. If radiotherapy is indicated, high fractionation doses are required. There is no standard therapy for distant metastases. Routine check radiographs and laboratory studies are unnecessary during the follow-up period. The follow-up period is normally 10 years.
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INTRODUCTION

THE NATIONAL Organization for Quality Assurance in Hospitals (CBO) has been conducting a consensus development programme in The Netherlands since 1982 and up to now 30 conferences have been held. The primary goal of this programme is to develop guidelines for daily medical practice in such a way that they can be used in quality assurance activities for physicians in hospitals.

The formulation of these guidelines on controversial clinical topics is considered to be an intermediate step towards change in medical behaviour. Emphasis is placed not only on the methods and means for implementing the guidelines but also on evaluating their impact on health practices and outcomes.

Because the validity, and therefore the acceptability, of consensus texts wanes with time, the CBO has decided to re-evaluate, and if necessary revise, all consensus texts every 5 years. Melanoma of the skin was the first subject that was revalidated by a second consensus development conference.

In 1984 the first consensus development conference on the management of skin melanoma was held. For evaluation of the effect of the guidelines formulated at that time on the daily practice of the specialists involved in the treatment of melanoma, pathologists' reports dating from 1983 (1 year before the consensus meeting) and from 1986 and 1988 were analysed. The data were derived from 19 laboratories associated with the Pathological Anatomical National Automated Archive of the Dutch Society of Pathology (PALGA). The evaluation was confined to the type of the diagnostic excision by the physician as it was described in the report of the pathologist. In the consensus text the following recommendations had been made: "For the diagnosis of a skin lesion suggesting melanoma, an excisional biopsy should be performed. Other types, i.e. the incisional biopsy, should not be considered." Of the reports received, 1091 were suitable for analysis, i.e. 324 from 1983, 383 from 1986, and 384 from 1988. General and plastic surgeons performed incisional biopsies (including punch biopsies) in only a small percentage of the cases (1983: 3%; 1986: 2%; 1988: 1%), whereas in 1983 the dermatologists performed the incisional biopsy frequently (45%). But after the consensus meeting this practice declined considerably (1986: 39%; 1988: 18%). In both 1983 and 1986, 11 dermatologists had performed an incisional biopsy on a suspected case of melanoma, but in 1988 there were only two [1].

Although a direct link between the introduction of consensus guidelines and a change in physicians' behaviour is difficult to prove, these results encouraged us to organise a second conference in order to further improve the management of melanoma. This second conference was held in 1990. A questionnaire was circulated beforehand to assess the opinion of the physicians on draft versions of the guidelines. The information gathered was used by the working committee to prepare the decision-making

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process of the consensus development. One of the characteristics of the Dutch approach is that there are two separate group processes: first preparation by a working committee, where the members of different scientific organisations meet several times to formulate a draft text, and then the actual consensus development conference, where audience participation is emphasised so that the results can be considered to truly reflect the opinion of the whole medical profession. The second consensus development conference on melanoma of the skin was attended by 187 participants from different medical specialities. The following text, translated and slightly modified from the Dutch original [2], is the product of these consensus activities.

Whenever used, the term (tumour) thickness indicates the maximal thickness measured according to Breslow.

DIAGNOSTIC AND THERAPEUTIC EXCISION

A wide excision is considered obsolete for thin melanomas

An excisional biopsy is the appropriate diagnostic procedure for a skin lesion suspected of being a melanoma. A fine needle aspiration must be regarded as an "incisional biopsy" and is therefore inappropriate. In erosive or ulcerating melanoma an "imprint" preparation may be considered.

When the index of suspicion is low, a narrow resection margin is appropriate. If the lesion is suspicious, the resection margin should be 0.5 cm. When the lesion is highly suspect and is likely to be a thin melanoma, a direct resection with a margin of 1 cm is preferred. This may save the patient a further surgical procedure. Undermining of the surgical resection edges should be avoided, because if the excision was not radical an extra wide re-excision may be necessary. Preference is given to anaesthesia at a distance from the tumour ("field block"). Local anaesthesia directly around the lesion is discouraged.

Once the diagnosis of melanoma has been established, a wider, definitive excision may be indicated. There is no complete consensus on the margins for therapeutic excisions. In general, the currently recommended margins are narrower than they used to be. The following guidelines are advised:

Tumour thickness ≤ 1.0 mm: excision with a 1 cm margin.
Tumour thickness 1.1–2.0 mm: excision with a 2 cm margin.
Tumour thickness 2.1–3.0 mm: excision with a 3 cm margin.
In melanomas more than 3 mm thick some consider a 3 cm margin adequate, while others prefer a wider excision (up to 5 cm) depending on how much the thickness exceeds 3 mm.

Narrower margins are justified in treatment of melanomas on the face, palm of the hand and sole of the foot. In thin melanomas a wide excision is considered inappropriate, except in thin melanomas with evidence of regression; here the presumed tumour thickness prior to regression justifies a wider excision.

The definitive excision, like the diagnostic excision biopsy, can usually be done on an outpatient basis using field block anaesthesia. Hospitalisation is needed when it is anticipated that the excision defect will need closing with a skin graft. If the wound cannot be closed primarily, there is no general agreement whether a skin graft should be used or whether in appropriate circumstances the wound can be closed with a local skin flap. The contralateral buttock or extremity is the preferred donor site for a skin graft.

The fascia should be removed during the definitive excision if the fascia was exposed during the diagnostic procedure or if the needle aspiration or punch biopsy was deep enough to reach the fascia, since, in these situations, there is a risk of contamination. Removal of the fascia is not indicated when the primary excision has been performed so as to leave a sufficiently thick layer of subcutis in place.

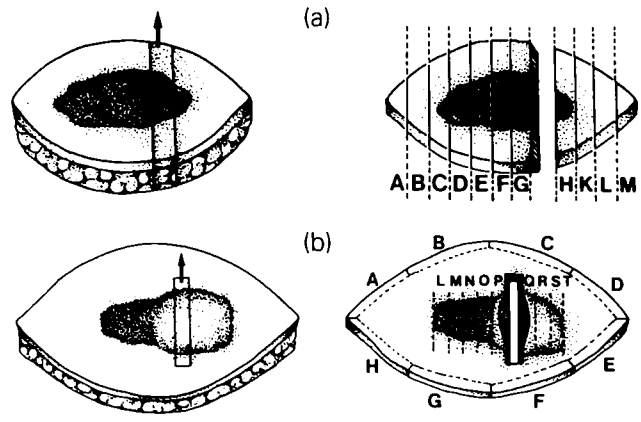

Fig. 1. Protocol for the sectioning of primary skin lesions suspect of melanoma. (a) Specimen with narrow excision margin. (b) Specimen with wide excision margin.

Amputation is usually the only possible curative treatment of melanomas on the fingers and the toes.

HISTOPATHOLOGY

The histopathological processing of a skin specimen with a suspect melanoma lesion should deal with the entire specimen

With lesions smaller than 0.8 cm the specimen should be fixed *in toto*. If the specimen is fresh and the lesion larger than 0.8 cm, it is justified to reserve a paracentral slice (about 2 mm thick) for research purposes. This slice should be snap-frozen as soon as possible (see Fig. 1); the remainder should be fixed for 24 h and subsequently sectioned.

When excision margins are 0.3 cm or less, the complete specimen should be cross sectioned. With lesions up to 2 cm all transverse slices (labelled A, B, C, etc., see Fig. 1a) should be embedded and processed for histology. With larger lesions at least four transverse slices should be taken, including the thickest part of the lesion, ulcerating parts, and the site where the surgical margin is narrowest.

With excision margins over 0.3 cm the edges of the specimen should be sectioned clockwise (see Fig. 1b). The lesion can then be sectioned transversely with a margin of a few millimeters, and, depending on its size, either completely or partially embedded.

Frozen section evaluation for diagnostic and prognostic purposes is generally not useful

Opinions on the value of frozen section diagnosis of primary pigmented skin lesions differ. Some use this method in cases which are highly suspicious of thick melanoma. In such instances, a narrow excision and frozen section diagnosis of melanoma allows a wide excision during the same operation. There are, however, more drawbacks than advantages:

General anaesthesis is sometimes given unnecessarily.
Evaluation of the lesion is incomplete and, therefore, less reliable than the examination of paraffin slides.
Thickness measurement is unreliable.
Relatively large amounts of tissue are lost.

These considerations have prompted the consensus conference to advise against the routine use of frozen section diagnosis of such lesions.

The conclusion of the histopathological report should state the histologic type of melanoma, the maximal thickness, the level of invasion, as well as the presence of ulceration, regression, microsatellitosis, and completeness of removal

The conclusion of the report should mention the prognostic indicators stated above. In the Netherlands, this conclusion is registered in the national database (PALGA). Any doubt about the diagnosis should be noted in the report. Possible diagnostic problems include:

There is a melanocytic lesion, but it is uncertain if it is benign, pre-malignant, melanoma *in situ*, or malignant. Referral to the panel of pathologists of the Dutch Melanoma Working Party is recommended in this instance.

The tumour is malignant, but it is amelanotic and cannot definitely be distinguished from an undifferentiated carcinoma, sarcoma, or a lymphoma. In these instances, additional immunohistological and possibly electronmicroscopical examination are suggested.

The tumour is a cutaneous melanoma, however, definitive classification (histologic type) and/or microstaging (Breslow, Clark) are impossible. This problem is posed usually by incomplete biopsies or local recurrences following inadequate primary treatment.

LYMPH NODE DISSECTION

In melanomas thicker than 1.5 mm, elective node dissection may be considered, but its value has not been proven. For thinner melanomas this procedure is discouraged

An 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 the tumour. In primary melanomas with a thickness of 1.5 mm or less, clinically innocent lymph node areas are usually left untouched. Here the chance of nodal micrometastases is so small that the disadvantages of elective dissection outweigh any possible advantages. Although patients with melanoma more than 4 mm thick have the highest risk of nodal micrometastases, they too are not likely to benefit from elective node dissection since most often haematogenous spread has already occurred, and this determines the prognosis. The place of elective lymph node dissection in patients with melanoma between 1.5 and 4 mm thick is controversial. Some favour a wait-and-see policy under strict follow-up conditions, basing their arguments on the results of a WHO prospective randomised trial. Others recommend elective node dissections in these patients, based on the results from a number of large, well-analysed retrospective studies and because of objections against the WHO trial.

In the presence of clinically suspicious regional lymph nodes a therapeutic lymph node dissection should always be performed; solitary lymph node removal is inappropriate

Solitary lymph node removal is inappropriate because of the risk of contamination of the surrounding tissue. Capsular invasion is a well-known phenomenon in melanoma. Metastases are frequently observed lying free in the fat between the lymph nodes. Clinically dubious findings can necessitate further diagnostic intervention, e.g. fine needle aspiration of the suspect lymph node. A negative outcome may justify a policy of waiting under strict follow-up conditions. If lymph node dissection is decided on after a fine needle aspiration, the needle track should also be removed because of the risk of contamination with tumour cells.

When a therapeutic lymph node dissection is indicated, extensive preoperative examination for distant metastases is usually unnecessary

Screening for distant metastases in patients with lymph node metastases may be limited to exploratory blood analysis (liver function) and a chest X-ray. In rare cases, a tomography or a computed tomography scan of the lungs may be indicated. The involved lymph node area will often be resected with palliative intent to avoid local complications such as ulceration, haemorrhage or neural invasion, even in the presence of distant metastases.

REGIONAL PERFUSION

Regional perfusion of primary limb melanoma with a thickness greater than 1.5 mm without evidence of metastases as adjuvant treatment should only be performed in the context of a clinical trial

The conventional surgical treatment of limb melanoma may be supplemented with regional isolated perfusion. The blood circulation of the extremity is isolated and connected to an extracorporeal circuit with oxygenation and temperature regulation. Subsequently the extremity is perfused with a high dose of a cytostatic drug (usually melphalan) for 60 min. In the Netherlands regional perfusions are carried out in three hospitals (Academic Hospital, Groningen, The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis), Amsterdam, and Dr Daniel den Hoed Cancer Center, Rotterdam). The indications for perfusion are similar in all three hospitals.

A distinction must be made between adjuvant and therapeutic perfusions. Adjuvant regional perfusion in stage I melanoma is of unproven benefit and therefore in the Netherlands it is carried out only in the context of a clinical trial.

Regional perfusion is the treatment of choice for satellitosis and/or in-transit metastasis of the extremities without evidence of distant metastases

The value of therapeutic regional perfusion is generally accepted. The main indication is extensive tumour growth in an extremity, such as local recurrence, satellitosis, and in-transit metastases which cannot be completely resected. In approximately one third of such patients, regional perfusion induces a complete remission which may last for months, but usually does so for some years. In another third a partial remission is obtained, while in the remaining third little change is produced. By means of perfusion, amputation of the limb can usually be avoided in these patients.

Similarly, regional perfusion is indicated in patients with local recurrences, satellitosis, or in-transit metastases which may be amenable to surgical removal. In these patients the tumour process cannot usually be controlled by means of local excision alone.

RADIOTHERAPY

If radiotherapy is indicated high fractionation doses are required

Curative radiotherapy is indicated in patients:

In whom curative resection of a primary melanoma or local recurrence is not possible or feasible, or when the patient refuses surgery.

In whom resection of nodal metastases is not possible. If the nodal metastases show a substantial reduction after radiotherapy, surgery can be considered once more.

With satellitosis and in-transit metastasis, if one or only a few metastases are present and if other treatments are not possible (surgery, perfusion). In these situations combined

treatment using radiotherapy with hyperthermia may be considered.

The following schedule is advised: 9 × 5 Gy, two fractions per week. In view of the risk of late adverse effects a higher dose per fraction is unwarranted.

Palliative radiotherapy may be indicated in painful metastases, inoperable recurrences in the skin or lymph node areas, deep abdominal nodal metastases, brain metastases, etc. The following schedule is advised: 1–3 × 8 Gy on days 1, 8, 22.

For brain metastases the proposed schedule is: 10 × 3 Gy, five fractions a week.

A boost dose can possibly be applied to a limited tumour area: 3 × 3 Gy.

Adjuvant radiotherapy may be indicated in the following situations: doubt if the node dissection has been radical, spill during the operation, irradical operation, narrow margins of the node dissection. However, these indications are rare. The following schedule is recommended: 9 × 5 Gy, two fractions per week, which is similar to the schedule applied in curative treatment.

CHEMOTHERAPY

There is no standard therapy for melanoma with distant metastases

Sometimes local therapy (metastasectomy, radiotherapy, intra-arterial infusion) yields good palliative results in patients with only a few metastases and slowly progressive disease. In the presence of extensive metastases or in rapidly progressing disease chemotherapy may be considered. Patients treated with chemotherapy should be entered in trials whenever possible.

When a patient is not eligible for a trial but wishes treatment, dacarbazine, is the drug of first choice. Dacarbazine, which has been most widely tested, produces responses of around 20–25%. These are usually partial remissions and of short duration. A remission lasting more than 6 months may occur in up to 5% of patients. The following treatment schedule is proposed: intravenous dacarbazine 800 mg/m^2, on days 1, 22, etc. Nitrosourea-derivatives give a similar remission rate but penetrate the blood–brain barrier and may sometimes produce remission of brain metastases. Combination therapy is more toxic and no more effective than single-agent chemotherapy. Evaluation should take place prior to the third cycle; treatment must be discontinued when progression occurs.

FOLLOW-UP

Routine chest radiographs and laboratory studies are unnecessary during the follow-up period

After treatment, follow-up examinations are normally required for a period of 10 years. The follow-up examination must focus on inspection and palpation of the treated area. The skin between primary tumour site and regional lymph nodes should be examined for satellitosis and in-transit metastases. The regional nodes must be thoroughly palpated at every follow-up examination. Curative treatment is usually still possible for local or regional recurrent disease.

The following schedule is recommended:

Follow-up period	Physical examination
1st year	1 × per 2–3 months
2nd year	1 × per 3–4 months
3rd year	1 × per 4 months
4th–5th year	1 × per 6 months
6th–10th year	1 × per year

Routine chest X-rays and blood tests are no longer recommended. The detection of an asymptomatic distant metastasis is of no therapeutic consequence so long as no curative systemic therapy is available.

For the follow-up of patients with melanoma associated with dysplastic naevus syndrome (DNS) we refer to the following statement. In general, a long follow-up period is required on account of the risk of other dysplastic naevi evolving into melanomas.

PRECURSOR LESIONS

Persons with the familial dysplastic naevus syndrome have a greatly increased risk of melanoma. Check-ups once to twice a year are required for a long period of time

The dysplastic naevus syndrome (DNS) is a genodermatosis, first described in 1978, in which multiple acquired atypical (dysplastic) naevi and/or melanomas occur in patients and their relatives. Besides the original familial form, a sporadic type of DNS is recognised, in which no family members with dysplastic naevi or melanomas are known. It must be realised that the differentiation between familial and sporadic DNS is not always clear. Estimates of the lifetime risk of melanoma range from 5% for persons with sporadic DNS to almost 100% for persons with familial DNS with two or more family members with melanoma. In view of the greatly increased risk of melanoma which is observed in persons with familial DNS, intensive evaluation of the affected persons and their first degree relatives is of the utmost importance. Examinations should take place on a regular basis, at least once a year. Some advise lifelong follow-up, in particular when there is a personal history of melanoma. Regular screening of the members of DNS families has been shown to result in the detection of thinner melanomas with consequently better prognosis.

Similarly, the risk of melanoma is increased with sporadic DNS. The number of dysplastic naevi and the degree of histologic atypia determine the check-up schedule. Patients with dysplastic naevi are urged to visit their physician whenever a naevus seems to be undergoing change.

To establish the histopathologic diagnosis "dysplastic naevus" one or more characteristics of architectural atypia and of cellular atypia have to be present

Besides these mandatory histopathological criteria, features of stromal reaction are usually observed.

Characteristics of architectural atypia are: increased number of melanocytes along the dermo-epidermal junction (lentiginous or/and in nests), reduced melanocytic preference for the tips of the rete ridges, irregularity of the shape and variation in the size of the nests along the dermo-epidermal junction (some more than twice the size of others), bridging (two adjacent rete ridges are connected through a bridge of melanocytes), absent or variable maturation of the dermal component.

Characteristics of cellular atypia are: large (epitheloid) melanocytes, large nuclei, prominent nucleoli, dustlike melanin pigment, nuclear pleomorphism, remarkable retraction-artifact. The most important four characteristics are:

Marked melanocytic proliferation (over 50% of the cells in the basal layer are melanocytes) along at least three adjacent rete ridges.
Irregularity of the melanocytic nests.
Large melanocyte nuclei.
Dust-like melanin.

The diagnosis of dysplastic naevus is restricted to those naevi exhibiting the entire spectrum of architectural and cytological features described above. In many instances where a naevus exhibits only some of the features of either cytological atypia or architectural irregularity, it does not qualify as a dysplastic naevus.

The stromal reaction shows the following features which may be present to a variable degree: lymphocytic infiltrate (perivascular or bandlike), increase in number of fibroblasts and amount of thin-fibred collagen (lamellar fibrosis), vascular proliferation, accumulation of melanophages.

It has become clear that the histological diagnosis has little practical meaning unless it is in the context of clinical features (number and macroscopical appearance of moles, personal and family history of melanoma).

However, it is also evident that the dysplastic naevus, as histologically defined above, is different from the large majority of junctional and compound naevi encountered in daily practice, and is identical histologically to the naevus which in the context of the familial dysplastic naevus syndrome constitutes the immediate melanoma precursor. For these reasons, it appears reasonable to diagnose these lesions under a separate heading, i.e. dysplastic (junctional or compound) naevus.

1. Everdingen JJE van, Rampen FHJ, Ruiter DJ, Casparie AF. Evaluation of consensus development conference on cutaneous melanoma in The Netherlands. *Br J Dermatol* 1990, **123**, 259–260.
2. Report of the Dutch Melanoma Working Party and the CBO: Melanoma van de Huid. Publisher: CBO, Utrecht, 1990, ISBN 906910104.1.

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BACR/ACP Joint Annual Meetings

The British Association for Cancer Research and the Association for Cancer Physicians are holding a joint meeting on 30 March to 1 April 1992, in Southampton. As well as annual meetings of the two groups, there will be a BACR symposium on cell adhesion and tumour spread, an ACP symposium on novel approaches to therapy and a joint symposium on viruses, genes and growth factors in haematological malignancies. For further details, contact Barbara Cavilla, BACR Secretariat, 20 Queensbury Place, London SW2 DZ, U.K. Tel: (071) 581 8333.

Annual Meeting of the AACR

The 83rd annual meeting of the American Association for Cancer Research will be held in San Diego on 20–23 May 1992. Plenary sessions include chemoprevention, innovative tumour immunology, cell adhesion in invasion and cell cycle control. For more information, contact the AACR, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, Pennsylvania 19106, U.S.A.

Metastasis Research Society

The 4th international congress of the Metastasis Research Society will be held in Paris on 1–4 September 1992. Plenary sessions will include molecular determinants, host interactions, therapy and genetics. Further details can be obtained from Dr Marie-France Poupon, IRSC–CNRS, 7 rue Guy Moquet, BP 89401, Villejuif, France. Tel: (33) 1 46 78 92 59, fax: (33) 1 46 78 79 76.