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Purpose
Melanoma of the skin is a type of cancer with a strong tendency to already metastasise with a small tumour load. The prevalence of this disorder has increased substantially in recent decades (see section 1: Epidemiology). Partly because melanoma is diagnosed in a relatively early stage and removed nowadays, the number of deaths has not increased as greatly as the incidence. Death occurs as a result of metastatic disease, because treatment possibilities in that stage are limited. Early diagnosis and treatment of melanoma are therefore of great importance for the prognosis of patients involved.
This requires a multidisciplinary approach and good collaboration between primary and secondary health care providers. The guideline provides guidance to this end. New insights and developments require the guideline to be updated regularly. The penultimate revision dates to 2005. The first guideline on melanoma was written in 1985. It was revised in 1990, 1997 and 2004, in which the NMW (Dutch Melanoma Working Group, established in 1986) played an important role.
In principle, the guideline has been formulated in an ‘evidence-based’ manner. The current revision is a part evidence-based, part-consensus-based update. The process of guideline development was managed by the Comprehensive Cancer Centre the Netherlands (IKNL).

Objective
A guideline is a document with recommendations to support daily practice. This guideline is based on scientific research results and opinions on these results, and focuses on determining good medical practice. The intention of the document is to be a guideline for daily practice in prevention, diagnosis, treatment and follow-up of patients with a skin melanoma. Melanomas at other locations in the body are not covered in this guideline. The guideline concerns all stages of the disease.

Target group
This guideline is intended for all professionals involved in diagnostics, treatment and guidance of patients with a skin melanoma, such as dermatologists, pathologists, surgeons, radiologists, internist-oncologists, general practitioners, oncology nurses, IKNL consultants, social workers and psychologists.

Working method of the 2012 evidence-based guideline development group
The guideline development group worked on revising the guideline for approximately two years. The guideline is a part evidence-based and part consensus-based revision. A number of clinical problems requiring revision were put forward at the start of 2010 by a group of four medical specialists (medical oncologist, pathologist, surgeon and dermatologist), all members of the NMW (Dutch Melanoma Working Group). These clinical problems were put forward to the remaining members of the NMW and further developed into nineteen clinical questions (see Appendix 8). For three of these clinical questions (5, 7 and 13), a systematic literature search was performed (evidence-based update). In doing so, clinical question 7 was subdivided into two sub-questions. For sixteen clinical questions (1-4, 6, 8-12, 14-19), references were made to studies that were put forward by the guideline development members themselves (consensus-based update). Separate chapters were incorporated in the revised guideline for pathology, aftercare and follow-up and organisation of care. In order to integrate the guideline Cancer rehabilitation in the melanoma guideline, two sub-questions for clinical question 13 were further researched in an evidence-based manner (also see Appendix 8).
A subgroup with representatives from relevant disciplines was formed for every clinical question. The members of the guideline development group formulated text, conclusions, considerations and recommendations which were discussed during plenary meetings and approved after comments were processed. For the evidence-based clinical questions, the (ME-TA) Medical Evaluation Technology Assessment agency performed the literature search, formulated the text and developed evidence tables. The methodological expert from the IKNL performed the literature search, formulated the text and evidence tables for sub-question 7.2 together with one of the guideline development group members.
The development group met five times to discuss the results of the subgroups. The texts of the subgroups have been merged and aligned by the process manager to form one document: the concept guideline. The concept was sent to all associations and organisations represented within this guideline development group as well as to all regional tumour groups for comment. After the comments were processed, the guideline was established by the full guideline development group and sent to the relevant professional associations for authorisation. The chairperson of the guideline
development group and process manager of the IKNL took care of the coordination and alignment of subgroups.

More information about:
Composition of the guideline development group (see Appendix 1)
Members of the 2012 guideline development group (see Appendix 2)
Independence of development group members (see Appendix 3)
Involved and authorising associations (see Appendix 4)
Scientific argumentation (see Appendix 5)
Classification of literature study results according to the level of evidence (Appendix 6)
Format of 'Considerations' and 'Formulation of recommendations' (see Appendix 7)
Clinical questions (see appendix 8)
Literature search (see Appendix 9)
Evidence tables (see Appendix 10)
'Considerations' tables (Appendix 11)
Update (see Appendix 12)
Ownership (see Appendix 13)
Legal significance of guidelines (Appendix 14)
Accountability (see Appendix 15)
Implementation and evaluation (see Appendix 16)
Format of melanoma aftercare plan (see Appendix 17)
Gaps in knowledge (see Appendix 18)
References (Appendix 19)
1.1 Epidemiology (editorial update)

In 2010 almost 800 people died from melanoma, approximately 350 women and almost 450 men. Translated to the European standard population, this concerns over 3.9 per 100,000 persons in the Netherlands per year (4.7 for men and 3.1 for women) [Hollestein 2011]. The death rate due to melanoma is somewhat increasing in the Netherlands, in contrast to neighbouring countries [Hollestein 2011; Vries de, 2003], together with an increase in incidence in melanoma with a high Breslow depth [Hollestein 2011].

The incidence of skin cancer has continuously grown over the last 40 years, according to data from the NKR (Netherlands Cancer Registry). Incidence in the Netherlands is currently one of the higher ones in Europe (standardised to the European standard population of 25.1 per 100,000 patient years for women and 20.4 for men), but the death rate is low on average (also see Figure 2) [Karim-Kos 2008; Vries de, 2003]. The increase in incidence is for a large part associated with excessive and intermittent exposure during childhood to sunlight by people with a white skin [Whiteman 2001; Lock-Andersen 1999]. This was already playing a role in the industrialised world in generations born around 1900. From research with migrants it has appeared that the risk of melanoma at a young and middle-age is especially influenced by sun exposure during childhood [Khlat 1992]. There may also be a limited contribution from other sources of ultraviolet radiation, such as sun lamps and tanning beds [IARC Rapport, 2006; Bataille, 2005].

All in all, a substantial increase in the incidence of melanoma in the Netherlands can be expected in the coming years based on current trends (also see Table 1 and Figure 1), [Vries de, 2005]. The incidence has increased annually by 4.1% in the period 1989-2008 [Hollestein, 2011]. The incidence is increasing in all age groups but is increasing the most rapidly in the elderly (≥65 years), where the increase is 6% for men and 4.3% for women [Hollestein 2011].

The prognosis is largely determined by timely discovery (expressed in the Breslow depth). Most melanomas develop slowly (1-2 years). However, there are fast growing variants (a few months) of melanoma that are often already thick and have a poor prognosis. Within Europe, the prognosis in the Netherlands in the last 20 years has been relatively good: adult cancer patients survive longer in the Netherlands [Karim-Kos, 2008; Siesling, 2011]. The increased awareness in the period after the campaign with the sproetenbus (‘freckles bus’ – a screening campaign for skin cancer) presumably contributed to this [Berrino, 2003].

As of 1994, the Breslow depth of each patient with melanoma has been registered in the NKR (Netherlands Cancer Registry). In contrast to what is being seen in many other countries, the incidence of both thick and thin melanomas is increasing at approximately the same pace [Hollestein, 2011]. Nonetheless, the prognosis has strongly improved in recent years: the 10-year survival rate in the Netherlands at the start of the 90’s was 70% for men and 85% for women; in the period 2004-2008 this improved to 77% and 88% respectively [Hollestein, 2011].

The relative survival of patients with melanomas thinner than 1 mm is around 98% [Vries de, 2007] and this is more favourable than in many clinical research trials, because clinical trials often monitor select patient groups, possibly with a somewhat more complex clinical picture than is the case in the general population (see Figure 3).
### Table 1: Trends in incidence in new patients with an invasive or in situ skin melanoma in the Netherlands, in the 2000-2010 period, for men and women (figures per 100,000 crude rate).

<table>
<thead>
<tr>
<th>Year</th>
<th>In situ melanoma</th>
<th>Invasive melanoma</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>2000</td>
<td>2.7</td>
<td>4.9</td>
<td>13.1</td>
</tr>
<tr>
<td>2001</td>
<td>3.4</td>
<td>5.3</td>
<td>15.3</td>
</tr>
<tr>
<td>2002</td>
<td>3.2</td>
<td>5.1</td>
<td>15.1</td>
</tr>
<tr>
<td>2003</td>
<td>3.4</td>
<td>5.8</td>
<td>15.3</td>
</tr>
<tr>
<td>2004</td>
<td>3.5</td>
<td>6</td>
<td>17.3</td>
</tr>
<tr>
<td>2005</td>
<td>4.1</td>
<td>6.5</td>
<td>19.4</td>
</tr>
<tr>
<td>2006</td>
<td>4.6</td>
<td>6.4</td>
<td>19.3</td>
</tr>
<tr>
<td>2007</td>
<td>5.2</td>
<td>6.9</td>
<td>20.5</td>
</tr>
<tr>
<td>2008</td>
<td>5.8</td>
<td>8.1</td>
<td>22.6</td>
</tr>
<tr>
<td>2009</td>
<td>6.6</td>
<td>9</td>
<td>23.7</td>
</tr>
<tr>
<td>2010</td>
<td>7.4</td>
<td>10.2</td>
<td>26.4</td>
</tr>
</tbody>
</table>

**Figure 1:** Trends in incidence in new patients with an invasive or in situ skin melanoma in the Netherlands, in the 2000-2010 period, for men and women (figures per 100,000 crude rate).

**Figure 2:** Deaths from invasive skin melanoma in the Netherlands, in the 2000-2010 period, for men and women (figures per 100,000, crude rate).
In summary:
The trends in incidence of and death from melanoma in the Netherlands are both reassuring and alarming: reassuring because the death rate is no longer increasing notably with women, despite a continuing increase in incidence in the coming years; alarming because the death rate is continuing to increase, especially with men of middle and elderly age.
CH2 PREVENTION

2.1 Prevention (consensus-based text)

Recommendations

Sunburn should be prevented for primary prevention of melanoma.

Use of tanning beds should be advised against for primary prevention of melanoma.

Literature discussion

In 2009, the International Agency on Research of Carcinogens (IARC) definitively declared ultraviolet light (UV-A and UV-B) carcinogen for humans [El Ghissassi, 2009]. Meta-analyses of case-control studies convincingly show that melanoma is predominantly caused by intermittent, intense exposure to the sun [Marks 1994; Whiteman 1994; Armstrong 1988]. People with a light skin are advised to moderate their sun exposure throughout their life [Gandini 2005]. The most important preventative measure to prevent melanoma is preventing sunburn, especially in children [Autier 1998]. A different mechanism has been found to be responsible for a subcategory of melanomas: that of cumulative UV exposure [Whiteman 2010]. Tanning beds also increase the risk of melanoma; this was demonstrated to be significant for the age group less than 35 years of age [Cust 2011; Héry 2010; Lazovich 2010; IARC, 2006]

Conclusions

<table>
<thead>
<tr>
<th>Level 1</th>
<th>It has been demonstrated that sunburn is a risk factor for the development of melanoma.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A1; Gandini 2005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 1</th>
<th>It has been demonstrated that the use of tanning beds by people under 35 years of age is a risk factor for developing melanoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1; Cust 2011; Héry 2010; Lazovich 2010; IARC 2007</td>
</tr>
</tbody>
</table>

Considerations

Strict sun avoidance is undesirable due to the chance of Vitamin D shortage [KWF Signalling report, 2010].
Recommendations

Systematic population screening for melanoma is not needed.

The guideline development group is of the opinion that screening for low-risk genes in people with a genetically elevated risk of melanoma is currently not worthwhile.

If there are five or more atypical nevi or more than 100 banal nevi, it is recommended to perform an annual check-up in consultation with the patient (relative indication).

It is recommended to use phenotypical characteristics to detect an elevated risk in patients, to make the patient aware of these and to provide information/ensure information is provided on these (such as through brochures, instructions for self-examination).

It is recommended to record the risk factors present for melanoma in the patient file for each patient that presents for evaluation of a melanocytic lesion. The guideline development group is of the opinion that the patient file is only complete if the risk factors present have been recorded.

It is not recommended to perform routine follow-up for congenital nevi (CN) with a diameter of 20 cm or smaller. However, it is recommended that parents are instructed to return for consultation if there are any changes of small and middle-sized CN (<20 cm) in children.

The guideline development group is of the opinion that discussion of large CN in a multidisciplinary team in a paediatric surgery centre as soon after birth as possible is desirable, in relation to the option of neonatal curettage. In addition, the development group is of the opinion that also after intervention of such a large or giant CN, regular follow-up with inspection and palpation is advisable.

It is recommended to refer melanoma patients for whom the diagnosis familial melanoma/FAMMM syndrome is being considered to a clinical genetic centre.

It is recommended to screen the skin of melanoma patients and their first-degree relatives from families in which the diagnosis familial melanoma/FAMMM syndrome has been determined over the life of the patient from the age of 12 years.

The guideline development group is of the opinion that for second-degree relatives from CDKN2A positive families, annual screening is desirable from 20 years of age, or (in consultation with the patient) instruction to perform self-examination. If a CDKN2A mutation has been excluded, second-degree relatives do not need to be screened.

The development group is of the opinion that it is desirable for CDKN2A mutation carriers from the age of 45 years to be referred to a gastroenterohepatology specialist in one of the centres in which pancreatic examination/analysis is taken place within a research context, in relation to the increased risk of pancreatic cancer.
Screening of persons with an increased risk of melanoma is generally called surveillance. Screening for skin cancer is regular checking of the entire skin of people without complaints or symptoms. The different types of screening that can be distinguished are outlined in the following sections:

1. the general population
2. persons with an increased risk of melanoma on the basis of:
   a) phenotypical characteristics
   b) congenital nevi
3. persons with a genetically elevated risk of melanoma

### 3.1.1 Screening of the general population (consensus-based text)

**Literature discussion**
The US Preventative Services Taskforce, a government organisation in the US that researches the desirability of population screening, has concluded in a systematic review in 2001 and in an update in 2009 that research results show an insufficient basis for recommending population screening for melanoma [US Preventive Services Taskforce, 2001; Wolff 2009].

**Conclusion**

<table>
<thead>
<tr>
<th>Level 1</th>
<th>The desirability of systematic population screening has not been demonstrated.</th>
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<tr>
<td>A1;US Preventive Services Taskforce, 2001; Wolff T, 2009</td>
<td></td>
</tr>
</tbody>
</table>

**Considerations**
At least approximately 40,000 basal cell carcinomas and at least 5,000 squamous cell carcinomas of the skin are diagnosed annually in the Netherlands. On an incidental basis, a screening campaign on a national level should generate attention for early diagnosis of skin cancer including melanoma. A “relative indication” for screening (in persons with 5 or more atypical nevi or with more than 100 banal nevi) refers to consultation with the patient whether he/she would like periodic follow-up or to check her/his skin/moles themselves and return if a mole (melanocytic nevus) changes. If the latter is chosen, the patient does need to be given instructions regarding self-examination.

### 3.1.2 Screening of persons with an increased risk of melanoma (consensus-based text)

**Literature discussion**
a) phenotypical characteristics
Persons with an increased risk of melanoma can be identified on the basis of a number of phenotypical characteristics. Phenotypical markers of increased risk of melanoma have been compared on the basis of literature data and used to determine if an increased risk of melanoma for an individual can be identified with sufficient certainty. The below table shows the phenotypical markers that are generally considered melanoma risk factors. Meta-analyses of these factors have been performed by Gandini et al., 2005 [Gandini 2005a; Gandini 2005b]. More recent publications confirm the outcomes of the study by Gandini (see Table 1).
Table 1: Phenotypical characteristics for an increased risk of melanoma.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk according to meta-analysis by Gandini 2005a and 2005b</th>
<th>More recent references with similar findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of nevi &gt; 100</td>
<td>7.0</td>
<td>Chang et al. 2009</td>
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<tr>
<td></td>
<td></td>
<td>Olsen et al. 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicolau et al. 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Han et al., 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nagore et al. 2010</td>
</tr>
<tr>
<td>Atypical nevi &gt; 5</td>
<td>6.4</td>
<td>Chang et al. 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olsen et al. 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nijsten et al.2005</td>
</tr>
<tr>
<td>Skin type: light, tan poor</td>
<td>2.1</td>
<td>Nicolaou et al. 2008</td>
</tr>
<tr>
<td>Hair colour: red : blond</td>
<td>3.6</td>
<td>Han et al. 2006</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>Naldi et al. 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nagore et al. 2010</td>
</tr>
<tr>
<td>Eye colour: blue</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Freckles</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Actinic damage/lentigines</td>
<td>2.0</td>
<td>Chang et al. 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nijsten et al. 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicolau et al. 2008</td>
</tr>
<tr>
<td>A medical history of basal cell carcinoma or squamous cell carcinoma</td>
<td>4.3</td>
<td>Nagore et al. 2010</td>
</tr>
</tbody>
</table>

Conclusion
It has been demonstrated that phenotypical characteristics make it possible to detect an increased risk of melanoma in an individual.

Level 1
A1; Gandini et al. 2005a, 2005b

b) congenital nevi
The below section is in force until the guideline development group of the children’s healthcare guideline on skin abnormalities (edited by the TNO (Netherlands Organisation for Applied Scientific Research), the NVDC (Dutch Association for Dermatology and Venereology), AJN (Youth Service Medical Association), V&VN (Dutch Nurses’ Association) and the NVDA (Dutch Association of Doctors’ Assistants) makes the evidence-based guideline text public in the course of 2013. See http://www.huidarts.info/.

Literature discussion
Melanomas can develop in congenital nevi (CN); a congenital nevus is therefore a risk factor for melanoma. CN are arbitrarily subdivided based on size, in which the highest risk of melanoma is associated with the largest CN.

Definitions:
- a small CN is smaller than 1.5 cm at adulthood
- a middle-sized CN is 1.5-20 cm at adulthood
- a large CN is greater than 20 cm at adulthood

Prospective studies have become available recently that show that the risk of malignancy is lower than earlier reported on the basis of retrospective studies with research populations from specialised centres. According to a systematic review, the melanoma risk of all CN together is only 0.7% lifetime risk [Krengel 2006]. These findings are confirmed in two recent reviews [Kovalyshyn 2009; Price 2010].

The study by Krengel mentioned above found that 75% of cases of melanoma occurred in the so-called giant CN, with a size greater than 40-50 cm and which are often densely hairy. Giant CN are very rare (incidence 1: 500,000). The risk of melanoma is less than 5% lifetime risk according to the mentioned meta-analysis, but sometimes a melanoma already develops during childhood; 50% develop before the age of five [Krengel 2006; Kovalyshyn2009; Price 2010].
Large and giant CN may be associated with neurocutaneous melanosis in 2.5-11% of cases. Neurocutaneous melanosis may manifest through epileptic seizures, hydrocephalus or a cerebral melanoma. Neurocutaneous melanosis is more common in localisation of the CN on the head and if there are multiple satellite nevi (>20) and localisations above the posterior midline. Neurocutaneous melanosis may be detected using an MRI (preferably before the age of 4 months), naturally in consultation with the child neurologist.

**Conclusions**

<table>
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<tr>
<th>Level 1</th>
<th>It has been demonstrated that congenital nevi with an expected diameter of 20 cm or smaller almost never leads to malignant deterioration in childhood.</th>
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<td>A1; Krengel 2006</td>
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<tr>
<th>Level 1</th>
<th>It has been demonstrated that the risk of melanoma in a giant nevus is smaller than 5% lifetime risk but in 50% of cases already develops before the age of five.</th>
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<td></td>
<td>A1; Krengel 2006; Kovalyshyn 2009; Price 2010</td>
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</table>

**Considerations**
Aside from an oncological dilemma, large CN and giant CN also form a cosmetic/psychosocial problem.

The treatment of giant CN needs to be tailored to the individual and requires consultation within a multidisciplinary team in a paediatric surgery centre. Regular follow-up with inspection and palpation is also recommended after intervention, because almost no technique is able to remove 100% of melanocytes and melanomas may also develop in deeper layers and in unaffected skin.

The website of the patient association Nevus Netwerk Nederland (NNN) is www.nevusnetwerk.nl.

### 3.1.3. Screening of persons with a genetically increased risk of melanoma (familial melanoma)
(consensus-based text)

With a genetically elevated risk, a distinction must be made between the presence of:

a) high risk melanoma-associated gene mutations: familial melanoma/Familial Atypical Multiple Mole-Melanoma syndrome (FAMMM syndrome, OMIM 155601). This also includes the category of families who satisfy the definition of familial melanoma on clinical grounds but who have not been found to have a melanoma-associated mutation or who have not (yet) undergone DNA research.

b) clustering of multiple low risk gene mutations or gene variants

**a) High risk gene mutations**

**Literature discussion**

High risk mutations can be detected in 40% of families where there are three or more melanoma patients in a family (in the same bloodline) [Goldstein 2006]. Definitions vary worldwide based on the chance of finding mutations [Leachman, 2009].

For the Netherlands, the definition of familial melanoma/FAMMM syndrome has been formulated as follows: three or more melanomas, of which two in first-degree relatives, or three melanomas of which two tumours are allowed to occur in the one individual (the affected persons must then also be first-degree relatives). Some reserve the term FAMMM syndrome or “hereditary” melanoma for the 40% of families in which a gene mutation has in fact been detected.

consanguinity as referred to in genetics (differs from legal consanguinity)

1st degree relatives: parents, children, brother and sisters

2nd degree relatives: grandparents, grandchildren, uncles and aunts, nephews and nieces

3rd degree relatives: cousins, great grandparents, great grandchildren, great uncles, great aunts
High risk mutations largely involve mutations in the CDKN2A gene; CDK4 mutations have not yet been discovered in the Netherlands. Most mutations concern mutations in exon 2 of the CDKN2A gene so that an amino acid change usually occurs in both the coding protein p16 and the protein p14arf. Due to a founder population in the Leiden area, a deletion in exon 2 of the CDKN2A gene (P16 Leiden deletion) is relatively common. Approximately 10% of all melanomas occur in a familial setting, in which a CDKN2A mutation is in fact present in approximately 40% of cases. The melanoma risk for gene carriers of these mutations is strongly elevated, the lifetime risk increases to 70% at 80 years of age [Bishop 2002]. The lifetime risk of CDKN2A mutation carriers at multiple primary cutaneous melanomas is 40%. Patients with three to five melanomas are regularly seen in this setting [van der Rhee, 2011]. An increased risk of pancreatic cancer is also seen in families with a P16 Leiden deletion in the Netherlands, the lifetime risk of this is 17-20%, on average around the age of 50 [Vasen 2000]. This combination is also known as melanoma pancreatic cancer syndrome, (OMIM 606719). Due to the elevated risk of pancreatic cancer, a periodic check-up of the pancreas by means of annual MRI(CP) and/or ultrasound endoscopy may be considered from 45 years of age. The value of surveillance has not been established, and this monitoring should therefore take place within a study context in a specialised centre.

An indication for screening of the skin once or twice per year by a dermatologist applies to first-degree family members of patients with melanoma from families in which a CDKN2A mutation occurs and from families in which the definition of familial melanoma/FAMMM syndrome has been satisfied on clinical grounds. There is no evidence that death from melanoma is reduced by periodic screening but thinner tumour thicknesses are reported with screened family members [Vasen 1989; Hansson 2007; Masri 1990]. Second-degree relatives also have an increased risk of melanoma because sometimes a child develops a melanoma before his/her parent. This appears to occur in 30% of second-degree relatives in CDKN2A-positive families who develop a melanoma in the course of their life. The lifetime risk of second-degree relatives is 25%, in which 30% develop their melanoma while they are still second-degree relatives. The lifetime risk of melanoma for second-degree relatives is therefore approximately 8%, comparable to having 5 or more atypical nevi, or more than 100 banal nevi, for which relative indications apply for screening and in which instructions for self-examination are recommended [Van der Rhee J, 2011]. The risk of melanoma for second-degree relatives of CDKN2A-negative families is unknown, but probably lower than CDKN2A-positive families.
Figure 1: Policy familial melanoma

CDKN2A mutation in family?

Yes

Carriers mutation

1st degree relative to Centre for Clinical Genetics (pre-symptomatic diagnosis)

Pancreatic screening from age 45

Surveillance 1 – 2 times a year plus 1st and 2nd degree relatives from age 12 and 20, respectively.

No or unknown

High risk’ family with ≥ 3 melanoma patients, pancreatic carcinoma, < 40 years, multiple melanoma

‘Low risk’ family, 2 melanoma cases, only 2nd degree, higher age, no pancreatic carcinoma

Surveillance 1 – 2 times a year plus 1st degree relatives from age 12

Instructie voor zelfonderzoek, cave andere indicatie voor screening bijvoorbeeld Atypische Nevi!

Conclusions

Level 3

There are indications that CDKN2A mutation carriers have a strongly elevated risk of multiple melanomas.

B; Van der Rhee 2011

Level 2

It has been demonstrated that first-degree relatives of melanoma patients in families with familial melanoma/FAMMM syndrome have a strongly elevated risk of melanoma; as a result there is an indication for lifelong screening of the skin from 12 years of age by a dermatologist.


Level 3

There are indications that gene carriers of a CDKN2A mutation, especially the p16 Leiden variant, have an elevated risk of pancreatic cancer.

C; Hille 1998, Vasen 2000, de Snoo 2008
Considerations:

New in this guideline is that the following situation is referred to as possible familial melanoma:
1) A family with two first-degree relatives with melanoma, of which at least one under the age of 40 at the time of diagnosis,
2) The presence of three melanomas or more in one person and
3) A family with two first-degree relatives with melanoma, and a family member with pancreatic cancer (on the same side of the family).

Families that satisfy the following criteria should be referred to a clinical genetics centre for counselling and possible DNA diagnostics:

- Three or more invasive melanomas, of which two in first-degree relatives (= familial melanoma)
- Two first-degree relatives with invasive melanoma in which one of the patients has multiple melanomas (= familial melanoma)
- Two first-degree relatives with invasive melanoma, of which at least one under the age of 40 at the time of diagnosis (= possible familial melanoma)
- The presence of three invasive melanomas or more in one person (= possible familial melanoma)
- Two first-degree relatives with invasive melanoma and one family member with pancreatic cancer (on the same side of the family) (= possible familial melanoma)

For DNA testing for gene mutations, one of the patients with melanoma must be tested first. Only if there is a CDKN2A in the family is it possible to offer pre-symptomatic DNA diagnostics to all members of that family. Carriers of a CDKN2A mutation (p16 mutation) have an increased risk (lifetime risk: 15-20%) of developing pancreatic cancer. Research has shown that surveillance with annual MRI (CP) and/or ultrasound endoscopy can be used to detect precursors of pancreatic cancer or early stages of pancreatic cancer (Harinck 2010, Vasen 2011). The value of surveillance (in terms of improved survival) has not been established and this examination should therefore be performed within a research context in a specialised centre by specialists with expertise in this area (gastroenterohepatology specialist, radiologist).

b) Clustering of multiple low risk gene mutations or gene variants

Literature description

Low risk genes are currently being discovered at great speed by the so-called genome-wide SNP association studies in sporadic patients with melanoma [Bishop, 2009]. Melanoma-associated mutations (or more so genetic ‘variations’ because they occur frequently) are common in pigment genes. As yet, these low risk genes currently do not have consequences for clinical practice. It was already known that having one or two variants in the melanocortin 1 receptor MC1R gene is associated with an increased risk of melanoma with an RR of 1.42-2.45 [Raimondi, 2008; Demenais F, 2010]. According to a meta-analysis, having one or more variants in the MC1R gene results in a double melanoma risk for CDKN2A mutation carriers [Fargnoli MC, 2010]. Research is currently being performed to see if clustering of variations in low-risk genes is the reason for melanoma in families in which there is no clear association with the high risk CDKN2A gene, such as families with at the most two melanomas.

Conclusion

The guideline development group is of the opinion that screening for low-risk genes is currently not worthwhile.

D; Expert opinion
CH4 TNM CLASSIFICATION

4.1 Stage classification (consensus-based text)

Recommendation

The guideline development group is of the opinion that the AJCC stage classification (version 2009) should be used in the Netherlands.

Literature discussion

In 2009, a new AJCC classification and staging system was published on the basis of data from more than 30,000 patients with stage I, II and III melanomas and almost 8,000 patients with stage IV melanomas, collected over 20 years in 17 large melanoma centres, spread over the whole world [Balch 2009]. The new staging already came into effect in the United States at the start of 2010.

Table 1 shows the TNM classification and Table 2 the AJCC staging system [Balch 2009].

Figure 1 from the publication of the new staging system is illustrative for the survival associated with different stages [Balch 2009].

New in the classification is the use of the mitosis index with T1a and T1b (primary melanomas with a Breslow depth of 1mm or less). This mitosis index was found to provide supplemental prognostic information in the multivariate analysis, therefore surpassing the level according to Clark. The Clark level has therefore disappeared from the classification. Finding one mitosis in the dermal component of a melanoma means at least stage T1b for the stage classification.

Another important difference is the definition of the extent to which the lymph nodes are affected in the N1 and N2 stages. In stage N1a and stage N2a this concerns micrometastases, as can be determined using the sentinel node procedure. This means that the sentinel node procedure must be conducted for full staging, because it is the only way to detect micrometastases. Patients with one small metastasis in one sentinel node are now included in the classification with N1 and end up in stage III. The sentinel node biopsy is recommended in patients with stage IB or higher. See ‘Indication for sentinel node procedure’ for further details.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Tumour thickness (mm)</th>
<th>Ulceration/mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Tis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</table>
| T1 ≤ 1.0      | a: Without ulceration and mitoses < 1/mm\(^2\)  
                 b: With ulceration of mitoses ≥ 1/mm\(^2\) |
| T2 >1.0-2.0   | a: Without ulceration  
                 b: With ulceration |
| T3 2.0-4.0    | a: Without ulceration  
                 b: With ulceration |
| T4 ≥ 4.0      | a: Without ulceration  
                 b: With ulceration |
| N0             | 0                    | N/A                |
| N1 1          | a: Micrometastasis\(^1\)  
                 b: Macrometastasis\(^2\) |
| N2 2-3        | a: Micrometastasis\(^1\)  
                 b: Macrometastasis\(^2\)  
                 c: In-transit metastases or satellites without affected lymph nodes |
| N3             | 4 or more lymph nodes affected, or conglomerate of node metastases or in-transit metastases and / or satellites with affected nodes |
| M              | Location of the metastases | Serum LDH |
| M0             | No distant metastases | N/A |
| M1a            | Skin, subcutaneous or distant node metastases | Normal |
| M1b            | Long metastases | Normal |
| M1c            | All other visceral metastases or any form of elevated distant metastasis | Normal |

Abbreviations: N/A, not applicable; LDH, lactate dehydrogenase.  
Micrometastases diagnosed after sentinel node procedure or elective node dissection.  
Macrometastases defined as clinically detectable lymph node metastases (histologically confirmed).
### Table 2 Staging for Melanoma [Balch 2009].

<table>
<thead>
<tr>
<th>Clinical staging</th>
<th>AJCC</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Pathological staging</th>
<th>AJCC</th>
<th>T</th>
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<tbody>
<tr>
<td>0 IIA T1a</td>
<td>N0</td>
<td>M0</td>
<td></td>
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<td>0 IA T1a</td>
<td>N0</td>
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<tr>
<td>0 IB T1b</td>
<td>N0</td>
<td>M0</td>
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<td>0 IA T1a</td>
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<td>0 II A T2a</td>
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<td>0 IA T1a</td>
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<td>0 II A T2b</td>
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<td>0 IA T1a</td>
<td>N0</td>
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<td>0 II B T3a</td>
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<td>M0</td>
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<td>0 IA T1a</td>
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<td>0 II C T4a</td>
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<td>0 IA T1a</td>
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<td>0 III All T</td>
<td>N &gt; N0 M0</td>
<td>III A T1-4a</td>
<td>N1a</td>
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<td>0 IA T1a</td>
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<td>0 III A T1-4a</td>
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Clinical staging: histology of the primary melanoma and clinical examination/testing for metastases. Pathological staging: histology of the primary melanoma and histological information on the regional lymph nodes after sentinel node procedure and any completion lymphadenectomy.
Figure 1 Survival curves of the different stages from the AJCC database [Balch 2009].

Conclusion

Level 1

It has been demonstrated that the AJCC melanoma staging classification published in 2009 results in an improved subdivision into prognostic subgroups compared to earlier melanoma stage classifications.

A1 Balch 2009

Considerations

The new staging is preferably implemented everywhere on 1 July 2012 in all hospitals and cancer registries. The implementation date must be noted for comparison purposes between facilities. A registration possibility needs to be available to indicate if the patient has (not) undergone a sentinel node procedure. Patients without clinically palpable metastases are noted as CN0 and after a negative sentinel node procedure as PN0. Patients without palpable metastases who are not undergoing a sentinel node procedure are also marked as CN0.

In patients with clinical stage I/II melanoma who decide not to undergo a sentinel node procedure, survival graphs of the AJCC group may be used for prognosis. These can be found on the internet at: http://www.melanomaprognosis.org/ [Soong 2010].
CH5 DIAGNOSTICS

5.1 Localised disease (consensus-based text)

Dermatoscopy

Recommendations

Dermatoscopy should have a permanent role in the clinical diagnosis of pigmented skin abnormalities, such as: distinction between melanocytic lesions and non-melanocytic pigmented lesions, symptomatic melanocytic lesions (itchiness, stinging pain, bleeding), changing clinically atypical nevi, melanocytic lesions that look different compared to surrounding moles (“ugly duckling”), de novo melanocytic lesions over the age of 35.

It is recommended that inexperienced physicians become skilled in this technique before clinical application.

Literature discussion

Does dermatoscopy increase the accuracy of clinical diagnosis?

Dermatoscopy has become indispensable in the diagnoses of pigmented lesions. It is a non-invasive technique in which a ten times enlarged image is obtained of a pigmented lesion. The required equipment is available in pocket format. Multiple meta-analyses are available in which the diagnostic accuracy of dermatoscopy is studied, all with the same conclusion: dermatoscopy improves the diagnostic accuracy compared to naked eye diagnostics, but especially with trained users [Mayer 1997, Bafounta 2001, Kittler 2002; Vestergaard 2008].

This field is still developing at full steam. There are still articles appearing in which new criteria for dermatoscopy are reported for special locations, such as the soles of the feet and for new diagnoses e.g. spitz nevus and pigmented basal cell carcinoma.

Digital storage of dermatoscopic images is now also easier to realise on a technical level (serial dermatoscopy), for which there is an application in the periodic follow-up of patients with multiple atypical nevi and in members of families with familial melanoma/FAMMM syndrome. Serial dermatoscopy must be supported with total body photography/mole-mapping in order to be able to find the nevi in the context back again [Rice 2010; Salerni 2011].

Conclusion

<table>
<thead>
<tr>
<th>Level 1</th>
<th>It has been demonstrated that dermatoscopy significantly improves the diagnostic accuracy in the evaluation of pigmented lesions.</th>
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</table>

Considerations

Similar to ‘naked eye’ evaluation, the experience of the clinician is crucial when it comes to dermatoscopy: in experienced hands (i.e. physicians who are demonstrably trained and experienced to this end), dermatoscopy leads to an increase in diagnostic capability; dermatoscopy by inexperienced clinicians leads to a reduction in clinical accuracy [Binder 1997]. It has also been shown that the systematic application of dermatoscopy by dermatologists experienced in this technique substantially reduces the number of benign pigmented skin abnormalities unnecessarily removed (and therefore the specificity of dermatoscopy) [MacKie2002].

More recent publications confirm these considerations, although one author will emphasise the improvement in sensitivity and the other the improvement in specificity. Recent developments can be summarised in two reviews by authorities in the area of dermatoscopy [Guitera 2011; Braun2009]. For your information: Lee and Hirokawa [Lee2010] take a critical look at dermatoscopy.
5.2 Diagnostic excision (consensus-based text)

**Recommendations**

It is recommended to submit every surgically removed pigmented lesion or uncertain benign skin tumour for histopathological diagnosis.

It is recommended to photograph as many pigment lesions removed for diagnostic reasons as possible and to make those photos available to the pathologist. It is therefore recommended to facilitate this (ICT/EPD).

**Literature discussion**

**Histological analysis**

For a number of melanomas, there is no suspicion at all prior to histological analysis that the skin abnormality concerns a melanoma. The prevalence of melanoma in two reported series of excised skin lesions in which melanoma was not suspected was approximately 0.5% [Izikson 2002; Collas 1999].

The added value of photographic documentation (consensus-based text)

There are studies that show that photographic documentation of the lesion, preferably also accompanied by dermatoscopic images, substantially improves diagnosis by the pathologist [Bauer 2001; Ferrera 2009; Ferrera 2004; Ferrera 2005; Ferrera 2008; Zalaudek 2004].

In the diagnostic approach of a skin lesion, an excision biopsy should be performed in general if melanoma is suspected. The shave biopsy is advised against when melanoma is suspected, because it may complicate measurement of the Breslow depth. In principle, puncture for cytological analysis and punch and incision biopsies are not applicable if lentigo maligna is suspected, or if there is doubt about progression to invasive growth in a lentigo maligna, a punch biopsy may be chosen. Histopathological analysis is necessary in any case. A number of arguments can be put forward for performing an excision biopsy. Firstly, it is important that the pathologist is able to evaluate the entire lesion in order to arrive at a diagnosis. Incomplete primary intervention may make evaluation of a number of prognosis-determining factors, such as the Breslow depth, less reliable. Furthermore, cutting through the tumour may cause contamination of surrounding tissue. For cosmetic or functional reasons, it may be decided to perform an incision biopsy nonetheless in the case of a large lesion. It is preferable to stitch the wound intracutanously or using very small stitches; this may be of benefit if a re-excision follows. The wound may also be left open until the definitive diagnosis is known.

The following factors are important in the diagnostic intervention:

**Anaesthesia**

Local infiltration anaesthesia amply surrounding the lesion, e.g. field block. Regional anaesthesia is also a good choice.

**Direction of the excision**

The ability to close a later re-excision wound should always be taken into account. The elliptical excision biopsy is performed in the direction of the regional lymph node station. The direction may deviate in some cases, such as at the location of the joints. For tumours on the extremities, it is desirable to make the incision in the length-wise direction on the extremity. The possibility of a re-excision with lymph node dissection ‘en block’ should be considered in locations nearby lymph node stations. If a melanoma is located in the face or joints, the specialist may deviate from the length-wise incision.

**Margin of the surrounding skin**

The guideline development group recommends a tumour-free margin of 2 mm for excision of a lesion where melanoma is suspected. Directly performing a therapeutic excision with ample margin is advised against for two reasons. The clinical diagnosis melanoma is not confirmed by microscopic analysis in approximately a third of cases. Many abnormalities that are not melanoma would therefore be removed in an unnecessarily ample manner.

The margin of the therapeutic excision is determined by the Breslow depth, and this cannot be clinically estimated in a reliable way.
Depth of the excision
The diagnostic excision is performed through to the subcutis, in which the underlying fascia or other structures are not unnecessarily exposed.

Undermining
Undermining the edges of the wound after a diagnostic excision is generally not necessary and should be avoided where possible.

Conclusions

<table>
<thead>
<tr>
<th>Level 3</th>
<th>There are indications that the prevalence of melanoma in excised skin lesions in which melanoma is not suspected is approximately 0.5%.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C; Izikson L, 2002; Collas H, 1999</td>
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</table>

<table>
<thead>
<tr>
<th>Level 2</th>
<th>It is plausible that accurate documentation of the clinical findings, in word and clinical image, has added value for the histopathological diagnosis of pigment lesions.</th>
</tr>
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<tr>
<td></td>
<td>B; Ferrera, 2009; Bauer, 2001; Zalaudek I, 2004; Ferrera, 2004</td>
</tr>
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5.3 Primary melanoma with suspected metastases (editorial update)
If locoregional lymph node metastasis is suspected, the diagnostic approach of the suspected skin lesion is in principle the same: an excision with a margin of 2 mm. In the case of suspected satellites or in-transit metastases, a biopsy may be taken of one of these lesions to verify the diagnosis.

Pathology request form (editorial update)
The following information needs to be stated on the request form when submitting material for histopathological analysis:
- localisation of the lesion
- clinical description of the lesion
- clinical diagnosis
- nature of the intervention
- excision margin
- (schematic) drawing with the location of the marking, if marked
- the clinical question

5.4 Sentinel node procedure (Evidence-based text, clinical question 5)

Recommendation:
- It is recommended to perform the sentinel node procedure in patients with a melanoma stage IB and higher in order to optimise staging of patients and the provision of information to patients in relation to the prognosis.
- It is recommended not to perform a sentinel node procedure in patients with a melanoma stage IA.

The guideline development group is of the opinion that it is doubtful if an additional lymph node dissection in patients with small (<0.1 mm) or subcapsular metastases in the sentinel nodes is worthwhile. Not performing an additional lymph node dissection may therefore be considered, as well as including patients in a trial to this end.

Literature discussion
The concept of sequential progression of metastases in the lymph node system has been demonstrated for melanoma [Reintgen D, 1994]. Knowledge of the tumour status of this system is achieved by removing the lymph node (sentinel node, first echelon node) via a small surgical intervention. In this manner, metastases can be detected before the node becomes palpable. This enables important prognostic information to be obtained. Morton and Cochran – who shaped the
modern sentinel node concept – define a sentinel node as a lymph node in which the primary melanoma directly drains into: the first echelon node [Morton DL, 1992]. Various researchers have developed variations on this definition, often prompted by the technique used and the specialty area the researcher has come from [Nieweg OE, 2001; Morton DL, 1999; Balch CM, 1999; Thompson JF, 2000]. The guideline development group prefers to use Morton's definition because it explains the concept of sequential dissemination well [Nieweg OE, 2001].

In practice, the first node visible on the scintigram is considered the sentinel node and that also applies to any other nodes to which a lymph duct directly runs. Multiple sentinel nodes may therefore be found in different lymph node regions.

**Technique**

The technique of the sentinel node procedure in patients with melanoma has gone through rapid development [Nieweg 1998; Nieweg 2001; Cochran 2000]. The biopsy usually takes place after the diagnostic excision of the primary tumour. Preoperative lymphoscintigraphy provides an insight in the pattern of lymph drainage. A radioactively marked colloidal protein is administered at the location of the melanoma. Scintigraphy shows the lymph duct that connects the skin zone of the melanoma with the node(s) to which it drains. Drainage has been found to quite variable and lymphoscintigraphy may show sentinel nodes that are unexpected node regions or even outside node regions [Uren 2000; Roozendaal 2001; Sumner 2002]. The sentinel node procedure is generally combined with the therapeutic excision of the primary tumour. A blue dye and gamma ray detector are used in the operation to detect the sentinel node(s). The node is found in almost all cases [Pijpers 1997; Morton 1999; Morton 2006; Harlow 2001]. Initially this appeared to be a sensitive method to detect lymph node dissemination. With a longer follow-up, false negative percentages for the sentinel node procedure of 9-27% have been reported [Vuylsteke 2003; Estourgie 2003; Clary 2001; Harlow 2001; Cascinelli 2000; Nieweg 2001]. False negative findings may be caused by variability in the lymph flow [Kapteijn 1996] due to incorrect technique and through lack of experience. How long the learning phase needs to be before a sentinel node biopsy can be performed is unclear [Tanis 2002]. While the sentinel node procedure is a minimally invasive technique, possible adverse effects of the sentinel procedure should be taken into account. Complications occur every now and then, such as (mild) lymphoedema (approximately 10%), lymph fistula (<2%) or an allergic reaction to the dye used (<0.5%) [Estourgie 2003].

**Indication**

The sentinel node procedure increases the accuracy of staging [Essner 1999; Dessureault 2001]. Recent studies have made it clear that the tumour status of the sentinel node is an important prognostic factor in patients with melanoma who present without clinically evident metastases [Morton 2006; Vuylsteke 2003; Estourgie 2003; Gershenwald 1998; Wagner 2000]. Studies performed in the Netherlands have found that survival after five years is approximately 90% if the sentinel node is tumour-free and approximately 65% if there is metastasis. [Vuylsteke 2003; Estourgie 2003; van Akkooi 2006]. The importance of the sentinel node for staging is great and this has been taken into account in the current staging system (see AJCC).

It is assumed that treatable lymph node metastasis with curative intent precedes haematogenous dissemination. This reasoning contains the potential value of the sentinel node procedure, namely the removal of micrometastases. The Multicenter Selective Lymphadenectomy Trial I tries to answer this. In this multicentre randomised study, amble excision only is compared to ample excision and a sentinel node procedure. This sentinel node procedure was directly followed by a lymph node dissection if micrometastasis was found, while in the observation arm a lymph node dissection was performed if a regional lymph node recurrence occurred [Morton 2005; Morton 2006]. Patients with a melanoma thicker than 1 mm were included in this study. Patients with thinner melanomas were not studied given the small chance of lymph node metastasis [Balch 1980]. In the 2006 analysis, 'only' the 1269 patients with a primary melanoma of 1.2-3.5 mm were described. The melanoma-specific 5-year survival was the same for both groups (87.1% (95% CI 85.8-88.4%) versus 86.6% (95% CI 85.0-88.2%)). In a subgroup analysis, a better 5-year survival was found for patients with a positive sentinel node compared to patients who developed a lymph node recurrence after observation (72.3% (95% CI 67.7-76.9%) versus 52.4% (95% CI 46.5-58.3%)). This large difference in survival is unexpected, given no difference in survival was found in the total study population. Detection bias probably does play a role here. After all, patients in the observation arm were not all checked for lymph node (micro)metastasis while a proportion of them does live with this (unnoticed). This group of patients has not been included in the subgroup analysis, so that a distortion in survival in favour of the patients with a positive sentinel node may develop. The disease-free 5-year survival was defined in the MSLT as
survival without recurrence, at any location. This disease-free survival was better for the group with the sentinel node procedure (78.3% (95% CI 76.7-79.9%)), compared to the control group (73.1% (95% CI 71.0-75.2%)) [Morton 2006]. The manner in which disease-free survival is defined has also been extensively criticised in literature; because the most important location of the recurrence is removed by the intervention itself, therefore leading to bias by trial design. A node recurrence should be excluded from the definition of recurrence or the outcome should be a distant recurrence [Thomas 2009].

Four other studies compared patients treated before introduction of the sentinel node procedure, with patients who were treated after introduction of the sentinel node procedure as standard treatment in a particular institute [Starz 2004; Gutzmer 2005; Koskivuo 2007; Leiter 2010]. One study compared a cohort of patients with sentinel node procedure, with a cohort of patients without sentinel node procedure, in which half the patients participated in the MSLT [van Polls 2005]. In three studies, no difference was found in the melanoma-specific survival [Gutzmer 2005; Koskivuo 2007; Leiter 2010]. One study found no difference in general survival, when a correction was made for gender, age, tumour location and thickness [Starz 2004]. In relation to recurrences, there was no difference between the treatment groups concerning local or in-transit recurrences in any of the studies, but of course in all studies lymph node metastases were more common in the group who did not undergo a sentinel node procedure [Gutzmer 2005; van Poll 2005; Koskivuo 2007; Leiter 2010]. Three studies found no difference in distant metastasis [Gutzmer 2005; Koskivuo 2007; Leiter 2010]. One study did find a difference in distant metastases, with less metastases in the sentinel node procedure group, in which a correction was made for gender, age, tumour location and thickness [Starz 2004]. However, there was a large difference in follow-up in this study: a median follow-up of 45.5 months in the sentinel node procedure group versus 95 months in the group receiving standard treatment. A difference in follow-up kept benefitting the sentinel node procedure group, and could explain the difference in distant metastases found in this study.

The generally accepted management plan is to perform an additional lymph node dissection in patients who have undergone a sentinel node procedure and where the sentinel node is positive (on haematoxylin-eosin staining or histochemistry). Given a survival advantage has not yet been demonstrated in studies randomising lymph node-positive patients (direct dissections versus a wait-and-see approach), this recommendation is not based on solid scientific evidence. The earlier mentioned subgroup analysis, in which a better 5-year survival was found for patients with a positive sentinel node, compared to patients who developed a lymph node recurrence after observation, seems to be distorted by detection bias [Morton 2006]. There is currently a randomised trial (MSLT II trial) researching the value of additional node dissection. Different studies have shown that patients with minimal metastasis or small subcapsular metastases have a very small chance of additional node metastases in non-sentinel nodes. Especially in patients with such loose tumour cells or very small micrometastases, an additional node dissection does not seem to provide any benefits. Survival of such patients is the same in patients with tumour-free sentinel nodes compared to historic control groups [Akkooi 2008, de Wilt 2008]. In the EORTC Minitub trial, patients with such limited metastases in the lymph nodes are registered if they do not undergo additional node dissection. It will still be a number of years before it is clear what the local recurrence percentage is in this patient group.
Conclusions

Level 2
It has been demonstrated that patients with metastases in the sentinel node(s) have a poorer prognosis than patients in whom metastases are not found.

A2 Morton 2006; B Gutzmer 2005; Koskivuo 2007; Leiter 2010

Level 2
It has not been demonstrated that the sentinel node procedure directly followed by lymph node dissection if metastasis is detected, improves the disease-specific survival in patients with a primary melanoma compared to observation and lymph node dissection if a regional lymph node recurrence develops.

A2 Morton 2006; B Gutzmer 2005; Koskivuo 2007; Leiter 2010

Considerations

It has been demonstrated that patients with metastases in the sentinel node(s) have a poorer prognosis than patients in whom metastases are not found. The sentinel node procedure is highly suited to patients who would like to be informed as much as possible about their prognosis and leads to a correct AJCC staging. The value of an additional lymph node dissection in patients with metastases in the sentinel node has not been conclusively demonstrated. This means that a completion lymph node dissection does not automatically need to follow a positive sentinel node. In patients with small micrometastases or subcapsular metastases, metastases are rarely found in other lymph nodes. The benefits and disadvantages of a lymph node dissection must be discussed with the patient and the patient must preferably be included in a trial for this purpose.

If new studies show that an effective adjuvant treatment is available for patients with regional metastatic melanoma, this may be reason to revise the indication for the sentinel node procedure.

It is recommended to discuss the sentinel node procedure and a possible lymph node dissection at least twice with the patient, with at least a week in-between. The possibility of a second opinion may be put forward in the first conversation. The treating physician can organise a second opinion if requested. It is recommended to check if the patient has understood the information and if they need help with processing and decision-making by informing the patient about contact with fellow patients via patient associations or otherwise.

It is preferable, due to logistic and patient-friendly reasons, to allow the sentinel node procedure to take place during re-excision.

The sentinel node procedure in the head-neck region has more variations and complications than at other locations. It is therefore recommended to only perform a sentinel node procedure in the head-neck region if there is sufficient experience and knowledge regarding potential complications of the intervention.

5.5 Additional examination/testing

(Evidence-based text, clinical question 7: influence of additional examination/testing on prognosis

Recommendations

It is recommended that additional imaging (CT, PET or PET-CT) is not performed in the case of stage I, II and IIIA.

For good staging, it is recommended to perform complete imaging of the breast, abdomen and pelvis (preferably CT) in the case of stage IIIB, IIIC and not to repeat this as a standard.

In the case of stage IV, it is recommended to perform complete imaging of the breast, abdomen and pelvis (preferably CT) in the case of stage IV and to repeat this (depending on the management plan).
For staging, it is recommended to perform a CT instead of PET or PET-CT, because PET or PET-CT does not provide added value in the majority of cases.

In the case of pathologically enlarged lymph nodes, it is preferable that an ultrasound with ultrasound-guided puncton (if required) is performed.

It is recommended that asymptomatic patients are not routinely screened for cerebral metastasis.

**Literature discussion**

**Imaging**

With many types of cancer, staging takes place on the basis of which the therapy plan is determined. The question is whether it is also worthwhile for the prognosis and therapy of melanomas to perform additional imaging to find (subclinical) metastases. In answering this question, it is important to distinguish between stage I/II and stage III/IV patients. Forms of imaging currently available are ultrasound, MRI, CT, PET and PET-CT.

**Melanoma stage I and II**

Two systematic reviews have been published on the value and diagnostic accuracy of the PET or PET-CT scan that summarise the data of ten and twenty-two studies respectively [Krug et al., Xing et al.]. In the first review, a pooled sensitivity is reported of 60% (95% CI 54-60); data on the specificity and likelihood ratio’s (LR) are not reported. The second more recent review has calculated a sensitivity of 30% (95% CI 12-55) and a specificity of 96% (95% CI 87-99) for PET and a sensitivity of 11% (95% CI 1-50%) and specificity of 97% (95% CI 78-100) for PET or PET-CT. However, there is only one study available for the calculation for PET or PET-CT. If analyses are limited to studies in which the sentinel node biopsy is used as reference standard to detect regional lymphogenous metastasis, the positive LR is 1.33 (95% CI 0.66-2.68) and the negative LR 1.00 (95% CI 0.83-1.19). The likelihood ratio is a measure for the information that adds a test to the information already available regarding the prevalence of a disease. The closer the likelihood ratio lies to 1.00, the less the result of the diagnostic test says something about the presence of the disease. A number of other small studies that have not been incorporated in the abovementioned reviews confirm the picture of limited value of PET or PET-CT in stage I and II patients. They report a low sensitivity (6-22%), high specificity (87-100), and non-significant likelihood ratios (LR + 1.5-2.7 and LR- 0.87-0.92) [Cordova 2006, Keil 2007, Klode 2010, Singh 2008].

The role of ultrasound in the evaluation of locoregional lymph node stations in stage I and II patients has been researched in five studies and one review. One of these [Kahle et al.] only reports the number of nodes that can be identified by ultrasound compared to scintigraphy, namely 85.4%. The remaining articles studied the diagnostic accuracy of ultrasound for the recognition of positive lymph nodes compared to the sentinel node procedure [Hocevar 2004, Sanki 2009, van Rijk 2006, Voit 2010, Xing 2011]. The sensitivity varies strongly ((23.2-71.4), the values of specificity and positive likelihood ratio are more consistent (80,1-97,3 en 2,3-8,6). The systematic review by Xing et al., reported a pooled sensitivity of 60% (95% CI 33-83) and a pooled specificity of 97% (95% CI 88-99). What is noticeable are differences in the definition of an abnormal node structure on the ultrasound used in the different studies. This is probably the explanation for the large differences in sensitivity. There is only very limited data available regarding the significance of other imaging modalities (MRI, CT scan and SPECT/CT) for stage I and II patients. There was one study identified regarding MRI that researched the diagnostic value for cerebral metastases [Fogarty 2006]. Of the 100 patients included in this study, fifteen were stage I-II. Cerebral metastases were found in eleven patients, all stage IV. No cerebral metastases were found in patients with stage I-II, also not in patients with complaints suggestive of possible cerebral metastases. For the detection of regional and distant metastasis using CT, the review by Xing et al. described a pooled sensitivity of 9% (95% CI 1-52) and 51% (95% CI 24-76) respectively and a pooled specificity of 92% (95% CI 50-99) and 69% (95% CI 30-92) respectively.

**Melanoma stage III and IV**

In the evaluation of the role of additional imaging in stage III and IV patients, the CT scan, PET scan and PET-CT scan are the most relevant. There are two overview articles available for the comparison of the diagnostic accuracy of PET (or PET-CT) and CT in literature [Facey 2007; Xing 2010]. The British Health Technology Assessment (HTA) report by Facey is less useful for this given it solely provides a description of the available literature up to August 2005 without meta-analysis [Facey
2007]. Only a small number of included studies directly compared PET and CT. The reported diagnostic accuracy of PET was poor (sensitivity of less than 20%) for the staging of regional lymph nodes in stage III melanoma. A comparison with CT was not reported for this indication. For detection of distant metastases in stage IV melanoma, the results were highly diverse for PET; the sensitivity varied from 40% to 100% [Facey 2007]. The sensitivity was low with small lesions in particular. One study reported better results with PET compared to conventional imaging (including CT and MRI), with more changes in the treatment plan [Gulec 2005].

In their review, Xing et al. included 8 studies that directly compared CT with PET and/or PET-CT within the framework of staging in stage IV melanoma [Swetter 2002, Finkelstein 2004, Brady 2006, Reinhardt 2006, Romer 2006, Iagaru 2007, Pfannenberg 2007, Veit-Haibach 2009]. A separate meta-analysis was not performed. For the detection of distant metastases, no significant difference was found between the median sensitivity and specificity of CT (51% (95% CI 24-76%) and 69% (95% CI 30-92%)), PET (74% (95% CI 51-88%) and 75% (95% CI 45-91%)) and PET/CT (80% (95% CI 76-93%) and 87% (95% CI 54-57%).

Differently, studies mentioned above are methodologically weak due to the presence of so-called incorporation bias, i.e. distortion because the index test forms part of the reference test [Brady 2006, Reinhardt 2006, Romer 2006, Pfannenberg 2007]. These studies are therefore left out of consideration. In the study by Finkelstein et al., the diagnostic accuracy of PET was compared to that of conventional imaging (CT and MRI), but the results for CT could not be evaluated separately. The three qualitatively good studies are discussed separately below [Iagaru 2007, Swetter 2002, Veit-Haibach 2009].

Lagaru et al. reported a better sensitivity of PET and PET-CT compared to CT for the re-staging of melanoma (89.5% (95% CI 78.9-95.1), 89.3% (95% CI 78.5-95%) and 68.5% (95% CI 55.3-79.3)) respectively, but a poorer specificity (81.6% (95% CI 68.6-90.1), 88% (95% CI 76.2-94.4%) and 94.2% (95% CI 84.4-98.1%) respectively [Lagaru 2006]. These differences were not significant. For PET or PET-CT, the best results were achieved in patients with a stage IIIC or IV melanoma (sensitivity 100% (95% CI 82.4-100%) and specificity 83.3% (95% CI 55.2-95.3%)). However, no comparison between CT and PET or PET-CT was performed for these subgroups [Iagaru 2006].

On the basis of a non-comparative analysis, Swetter et al. reported a significantly higher sensitivity and specificity of PET (85% (95% CI 78-89) and 97% (95% CI 91-99%)) compared to CT (58% (95% CI 49-66%) and 70% (95% CI 51-84%)) for the detection of metastases [Swetter 2002]. On the basis of a direct comparison, the sensitivity of PET was also found to be higher than that of CT (81% versus 57%). However, specificity and confidence intervals were not reported for this direct comparison.

Veit-Haibach et al. did not find significant differences between PET and CT. A sensitivity of 38.5% (95% CI 14-68%) and specificity of 100% (95% CI 92-100%) were found in the detection of lymph node metastases with PET. A sensitivity of 23.1% (95% CI 5-53%) and specificity of 100% (95% CI 92-100%) were found for CT. Significant differences were also not found between PET and CT (sensitivity 33.3% (95% CI 9-65%) versus 25.0% (95% CI 5-57%); specificity 90.9% (95% CI 78-97%) versus 93.2% (95% CI 81-99%))[Veit-Haibach, 2009].

Bastiaannet et al. also did not find large differences between the sensitivity (86% versus 78%) and specificity (both 94%) for PET and CT [Bastiaannet 2009]. Confidence intervals were not reported. More distant metastases were found with PET than CT (133 versus 120; p=0.03). Especially the number of detected bone and subcutaneous metastases was significantly higher with PET than CT (27 versus 10, p< 0.0001; 11 versus 5, p=0.03, respectively). In a number of cases, PET and CT contributed to a change in treatment plan: 17% of the therapy changes were due to PET only, 4% due to CT only and 79% as a result of a combination of both.

**Effect on mortality**

No randomised studies have been found that have researched the effect of adding imaging to the initial staging of stage I-II patients. It is therefore unknown whether the addition of these techniques has an effect on patient survival.
## Conclusions

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<td><strong>Level 1</strong></td>
<td><strong>It has been demonstrated that PET or PET-CT has a moderate to high specificity, but a very low sensitivity for the detection of regional metastases in stage I-II patients. As a result, the power of PET or PET-CT as a detection or exclusion technique is very limited for this indication. In general, PET and PET-CT do not provide added value above CT in staging.</strong></td>
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<td><strong>Level 1</strong></td>
<td><strong>It has been demonstrated that ultrasound has a high specificity for positive regional lymph nodes.</strong></td>
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<td><strong>Level 3</strong></td>
<td><strong>There are indications that the chance that MRI detects cerebral metastases in patients with stage I-II is small, also in the case of suggestive symptoms.</strong></td>
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<td><strong>Level 3</strong></td>
<td><strong>There are indications that the sensitivity of ultrasound for positive regional lymph nodes is dependent on the echographic characteristics used to define an abnormal test, and that peripheral perfusion and/or loss of central ultrasound waves and/or ballooning has the highest sensitivity.</strong></td>
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<td><strong>Level 4</strong></td>
<td><strong>There is no evidence that the addition of imaging to initial staging improves patient survival.</strong></td>
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Considerations

Patient perspective
When imaging techniques are applied (X-thorax, CT, PET, PET-CT, MRI), the number of actual metastases will be small, while there is a high frequency of false-positive findings. This often leads to further investigation, which is rarely cost-effective, but causes agitation for the patient.
Stage IV patients have a much greater risk of cerebral metastases, but the routine screening of cerebral metastases in asymptomatic patients is not generally worthwhile due to the lack of therapeutic consequences in most cases.

Professional perspective
Ultrasound of the locoregional node stations may be helpful in identifying lymph node metastases. The precise diagnostic value cannot be defined well yet due to the lack of unanimity regarding the characteristics that determine which lymph nodes are pathological. A limitation of ultrasound is that interpretation of the imaging is very dependent on the experience of the ultrasound technician. After clear criteria are determined, ultrasound could start to play a role in the selection of patients for a sentinel node procedure if reliability in combination with cytology is found to be adequate.
The literature on PET and PET-CT is interpreted differently by guideline writers in Europe. The German guideline writers see a much greater role in literature on PET and PET-CT than the guideline development group in the Netherlands. The English guideline writers are pro-PET and PET-CT.

Cost effectiveness
CT has lower costs than PET-CT and is up with PET-CT and is currently more available.
The prevalence of distant metastases is low with the lower stages of melanomas (stage I, II and IIIA); this is important when evaluating whether imaging needs to be performed.
When making a choice, the additional cost of PET and PET-CT must be considered. PET or PET-CT is preferable in incidental cases. For example, when considering surgical resection of an isolated metastasis in a stage IV patient it may be important to exclude other distant metastases and to use the high sensitivity of PET or PET-CT for this.
Screening for cerebral metastases by means of an MRI in stage I, II and III patients is not necessary because the chance of intracerebral metastases in patients without complaints is minimal.

Organisational factors:
A limitation of PET or PET-CT is the availability of this modality in only a small number of hospitals

5.6 Unknown primary tumour (editorial update)

Incidence and diagnosis
Patients with melanoma present in approximately 3-5% of cases with a metastasis as first manifestation of the disease. In this case, the medical history will sometimes provide a probable diagnosis. There may have been a skin tumour that spontaneously disappeared with time. The primary melanoma has then probably regressed. It is also possible that the cause was removed previously as a skin tumour where melanoma was not suspected, without the true diagnosis being determined. For other patients, the medical history does not lead to an associated primary tumour being found.
Inspection of the regional skin and biopsy of suspicious lesions are indicated. In doing so, knowledge of the lymph drainage is used as a guide. The scalp and anus are known locations for a missed primary tumours. Additional examination/testing, such as ophthalmoscopy and endoscopy, rarely yields results and is not necessary. Half of metastases are located in a lymph node, usually in the axilla. Approximately 40% are located in the subcutis, the rest in the skin and internal organs. It is not necessarily a question of metastasis derived from a skin melanoma. Normal pigment cells also occur in the digestive tract and lymph nodes that turn malignant. In the case of melanoma metastasis in a neck lymph node, a primary mucosal melanoma of the upper airway and oesophagus must also be considered. Specific examination by an ophthalmologist and head-neck surgeon (ENT specialist or maxillofacial surgeon) is then indicated.
In contrast to what is often assumed, the prognosis of patients with an unknown primary tumour is not worse than that of patients with comparable metastases of a known primary tumour. Treatment with curative intent is indicated if it concerns tumour manifestations in the skin, subcutis or lymph nodes (see diagnosis of a local recurrence). Investigating visceral metastasis is usually not required here;
also in the case of visceral metastases, the tumour process will often be removed in order to prevent problems such as local ulceration, bleeding or nerve invasion. Limited visceral metastasis may also be treated surgically, especially if this is localised in the lung or digestive tract. While curative resection is rare, there is a small group of patients for whom this goal is a realistic possibility. In this case, careful staging is indicated (see radiotherapy treatment).

5.7 Systemic disease (editorial update)

**Literature discussion**

**Diagnostics and staging [Hwu, 2003; Balch, 2001]**

Haematogenous metastases are the initial location of recurrence in 10% of patients in whom the disease returns. Occasionally, a distant metastasis may be the primary presentation of a melanoma. In three-quarters of cases, distant metastasis occurs within three years after initial diagnosis of the primary tumour. Melanomas can metastasise to practically any organ or tissue. When haematogenous metastasis (stage IV) has developed, cure is virtually excluded. Systemic treatment of patients with metastatic melanoma is palliative. The median survival in various studies varies between five and eleven months, and less than 10% of patients achieves survival spanning several years or more. Various prognostic factors that may influence survival have been identified, such as location and number of metastases and serum LDH level.

On the basis of differences in prognosis in relation to survival, patients with a distant metastatic melanoma can be subdivided into three categories: patients with visceral metastases (M1a), with lung metastases (M1b), and with other visceral metastases and/or increased serum LDH (M1c).

In light of the above mentioned, additional clinical imaging is performed in a patient with indications for distant metastases in order to determine the extent of the metastasis. Initial laboratory analysis is performed with at least a serum LDH determination. Routine CT and MRI examination of the brains is not recommended with asymptomatic patients. The aim must be histological or cytological confirmation of the diagnosis, unless there is no doubt on clinical grounds. If there is a single abnormality, histological or cytological confirmation does need to be obtained.

**Cytopathological analysis**

If an abnormality is suspect for melanoma metastasis (regional or distant), a cytological (thin needle) puncture is performed to determine if it indeed concerns a melanoma metastasis. In principle, the puncture can be performed by the treating physician, the radiodiagnostic technician or the pathologist. In order to build sufficient experience, it is recommended to concentrate this technique and have a small number of physicians within the hospital perform this intervention. It is generally not difficult to detect or exclude the presence of melanoma cells using standard (Giemsa or PAP) stained smear or cytopsin samples. In a few cases, when the morphological result is unclear, additional immunocytochemical analysis may be performed and/or it may be decided to perform an additional intervention, such as a thick needle biopsy or surgical biopsy for histological analysis.
6.1 Localised disease (consensus-based text)

Therapeutic re-excision

Recommendation

In the therapeutic re-excision of a melanoma, it is recommended to adhere to the following margins of normal skin around the scar:
- in situ melanoma: 0.5 cm;
- Breslow depth through to 2 mm: 1 cm;
- Breslow depth more than 2 mm: 2 cm.

The guideline development group is of the opinion that the amputation of a complete finger in melanomas, especially subungual melanomas, is often unnecessary.

Literature discussion

The definitive treatment of skin melanoma deviates from that of other skin malignancies (basal cell carcinoma, squamous cell carcinoma). The reason for this is that satellites may occur with melanomas that are not always clinically detectable. These satellites are located in the immediate vicinity of the primary tumour, and therefore a therapeutic re-excision (≡definitive excision) should be performed after the diagnostic excision with the aim of removing any satellites. The chance of (micro) satellites is greater as the Breslow depth increases [Day 1981; Kelly 1984].

Anaesthesia

The therapeutic re-excision may, similar to the diagnostic excision, be performed with local infiltration anaesthesia: such as a ‘field block’. Narcosis and clinical admission usually occur when it is expected that the defect cannot primarily be closed after re-excision.

Margin of the surrounding skin

There are no comparative studies available on in situ melanomas. Therapeutic re-excision with a margin of 0.5 cm normal skin surrounding the lesion or wound of the diagnostic excision is generally recommended [NIH Consensus Conference, 1992], to ensure that any lentiginous component is radically removed. The guideline development group recommends performing the re-excision with inclusion of some subcutis.

For infiltrating melanomas, the choice in margin depends on the thickness of the tumour (measured in millimetres according to Breslow. For melanomas through to a thickness of 4 mm, there are six prospective randomised studies [Veronesi 1991; Khayat 2003; Cohn-Cedermark 2000; Balch 2001; Thomas 2002; Gillgren 2011]. In a study under the auspices of the WHO Melanoma Programme, patients with a melanoma of 2 mm thick at the most were randomised between two treatment possibilities: re-excision with a margin of 1 cm or at least 3 cm [Veronesi 1991]. The conclusions of this study are that the disease-free interval and survival in both groups does not significantly differ.

Local recurrence was more common in the group that underwent a narrow excision. Patients with the same Breslow thickness were also studied in a French study [Khayat 2003], in which randomisation took place between re-excision with a margin of 2 cm and 5 cm. There was also no significant difference in survival or local recurrence found between the two groups. In a third study, conducted in Sweden, patients with a melanoma thicker than 0.8 mm and at the most 2 mm were randomised between re-excision with a margin of 2 cm and a margin of 5 cm [Cohn-Cedermark 2000]. There were no differences between the two groups in survival, local recurrence and in-transit metastases. In a fourth study, which predominantly took place in the United States, patients with melanomas of 1 mm through to 4 mm thick were randomised between re-excision with a margin of 2 cm and 5 cm. There was also no significant difference in survival or local recurrence found between the two groups. In a fifth study, which predominantly took place in the United States, patients with melanomas of 1 mm through to 4 mm thick were randomised between re-excision with a margin of 2 cm or 4 cm surrounding the wound of the diagnostic excision [Balch 2001]. Again, no difference was found in survival and local recurrence. A fifth study was performed in Great Britain [Thomas 2002], in which patients with a melanoma of 2 mm or thicker were randomised between excision with a margin of 1 cm and a margin of 3 cm. There were more locoregional recurrences in patients who underwent a narrow excision, especially lymph node metastases. However, there was no difference in survival between the two groups. Meta-analyses also showed an ample re-excision did not yield a statistically significant survival advantage compared to a narrower re-excision [Lens 2002; Haigh 2003].
On the basis of the RCT’s researched (5, with a total of 1633 patients in the narrow margin (1-2 cm) and 1664 in the ample margin (3-5 cm), the more ample margins appeared to yield a better outcome (which was not significant) [Sladden 2009].

For melanomas thicker than 4 mm according to Breslow, there is often haematogenous dissemination and this has more influence on the prognosis than the chance of a local recurrence. To prevent unnecessary mutilation, a margin of 2 cm appears to be adequate for these patients [Heaton1998; Ng2001].

**Depth of the excision**

There is no clear data available in literature that indicates how deep the excision must be performed. The guideline development group recommends performing the therapeutic re-excision through to the underlying fascia. It is also recommended to excise the fascia when the subcutis is thin. Also if the fascia has been exposed during the diagnostic excision, it is recommended to remove it.

**Closing or covering the defect**

From a cosmetic and functional viewpoint, primary closing of the defect is preferable. This is usually possible. If necessary, the skin is undermined over some distance in order to bring this about. If primary closing is not possible, a free skin transplant or local tissue transplant can be used to cover the defect. Local tissue transplantation is sometimes an option, especially for locations that are important for cosmetic or functional reasons.

No recommendations based on research results are available in relation to the choice between an ipsilateral and a contralateral donor location for a free skin transplant in a patient with a melanoma on an extremity.

**Conclusions**

<table>
<thead>
<tr>
<th>Level 4</th>
<th>The guideline development group is of the opinion that a margin of 0.5 cm is adequate in the therapeutic re-excision of an in situ melanoma.</th>
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<td>D: NIH Consensus Conference, 1992</td>
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<tr>
<th>Level 1</th>
<th>It has been demonstrated for melanomas with a Breslow depth through to 2 mm that therapeutic re-excision with ample margins of 3-5 cm does not provide a better survival than re-excision with narrow margins of 1 or 2 cm.</th>
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<td>A1; Lens MB, 2002; Haigh PI, 2003</td>
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<th>Level 3</th>
<th>There are indications that for melanomas with a Breslow depth of more than 2 mm and a maximum of 4 mm, a therapeutic re-excision with a margin of 4 cm does not provide better survival than re-excision with a margin of 2 cm.</th>
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<td>A2; Balch CM, 2001</td>
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<th>Level 3</th>
<th>There are indications that a margin of 2 cm is adequate for a melanoma with a Breslow depth of more than 4 mm.</th>
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<td>C; Heaton KM, 1998; Ng AK, 2001</td>
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<th>Level 4</th>
<th>The guideline development group is of the opinion that an optimal excision margin cannot be indicated.</th>
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<td>D; Sladden MJ, 2009</td>
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Considerations
The guideline development group is of the opinion that narrower margins than indicated in the recommendation must be considered when it concerns excisions of melanomas that are localised in areas important for cosmetic or functional reasons. However, amputation is often required for melanomas localised on fingers or toes. There often does not need to be a full amputation of a finger however, especially in the case of subungual melanomas.

6.2 Therapy for lentigo maligna (M. Dubreuihl) (consensus-based text)

Recommendations
The guideline development group is of the opinion that excision is the therapy of first choice in the case of lentigo maligna.

In terms of diagnostics and treatment, LMM (lentigo maligna melanoma) is the same as melanoma, where lentigo maligna can be considered as a specific type of in situ melanoma.

Literature discussion
LM occurs mostly in Caucasian elderly people in chronically sun-damaged skin, especially in the head-neck area. The lifelong risk of progression to melanoma is not precisely known, but is reported by Weinstock and Sober to be less than 5% lifetime risk [Weinstock MA, 1987]. Excision with a margin of 5 mm can be considered the therapy of first choice with LM because the tissue can then be examined in its entirety for (micro) invasive growth and because the chance of local recurrence, and following on from this the chance of lentigo maligna melanoma, is smaller [Clark GS, 2008; Veronesi, 1991]. Functional, cosmetic and surgical technical considerations are of course also important in determining the margin.

Mohs surgery
In a small comparative retrospective study it was demonstrated that classic Mohs surgery (with frozen sections) lead to more recurrences than micrographic surgery with the use of formalin sections (in 2 or more tempi) [Walling 2007]

Conclusions
Level 4
The guideline development group is of the opinion that complete excision is the therapy of first choice in the treatment of lentigo maligna.

D; Expert opinion

Level 3
Classic Mohs micrographic surgery (MMS) with frozen sections is not a treatment for lentigo maligna and lentigo maligna melanoma. An excision in two tempi(micrographic surgery with formalin analysis) may be applied.

B; Walling HW, 2007

Considerations
An alternative therapy such as radiotherapy or observation only may be chosen in certain clinical circumstances (e.g. older patients, mutilating intervention), [Schmid-Wendtner 2000]. There is little evidence in literature that cryotherapy is an effective treatment. There are incidental reports of good results with topical treatment with imiquimod, but this therapy has also not been researched in randomised studies [Rajpar 2006].

Recurrence after surgery occurs in approximately 5% of patients. Even lower recurrence percentages have been described for micrographic surgery (surgery with full margin control) [Moehrle 2006].
6.3 Radiotherapy with curative intent (consensus-based text)

**Recommendation**

It is recommended in the case of radiotherapy with curative intent to administer a dose that is equivalent to >70 Gy in 7 weeks (or in daily fractions of 2 Gy).

**Literature discussion**

Curative treatment through surgery has been the preferred method of treatment since the birth of anaesthesia. Melanoma has long been considered a radioresistant tumour. More recent studies show that this view is outdated: melanoma is sensitive to irradiation, but a high total dose (between 70-80 Gy) is required for definitive tumour control. Patients are eligible for curative irradiation if there is a primary melanoma or a lentigo maligna (Dubreuihl) and curative resection is not possible or not deemed desirable or when the patients refuses surgical intervention. Patients with tumour-positive lymph nodes are also eligible if surgery is not possible or is refused.

While there is biological data that makes it clear that melanoma is relatively more sensitive to a high dose per fraction, a clinical Radiation Therapy Oncology Group (RTOG) study showed that when a schedule of 4 x 8 Gy is compared to 20 x 2.4 Gy there is no difference in overall response rate; this corresponds to a low intrinsic irradiation sensitivity (α/β = +8 Gy) [Overgaard, 1985]. This study was prematurely closed because the local control of 60% was worse than the 90% seen in a previous study in which 3 x 9 Gy en 5 x 8 Gy was used. A small retrospective study also did not show an effect for a high day fraction [Chang, 2006]. Increasing the total dose from 3 x 8 Gy to 3 x 9 Gy in a small study did give an improvement in local control [Overgaard, 2009]. A comparable high local control was also seen with a schedule of 24-30 Gy in four to five fractions of 5-6 Gy [Ang, 1990]. In summary, the chance of tumour control increases with increasing total dose, but the therapeutic range barely increases due to the dose to be fractionated.

Recommended dosage schedules correspond biologically to approximately 70 Gy in 2 Gy fractions [Ang 1990, Overgaard 2009].

**Conclusions**

<table>
<thead>
<tr>
<th>Level 3</th>
<th>There are indications with radiotherapy of melanoma that there is a dose-effect relationship above a dose of 3 x 8 Gy.</th>
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<td></td>
<td>A2; Overgaard, 2009</td>
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<th>Level 2</th>
<th>There are no indications that melanoma has a low α/β in terms of radiobiology.</th>
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<td></td>
<td>B; Overgaard 1985, Chang 2006</td>
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**Considerations**

With an inoperable melanoma with usually cutaneous localisation, in which the late radiation toxicity of surrounding normal tissue does not play a large clinical role of significant, a hypofractionated schedule may also be chosen as treatment with curative intent. The hypofractionated schedule is biologically equivalent to 70 Gy in 7 weeks at an α/β of ±8, in which daily fractions of 5 through to 9 Gy are often used.
6.4 Systemic disease (consensus-based text)

Systemic therapy

Recommendation

The guideline development group is of the opinion that in patients with inoperable or metastatic melanoma with an activating BRAF mutation, treatment with a BRAF inhibitor must be considered and discussed with the patient.

The guideline development group is of the opinion that for patients with a melanoma without activating BRAF mutation and who are not eligible for a treatment within a research study context, there is no better alternative than dacarbazine.

The guideline development group is of the opinion that after failure of first-line treatment, application with ipilimumab (Yervoy) should be considered as a second-line treatment and discussed with the patient.

The guideline development group is of the opinion that therapy with ipilimumab should be performed in a centre with expertise in the use of this drug.

The guideline development group is of the opinion that patients with a haematogenous or distant metastatic melanoma should preferably be treated within a research study context.

Literature discussion

Patients with a distant metastatic melanoma can be subdivided into three different categories, patients with:
- non-visceral metastases
- lung metastases
- remaining visceral metastases and/or elevated serum-LDH [Balch CM, 2001]

The prognosis in relation to survival differs for these subgroups; this may influence the selection of patients for treatment within a research study context.

The chemotherapeutic agent dacarbazine (DTIC) is the most commonly used drug with haematogenous metastatic melanoma. Treatment with dacarbazine yields a remission percentage of around 5-20, comprising 1-5% complete remission [Huncharek2001; Eggermont2004; Agarwala 2009; Robert 2011]. Only a very small number of patients in complete remission achieve a survival of several years or more. There is no data from studies in which treatment with dacarbazine is compared to observation, so that the influence of treatment with dacarbazine on survival is not known. Given systemic therapy is generally offered to patients in any case, dacarbazine has been preferred so far for pragmatic reasons, because it has been the most simple and least taxing therapy [Cochrane Database Syst Rev 2000]. Other chemotherapeutic agents with an efficacy comparable to dacarbazine are cisplatin, nitrosourea derivatives, vinca-alkaloids and taxanes. Studies with combination chemotherapy show higher remission percentages, but an improvement in survival has not been demonstrated [Huncharek 2001; Cochrane Database Syst Rev 2000; Chapman1999]. The addition of tamoxifen to chemotherapy does not have additional value [Falkson, 1998; Creagan1999]. The oral agent temozolomide is converted to the active metabolite of dacarbazine, which has a better penetration of the blood-brain barrier on the basis of animal studies. Comparative studies with dacarbazine have not shown a significant difference in response or survival [Middleton 2000; Patel 2009]. Temozolomide is not registered in the Netherlands for this indication.

Immunotherapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2) gives comparable remission percentages compared to dacarbazine [Middleton 2000]. While a retrospective analysis of treatment with high dose IL-2 suggests better survival of the subgroup patients with a complete remission, [Chapman 1998], this may be explained by selection bias. Treatment with cytokines is often accompanied with substantial toxicity. IFN-α nor IL-2 have been compared with dacarbazine in prospective randomised research.

The combination chemo-immunotherapy has not shown survival advantage so far compared to chemotherapy or immunotherapy [Huncharek 2001; Chapman 1999; Keilholz 1997; Rosenberg 1999; Eton 2002]. However, it does increase toxicity associated with treatment.
On the basis of the immunogenicity associated with melanoma, clinical trials are often conducted with different vaccines. These treatments should still be considered experimental. The same applies to allogeneic stem cell transplantsations and donor lymphocyte infusions.

A new immunotherapeutic agent is ipilimumab (Yervoy), a monoclonal antibody aimed at the CTLA-4 protein. In a phase III study with patients with metastatic melanoma that were not yet treated, the combination ipilimumab and dacarbazine was compared to dacarbazine and a placebo [Robert 2011]. The ipilimumab dose in this study was 10 milligram/kg. The combination ipilimumab and dacarbazine resulted in a significantly better survival (median survival of 11.2 months versus 9.1 months (p < 0.001). The survival percentages in the ipilimumab and DTIC group were higher than in the dacarbazine with placebo group (1 year: 47.3% versus 36.3%; two years: 28.5% versus 17.9%; three years: 20.8% versus 12.2%). In another phase III study with pre-treated patients who were HLA-A2 positive, treatment with ipilimumab (3 milligram/kg dose) after failure with dacarbazine showed a remission percentage of 11%, disease stabilisation of 17.5% and a survival longer than two years of 21% [Hodi 2010]. Compared to the control arm of the study, treatment with ipilimumab resulted in a doubling in survival. A limitation of the study was that the control arm did not consist of best supportive care but of experimental immunisation with gp100.

Treatment with ipilimumab can lead to serious, often immune-related side effects with a mortality rate of up to 2%. The most common side effects are fatigue, pruritus, dermatitis, colitis, hepatitis, hypophysitis, adrenalinitis. It is therefore recommended to only perform treatment with ipilimumab in experienced centres with expertise in the treatment of these side effects.

Mutations in the BRAF gene leading to uncontrolled signal transductions occur in 50-70% of skin melanomas [Curtin 2009; Viros 2008]. Phase I and II studies with selective BRAF inhibitors (vemurafenib, GSK2118436) in patients with metastatic melanoma with a BRAF600E mutation showed remission percentages of 50-70% and a progression-free survival of 6.5 (phase I) and 6.8 (phase II) months [Flaherty 2010, Sosman 2012, Kefford ASCO 2010, abstr 8503]. These favourable results have recently been confirmed in a phase III study [Chapman 2011]. In this study with not previously treated patients with a metastatic melanoma with activating BRAF mutation, the BRAF inhibitor vemurafenib was compared with dacarbazine. Response percentages were 48% for vemurafenib and 5% for dacarbazine. The hazard ratio for death in the vemurafenib group was 0.37 compared to the dacarbazine group (p < 0.001). The follow-up was still too short to determine the median survival. The hazard ratio for the progression-free survival was 0.26 (p < 0.001) for the vemurafenib group 5.3 months compared to 1.6 months in the dacarbazine group.

Conclusions

<table>
<thead>
<tr>
<th>Level 1</th>
<th>It has been demonstrated that treatment with chemotherapy with dacarbazine results in a remission percentage of less than 20%, of which less than 5% complete remission. Only a small number of patients in complete remission achieve a survival of several years or more.</th>
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<th>Level 3</th>
<th>There are indications that treatment with ipilimumab in combination with dacarbazine gives a significantly better survival than dacarbazine alone.</th>
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<td>A2; Robert NEJM 2011</td>
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<th>Level 3</th>
<th>There are indications that second-line treatment with ipilimumab after progressive disease in which dacarbazine treatment is given, results in survival advantage in comparison to conducting a wait-and-see approach.</th>
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<td>A2; Hodi, NEJM 2010</td>
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There are indications that treatment with the BRAF inhibitor vemurafenib results in a significant improvement in the progression-free survival in patients with a metastatic melanoma with a BRAF V600E mutation. 

A2; Flaherty NEJM 2010, Chapman, 2011 NEJM

Considerations

With the development of new classes of drugs (monoclonal antibodies, BRAF inhibitors, MEK inhibitors, PI3K/AKT/mTOR inhibitors), the situation in relation to the systemic treatment of metastatic melanoma is drastically changing. The promising results of the first studies with ipilimumab and vemurafenib indicate that new modalities may become available as standard treatment in the near future. Further studies are necessary in order to determine the position of these drugs in more detail, identify patients who truly benefit from treatment and in order to develop even more effective (combination) treatment schedules. It is therefore still preferable for patients with a metastatic melanoma to be treated as much as possible within a research context. Both agents have been registered in the Netherlands. The high costs associated with a treatment with ipilimumab or vemurafenib are cause for concern. The side effect profile must also be considered when applying ipilimumab and vemurafenib. Ipilimumab can be associated with serious, sometimes life-threatening toxicity. Vemurafenib can also have unusual side effects, such as inducing squamous skin carcinomas. The use of these drugs should therefore occur in centres with a good infrastructure and with extensive experience in the treatment of patients with melanoma. In addition, the molecular analysis of the melanoma, determining the indication and timing of treatment requires special expertise.

The new drugs are very costly and their use may lead to serious side effects requiring experience in recognising and dealing with these side effects, so that structured implementation of these drugs in the Netherlands is necessary. Various forums such as NVMO, WINO and NMW have worked towards the centralisation of care.

The minister of Health, Welfare and Sport has decided to reimburse ipilimumab and vemurafenib for 95% and has freed up extra budget for this purpose. This reimbursement comes with the express condition that the treatment of patients with metastatic melanoma takes place in a limited number of centres and that a register is kept of all patients with a metastatic melanoma. On the basis of criteria incorporated in the multidisciplinary oncology standard report by SONCOS (see www.soncos.org for the entire report), so-called melanoma centres have been selected in which, aside from expertise, geographical distribution has been taken into account. The following function as melanoma centres: Erasmus Medical Centre, University Medical Centre Leiden, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI/AVL), University Medical Centre Groningen, University Medical Centre Nijmegen, University Medical Centre Maastricht, University Medical Centre Utrecht and VU University Medical Centre. Aside from these centres, a number of partner hospitals have been selected, namely: Amphia Hospital (Breda), Isala Clinics (Zwolle), Leeuwarden Medical Centre, Maxima Medical Centre (Veldhoven), Medical Spectrum Twente and Orbis Medical Centre (Heerlen). Centres as well as partner hospitals must treat at least 20 patients per year with a metastatic melanoma with ipilimumab or vemurafenib. Partner hospitals consult with the melanoma centre prior to the primary treatment to ensure patients receive the right treatment. It can also be decided then if a patient is eligible for an experimental study treatment. The current agreement is that all hospitals in the Netherlands consult with a melanoma centre or partner hospital in relation to all patients with a metastatic melanoma. Patients are preferably also seen once in the centre. If patients are going to be treated with one of the new drugs, this occurs in a melanoma centre or partner hospital. If this is not the case, or when treatment is ended, the patient is referred back to the original hospital. It is compulsory for the centres and partner hospitals to maintain a register, also for untreated patients. The other hospitals are obligated to be helpful in the registration of patients who are not treated with the costly drugs.
6.5 Surgical treatment of systemic disease (editorial update)

**Literature discussion**

**Incidence and patient management**

Approximately 20% of patients with melanoma develop haematogenous metastasis. Their prognosis is poor; the average survival duration is seven months. Surgery, irradiation and systemic therapy all play a role in the palliative treatment. The choice is determined by the chance of reducing or preventing complaints. Not doing anything is also an option, certainly if the life expectancy is limited. While cure is rare, there is a small group of patients with limited stable metastasis for whom this goal is a realistic possibility. Surgery then provides the greatest chance of success. It often occurs that a patient who appears to receive surgery for a solitary haematogenous metastasis, is later found to have more lesions that are no longer resectable. These abnormalities escaped the attention during the initial staging process due to their small size. However, the continuous improvement in sensitivity of ultrasound, CT, PET-CT and MRI means it is becoming easier to select those patients for whom removal of all residual tumour is possible.

**Surgery**

Surgery is indicated if, after careful staging, there are a limited number of cutaneous or subcutaneous lesions or when it concerns lymph node metastases past the regional node station. Limited visceral metastasis may also be treated surgically, especially if this is localised in the lung, digestive tract, or brains, resulting in a five-year survival of approximately 25% [Wood, 2001; Hsueh, 2002; Karakousis, 1994].

6.6 Radiotherapy (consensus-based text)

**Recommendation**

The guideline development group is of the opinion that for metastases causing complaints, a short hypofractionated irradiation is worthwhile.

In the case of extensive cutaneous or lymphogenous metastasis with a reasonably general condition and prognosis, the guideline development group is of the opinion that radiotherapy in combination with hyperthermia should be considered.

For the indication for stereotactical radiotherapy and dosing for brain cancer, refer to the guideline Cerebral Metastasis on www.oncoline.nl.

**Literature discussion**

Palliative irradiation may be indicated if there is pain or other complaints caused by metastasis. In the 4-arm study by Overgaard et al. (1996) in patients with cutaneous or lymphogenous recurrences of a melanoma, two irradiation schedules were compared, 3 x 8 Gy or 3 x 9 Gy, with or without hyperthermia. The best tumour control was obtained after the high dose with hyperthermia. The complete response rate was >70% in patients who were treated with 3 x 9 Gy in combination with hyperthermia, compared to a CR of < 40% for patients with 3 x 8 Gy without hyperthermia [Overgaard 1996].

Painful bone metastases are routinely treated with 1 x 8 Gy. In patients with solitary bone metastases and a good general condition, a higher dose is usually administered in order to affect a longer palliation. For the indication for stereotactical radiotherapy and dosing for brain cancer, refer to the guideline Cerebral Metastasis on www.oncoline.nl.

Given radiotherapy is usually employed for palliation, a type of hypofractionation is chosen such as 3 x 9 Gy, 1 fraction per week, 9 x 5 Gy, three fractions per week; 5-6 x 6 Gy, two fractions per week; or >60 Gy, five fractions of 2 Gy per week. The choice is dependent on the tumour location and the volume of healthy tissue irradiated. Hyperthermia strengthens the effect of radiotherapy and is desirable with irresectable tumours in which the aim is radical treatment [Overgaard 1996].

**Conclusion**

**Level 3**

There are indications that hyperthermia added to radiotherapy in tumour control increases palliation of cutaneous and lymphogenous recurrences.

A2; Overgaard, 2009
Considerations
Hyperthermia is a relatively time-consuming treatment that can only be administered at the moment at a few locations in the Netherlands. The gain in local control using hyperthermia should be weighed up against the time it requires and the prognosis of the patient.
CH7 ADJUVANT SYSTEMIC TREATMENT AFTER INITIAL TREATMENT
(consensus-based text)

Recommendation

It is recommended not to administer systemic adjuvant treatment to patients with melanoma unless it is within a research context. This also applies to adjuvant treatment with IFN-α.

Literature discussion

On the basis of various prognostic characteristics, such as Breslow depth, the presence of ulceration, presence of regional lymph node metastases (microscopic or macroscopic), different categories of patients with melanoma can be identified that have an increased risk of a local recurrence and/or distant metastasis [Balch 2001]. All types of adjuvant systemic treatment, such as chemotherapy, hormonal therapy and immunotherapy have been studied in patients with a stage I-III-melanoma. The different randomised clinical studies with chemotherapy, hormonal therapy or immunotherapy have not shown a gain in progression-free survival or total survival compared to observation [Veronesi 1982; Meyskens 1994; Barth 1995]. Interferon-α (IFN-α) deserves further consideration. This agent has been most extensively studied in the adjuvant setting and results obtained so far are not so clear. Data from 24 randomised studies are available, of which some are of less use because multiple treatments or different IFN-α schedules are compared. After removing those, fourteen studies remain (with more than 8000 patients) in which treatment with IFN-α is compared with the standard wait-and-see approach [Pehamberger 1998; Grob 1998; Cameron 2001; Cascinelli 2001; Hancock 2004; Kirkwood 2000; Creagan 1995; Kirkwood 1996; Kirkwood 2001; Kirkwood2001; Kleeberg 2004; Eggermont 2005; Garbe2008; Eggermont 2008]. The composition of patient populations in these studies is heterogenous in relation to stage (II and/or III) as well as staging method (e.g. whether or not a sentinel node biopsy is performed). In addition, the doses, treatment schedules and administration method vary strongly in these studies.

Based on the doses used, a subdivision can be made into studies with a low (1-3 MU), intermediate (5-10 MU) and high (> 10 MU) dose IFN-α per administration. Three [Pehamberger 1998; Grob 1998; Garbel 2008] of the seven randomised studies with a low dose IFN-α showed a significant advantage in disease-free survival. An advantage in total survival was observed in two studies [Pehamberger1998; Grob 1998; Cameron 2001; Cascinelli 2001; Hancock2004; Kirkwood2000; Kleeberg 2004; Garbe 2008]. A study was conducted by the European Organisation for Research and Treatment of Cancer (EORTC) using an intermediate IFN-α dose. Results showed an improvement in disease-free survival without significant effect on total survival [Eggermont 2005].

Treatment with high IFN-α doses has been researched in five randomised studies [Kirkwood 2000; Creagan1995; Kirkwood1996; Kirkwood 2001; Kirkwood 2001]. Three of these showed a positive effect on disease-free survival. Two of these studies also showed an advantage in total survival. The EORTC has also conducted a study with pegylated IFN-α in a dose of 6 microgram/kg as induction, followed by 3 microgram/kg as maintenance dose for five years. This study also showed a significant effect on disease-free survival without improvement in total survival [Eggermont 2008]. Three meta-analyses have tried to draw a conclusion from the inconsistent result [Pirard 2004; Wheatly 2003 (updated ASCO 2007, abstr 8526); Mocellin2010]. All three conclude that an advantage in disease-free survival can be achieved used IFN-α in an adjuvant setting. [Pirard 2004; Wheatly 2003] did not show a survival advantage. The most recent analysis by Mocellin et al. used original data from fourteen randomised and revised versions. Mocellin et al. found a significant reduction in percentage of death in the IFN arms (HR 0.89, 95% CI = 0.83-0.96). Subgroup analyses did not show a survival advantage for IFN in studies in which stage III patients were exclusively registered or for high doses of IFN.

In summary, it can be said that the results of studies conducted so far on the value of adjuvant treatment with IFN-α are inconsistent and that a clear advantage of IFN-α therapy on the survival of patients with melanoma has only been shown in one of three meta-analyses [Pirard, 2004; Wheatley, 2003; Mocellin, 2010]. Various studies were of insufficient size in order to show a small but still clinically relevant difference in survival. It should also be realised that suboptimal staging techniques were used to select patients in a number of the studies performed. The toxicity associated with IFN-α treatment (chronic fatigue, general malaise and neuropsychiatric side effects) should also not be underestimated, especially because IFN-α must be administered for a relatively long period in order to have a possible effect on survival. Subgroups have been identified (including melanoma with
ulceration) in various retrospective subgroup analyses that may benefit more from treatment with IFN-α. However, this will need to be confirmed in well-conducted prospective phase III studies.

Conclusions

<table>
<thead>
<tr>
<th>Level 1</th>
<th>In patients with melanoma in stage II and III, adjuvant systemic therapy with interferon does not lead to significant improvement in total survival.</th>
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<td>A1; Punt CJA, 2001; Lens MB, 2002; Wheatley K, 2003; Mocellin 2010</td>
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</table>

Considerations

It can therefore be said in general that there are no arguments to treat patients with melanoma with adjuvant IFN-α outside of a research context. The possible advantage of extending the disease-free interval without substantial effect on total survival does not appear to weigh up against the burden of treatment, but this is a consideration that takes place between the treating physician and patient. New laboratory techniques make a rational development of anti-melanoma vaccines possible, of which the adjuvant value is currently being researched in clinical studies. These vaccines/antibodies are not currently being applied outside of a research context.
CH8 PATHOLOGY

8.1 Pathological examination of a diagnostic excision specimen (consensus-based text)

**Recommendations**

In case of doubt regarding the diagnosis melanoma, it is recommended that a colleague pathologist is consulted about the patient case who has special expertise in the diagnosis of melanocytic tumours.

**Literature discussion**

'Expert opinion' in the case of uncertain pathology diagnosis (consensus-based text)

In case of doubt regarding the (pathology) diagnosis, revision of the patient case by an expert in the diagnosis of melanocytic tumours results in a substantial number of clinically relevant changes in diagnosis. This has been demonstrated for the situation in the Netherlands in a study of consultation, sent to the pathology panel of the Dutch Melanoma Working Group [Veenhuizen1997].

**Conclusion**

<table>
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<th>Level 3</th>
<th>There are indications that consulting an expert when the diagnosis is uncertain decreases the number of incorrect or uncertain diagnoses.</th>
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<td>B: Ferrera, 2009</td>
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**Considerations**

When pigmented lesions that are removed for diagnostic reasons are photographed in a standard manner and sent to the pathologist, this will in some cases prevent a melanoma being missed or a naevus being over diagnosed.

It is the guideline development group’s opinion, however, that it is not yet feasible to require standard photography of pigmented lesions removed for diagnostic reasons.

**Tissue processing**

**Recommendations**

It is recommended to fixate skin excision samples in their entirety.

**Considerations**

It is acceptable to freeze a small sample of a large melanoma for scientific research, if current regulations in relation to consent and privacy are satisfied, and it is also clear that this tissue is not the thickest part of the melanoma or involves a surgical margin that is threatened.
Reports

Recommendations

As a minimum, it is recommended to include the following data in the pathology request form:
- personal details
- location of the pigment lesion
- indication for removal (cosmetic versus diagnostic)
- in the case of diagnostic excision: specification of the cause of the clinical suspicion (irregular shape; multiple colours; growth; itchiness etc.)
- nature of the intervention, any earlier interventions

It is recommended to include a conclusion text in the pathology report in which, in the case of melanoma, at least the following data are reported:
- anatomical location
- nature of the intervention (shave, punch, ellipse excision, incision biopsy)
- melanoma diagnosis (if possible, with the histological subtype reported)
- outcome in thickness measurement (according to Breslow)
- presence/absence of ulceration
- presence/absence of intradermal mitotic activity
- presence/absence of micro-satellitosis
- presence/absence of (partial) regression
- completeness in removal

If the melanoma reaches through to the base of the biopsy/excision, it is recommended to measure the distance from the granular layer or bottom of the ulcer to the biopsy base: the thickness of the melanoma is therefore at least that measured distance.

For markedly tangentially cut skin fragments, it is recommended that it is explicitly stated in the pathology report that based on the samples the thickness measurement is unreliable.

Considerations

Clinical information for the pathologist
The pathologist must be informed about the clinical findings that have led to the decision to remove the abnormality for histological analysis.

Pathology report
The pathology report must contain all the information required to make a choice about further patient management and in order to make an optimal assessment of prognosis.
8.2 Procedure if there is uncertainty about the correct diagnosis after pathology analysis

(consensus-based text)

Recommendations

If a diagnosis of Melanocytic tumours of uncertain malignant potential (MELTUMP) or Spitzoid tumour of uncertain malignant potential (STUMP) is being considered, it is recommended that a second evaluation by a colleague pathologist within the same pathology department is requested, possibly followed by a consultation with an external expert pathologist in the area of melanocytic tumours.

It is recommended to request an external consultation if consensus is not reached after evaluation within the own pathology department.

It is recommended to discuss the diagnostic uncertainty with the patient in the case of a MELTUMP or STUMP diagnosis (after re-evaluation by an expert).

It is recommended that the decision regarding further treatment is made after discussion of the case with the pathologist.

The guideline development group is of the opinion that the FISH and CGH analysis does not provide added value for the time being in demonstrating or excluding malignancy in the case of MELTUMP and STUMP.

It is recommended in the case of MELTUMP or STUMP to always insist on histologically tumour-free surgical margins. Dependent on the level of suspicion, the location of the lesion and clinical context, the choice can be a more ample margin (e.g. 0.5 cm) to a maximum of 1 cm with lesions where there is a low and high suspicion of malignancy, respectively.

It is recommended that a sentinel node procedure will not be performed in the case of MELTUMP and STUMP.

Literature discussion

Terminology use

Problems in the histological differential diagnosis of melanoma are the result of the many and complex differential diagnostic criteria required in differentiating between the numerous naevus and melanoma variants. There is no (inter)national consensus on which criteria should be used. This leads to lack of consensus on diagnosis in difficult to diagnose melanocytic tumours. This is illustrated by results of an inter observer study of 57 MELTUMPS evaluated by a panel of experienced pathologists [Cerroni 2008].

The above illustrates that sometimes, a diagnosis of melanoma cannot be made with certainty but cannot be excluded either. This group of melanocytic tumours is mostly referred to with the term MELTUMP (melanocytic tumour of uncertain malignant potential) [Elder 2004]. In a proportionally large number of such cases, it concerns the differential diagnosis Spitz naevus versus melanoma: these lesions are mostly referred to as STUMP (Spitzoid tumour of uncertain malignant potential).

Diagnostics

The presence of an activating HRAS mutation provides a strong argument against malignancy. Finding an HRAS mutation in a spitzoid lesion indicates with well-nigh certainty that the lesion is benign [van Dijk 2005; van Engen-van Grunsven 2010; Da Forno 2009]. In many cases however, mutation analysis will not be conclusive, namely when a BRAF mutation or no mutation is found.
Conclusions

It is plausible that the BRAF/HRAS mutation analysis is a reliable method to exclude malignancy in the case of STUMP. This determination will only yield conclusive information in a minority of cases.

B; van Dijk MC, 2005; van Engen-van Grunsven AC, 2010; Da Forno PD, 2009

Considerations

Diagnostics

It is the role of the pathologist, in collaboration with his colleagues within and external to his department, to keep the group of non-classifiable melanocytic tumours as small as possible. Expert opinion is currently divided regarding the technique and interpretation (and associated practical feasibility) of FISH and CGH analysis in daily routine practice.

Management in the case of MELTUMP and STUMP

If a melanocytic lesion is considered to be a MELTUMP or STUMP, consultation of a pathologist with special expertise in the area of melanocytic lesions within or outside the laboratory is indicated. When doubt is not resolved by this consultation, an individual therapy choice needs to be made on the basis of the uncertainty that cannot be dispelled. The level of histological suspicion, while subjective, is considered here. In consultation with the pathologist, the clinician should discuss the uncertainty regarding the diagnosis and level of histological suspicion with the patient. The clinician can subsequently discuss the option of more extensive treatment versus a more conservative approach with the patient, against the background of consequences and risks of over and undertreatment [Scolyer 2010]

The optimal (re) excision margin in case of MELTUMP or STUMP is determined by the level of histological suspicion, localisation of the lesion and preferences of the patient (amongst other factors). In any case, the aim must be histologically free margins. BRAF/HRAS mutation analysis in the case of STUMP may be considered as an additional molecular diagnostic method. An HRAS mutation is found in the minority of these lesions. If there is such a mutation, this is indicative of a benign course.

Sentinel node procedure

There is good reason to doubt if spread of a MELTUMP of STUMP to a sentinel node can be considered evidence of malignancy and whether the prognosis then corresponds to that of stage III melanoma. Benign melanocytic capsular naevi may well be present in sentinel nodes and a review of 5 studies of sentinel node biopsies with STUMP (a total of 71 patients, of which 26 had a positive sentinel node) did not yield a single case of death as a result of metastatic melanoma [Busam 2008]. While the follow-up was sometimes short in this reviewed 5 series, currently available data now do not support the idea that a positive sentinel node with STUMP should be considered indicative of stage IIIA melanoma.
8.3 Pathology analysis of the re-excision specimen (consensus-based text)

**Recommendations**
- If the surgical margins of the primary excision of a melanoma have been free, it is recommended to investigate histologically a single tissue block of the scar in the re-excision sample.
- If the surgical margins of the primary excision of a melanoma are not free, it is recommended embedding the scar fully and examine the surgical margins of the re-excision sample. Analysis of the surgical margins is also indicated if remaining melanoma is found in the re-excision sample.
- It is recommended to always perform histological analysis of pigmented lesions or other focal abnormalities in the re-excision specimen.

The guideline development group is of the opinion that the following should be stated in the diagnosis text of the pathology report:
- the location of the re-excision
- any residual melanoma tissue present
- the location of this residual tissue, i.e. in the scar or distant satellites
- the presence or absence of melanoma cells in the surgical margins, if surgical margins have been analyzed (indication for this: see above)

**Literature search**
**Macroscopic analysis**
Only in extremely rare cases is residual tumour detected at in histopathological analysis of re-excision specimen following diagnostic excision of melanoma. Taking many little tissue blocks of such samples has a very low ‘yield’. In a systematic analysis of 167 re-excisions after diagnostic melanoma excision with free surgical margins according to the pathology report, residual tumour was found in 4 cases. There was no relationship with the number of tissue blocks analysed (average number: 3, range: 1 tot 12) [Martin 1998]. In another study of 109 re-excision samples, residual tumour was found in two cases in which the initial excision was stated to be complete. This study also did not find a relationship between the number of tissue blocks researched and the chance of detecting residual tumour [Johnson1998]. McGoldrick et al. (2008) researched the pathology results of 1007 re-excision samples after diagnostically complete excision of melanoma and did not find a single case of residual tumour. In this series, standard analysis of three tissue blocks of the re-excision sample was performed. If the surgical margins of the initial excision were free and no focal abnormalities were seen in the re-excision sample. The authors recommended not performing pathology analysis of re-excision samples at all. It must be noted that these results do not appear to fully correspond to those of the two studies mentioned earlier. Not submitting re-excision samples for pathology analysis would mean that independent evaluation of the presence of a central scar, the presence of focal abnormalities and the re-excision margins is no longer possible [Boon 2008].

Incidental cases of melanoma residue in re-excision samples are reported, and have substantial prognostic consequences in case of satellitosis [Patel 2010]. Taking one tissue block for histological analysis is currently the standard in the United Kingdom [Boon 2008].
Conclusions

<table>
<thead>
<tr>
<th>Level 3</th>
<th>There are no indications that there is a relationship between the number of tissue blocks taken and the chance of detecting residual melanoma after complete diagnostic excision.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>C; Martin 1998</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3</th>
<th>There are no indications that could serve as argument for fully omitting histological analysis of re-excision samples.</th>
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<td></td>
<td>C; McGoldrick 2008</td>
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</tbody>
</table>

Considerations

The extensiveness to which the excision sample is processed is dependent on the radicality of the primary excision. If the excision was complete and no focal abnormalities are identified in the re-excision sample, taking a single block from the centre of the re-excision specimen will suffice. Focal abnormalities, together with the scar or at a distance, are always included.

In the case of irradicality or doubt about the radicality of the primary excision, the sample is inked and cross-lamellated as above. In this case, both end points and the entire scar and/or any other macroscopic abnormalities are fully included.

Macroscopic analysis

Inspection

Attention is paid to:

- the location and dimensions of the scar
- how the scar relates to the surgical margins
- any abnormalities of the skin and subcutis relating to the scar
- any accompanying abnormalities of the skin and subcutis

Excision

After fixation, the sample is cross-lamellated in slices of approximately 2 mm and inspected for the occurrence of focal changes.
8.4 Pathology analysis of the sentinel node (consensus-based text)

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended not to perform peroperative frozen section analysis or peroperative cytological evaluation of imprint samples of the sentinel node.</td>
</tr>
<tr>
<td>It is recommended to fixate the sentinel node in its entirety and to process it fully for histopathological analysis.</td>
</tr>
<tr>
<td>It is recommended to bisect a small sentinel node and for large nodes with a thickness &gt; 4 mm, it is recommended these are lamellated parallel to this central section.</td>
</tr>
<tr>
<td>It is recommended to analyse at least three levels per paraffin block, including immunohistochemistry of each of the levels. Optional: six levels with a distance of 50 μm (in concordance with the EORTC guideline).</td>
</tr>
<tr>
<td>It is recommended to perform, in addition to the HE stain, immunohistochemical analysis of sentinel nodes with melanoma using antibodies against S-100 and at least one additional, more specific marker, preferably MART-1/Melan-A.</td>
</tr>
<tr>
<td>It is recommended to report the diameter of the largest tumour deposit in the conclusion of the pathology report of the sentinel node. Any extranodal growth of a melanoma metastasis is also reported.</td>
</tr>
<tr>
<td>For the time being, it is recommended not to use the RT-PCR method for detection of melanoma metastases or for prognosis.</td>
</tr>
<tr>
<td>The guideline development group is of the opinion that there is no internationally accepted protocol for the macroscopic pathological processing of a sentinel node in the case of melanoma.</td>
</tr>
</tbody>
</table>

**Literature discussion**

**How should pathological analysis of the sentinel node be conducted?**

**Frozen section procedure**
The frozen section procedure of the sentinel node for melanoma has limited sensitivity [Stojadinovic 2002; Koopal 2000; Prieto 2010]. Intra-operative frozen section analysis and peroperative cytological evaluation of the sentinel node during surgery has a sensitivity of only a maximum of 75% [Creager 2002; Soo 2007; Badgwell 2007, Badgwell 2011]. The loss of material is substantial in the frozen section procedure, so that metastases may have been lost in the definitive evaluation on paraffin sections [Stojadinovic 2002; Koopal 2000; Prieto 2010]. Peroperative cytological evaluation of imprint samples does not have this last disadvantage, but also has limited sensitivity [Creager 2002; Soo 2007; Badgwell 2011].

**Macroscopic pathological processing**
The classic method, in which the lymph node is halved at the hilum, is based on an early study in which most metastases were detected in the central plane at the hilum of the lymph node [Cochran 1988]. A study from 2009 contradicts results from the study by Cochran and outlines that metastases also occur frequently elsewhere in the lymph node [Riber-Hansen 2009].

In relation to excision and staining of the halved sentinel node, multiple studies confirm that analysis of multiple levels of the lymph node and use of immunohistochemistry increase the detection of metastases. Various studies have found that there is a higher incidence of positive sentinel nodes if multiple levels of the sentinel node are analysed [Cook 2008; Cook 2003], or additional metastases are found at deeper cross sections of the tissue blocks in combination with additional immunohistochemistry. Based on experience with the evaluation of sentinel nodes in other tumours, such as breast cancer, and theoretic considerations, it is plausible that analysis of deeper levels leads to the detection of more metastases. This also applies to sentinel nodes of melanoma patients. Indirect, but strong indications for this were also found by Cook et al. in relation to melanoma. Cook demonstrated that
Immuno-histochemical analysis
That additional immuno-histochemical evaluation increases the sensitivity of detecting small numbers of melanoma cells, has been demonstrated in various well-controlled studies [Cochran1988; Messina 1999; Yu1999; Shidham2001; Mahmood 2002]. Antibodies against S-100 are generally used supplemented with antibodies against a more melanocyte-specific antigen, such as gp-100 or MART-1. MART-1 is preferably in the immuno-histochemical detection of melanoma cells in sentinel nodes above gp-100 due to the demonstrated substantially higher sensitivity [Mahmood 2002]. A study found that a cocktail of antibodies with MART-1/ Melan-A and tyrosinase yielded better results than MART-1 only [Shidham 2003].

Various studies have studied the relationship between the size and location of sentinel node metastases, and also measured the infiltration depth of the metastasis from the capsule, in relation to survival and additional positive lymph nodes in the complete lymph node dissection followed. The maximum diameter of the largest metastasis has a relationship with survival and the involvement of non-sentinel nodes in multiple studies [Gershenwald 2008; van Akkooi 2006; Sheri2007; Govindarajan 2007]. The findings are clearly significant in a number of studies but the studies are difficult to compare due to differences in cut-off values (diameter 0.1mm to 0.5mm) and difference in measurement (the largest diameter, or the surface area of the tumour deposit). The two studies with a significant relationship have used a diameter of 0.1 mm [van Akkooi AC, 2006] and 0.1 mm² as surface area [Gershenwald 2008] as cut-off value. On the basis of results of the first study, a European EORTC registration study was started for patients with very small micrometastases < 0.1mm (MINITUB).

Dewar et al. demonstrated that the micro-anatomical location of the melanoma metastasis in the sentinel node is also predictive of the involvement of non-sentinel nodes [Dewar, 2004]. Patients with only subcapsular localised metastases in the sentinel node never had positive non-sentinel nodes. However, in lymph nodes with a parenchymatous, multifocal or extensive metastasis in the sentinel node, there were positive non-sentinel nodes present in 22.2%. This study also showed a correlation between invasion depth of the sentinel node metastasis and the presence of melanoma in non-sentinel nodes, but this factor alone was found to be insufficient to be reliable in predicting the presence of tumour-positive non-sentinel nodes. In a multicentre study [van der Ploeg, 2011], the combination of the largest diameter and micro-anatomical location was found to be the best predictive parameter for both survival and non-sentinel node positivity. Patients with very small micrometastases <0.1mm, subcapsular only, had a non-sentinel node positivity of 2% and a 5-year and 10-year survival of 95% (comparable to patients with a negative sentinel node). All lymph nodes in this study were processed according to the EORTC protocol and the invasion depth was not determined.

In another study, in which all three parameters studied (largest diameter, invasion depth and micro-anatomical location) were compared, invasion depth and largest diameter correlates best with non-sentinel node positivity, whilst invasion depth was the best predictor of survival [van der Ploeg, 2009]. All lymph nodes were analysed according to the EORTC protocol. No positive non-sentinel nodes were found at an invasion depth of <0.4 mm. This data forms the basis for the recommendation to state at least the largest diameter in the report of the sentinel node; the depth of the metastasis in the lymph node measured from the inside of the capsule and the micro-anatomical location are preferably also indicated. In this manner, the guideline also aligns with the recommendation in the British guideline [Marsden 2010]. Detection of mRNA of melanocytic differentiation genes, such as gp-100, MART-1 and tyrosinase, as indication of the presence of melanoma cells, is possible with the aid of RT-PCR [Shivers 1998; Blaheta 1999; Shivers 2001; Blaheta 2001; Palmieri 2001; Hochberg 2002]. The significant correlation of test outcomes with parameters (thickness, ulceration) of the primary tumour, and with survival indicate that the positive test signal is presumably often derived from metastatic melanoma cells. The technique is not generally accessible. Sensitivity and specificity of the PCR-based tumour cell detection are certainly not complete, however; naevus cells in lymph nodes form an important source of false-positivity [Gutzmer 2002]. Tissue used for RT-PCR analysis is lost for microscopic evaluation,
so that it is not possible to perform a check of the RT-PCR test result in the same tissue and there is no possibility to recognise and correct a false positive test result. Two independent studies have shown that RT-PCR techniques do yield positive sentinel nodes more often compared to histology only. But that RT-PCR does not have added prognostic value in relation to predicting the chance of recurrence compared to histology only [Kammula, 2004; Mangas, 2006].

**Processing (example)**

**Protocol: pathological processing of the sentinel node**

After fixation in its entirety, the lymph node is bisected at the greatest diameter at the location of the hilum. Six levels are cut from the halves/slice with 50 µm increments. Three sections are taken from each level: the first is HE stained, the second and third are used for immunohistochemistry with antibodies against S-100 and MART-1 (Melan-A). Ribbons are retained from all levels for a potential repeat of a stain or additional stains [Cook 2008].

**Conclusions**

<table>
<thead>
<tr>
<th>Level 2</th>
<th>It is plausible that the sensitivity of the intra-operative frozen section analysis and of the peroperative cytological evaluation of the sentinel node is low during surgery.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>B; Creager 2002, Soo 2007, Badgwell BD 2007</td>
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<table>
<thead>
<tr>
<th>Level 4</th>
<th>The guideline development group is of the opinion that there is no internationally accepted protocol for the macroscopic pathological processing of a sentinel node in the case of melanoma.</th>
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<tr>
<td></td>
<td>D; Expert opinion</td>
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<table>
<thead>
<tr>
<th>Level 2</th>
<th>It is plausible that halving through the hilum is preferred for the time being.</th>
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<tr>
<td></td>
<td>B; Marsden JR, 2010; Cook MG, 2008</td>
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<tr>
<th>Level 3</th>
<th>There are indications that analysis of six levels of the halved sentinel node with 50µm increments gives an optimal yield of detected melanoma metastases in the sentinel node in relation to the workload.</th>
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<tr>
<td></td>
<td>B; Cook 2003</td>
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<table>
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<tr>
<th>Level 2</th>
<th>It is plausible that immunohistochemical analysis increases detection of melanoma metastases in sentinel nodes.</th>
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<table>
<thead>
<tr>
<th>Level 2</th>
<th>It is plausible that histological analysis of multiple levels of the sentinel node leads to detection of more metastases.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B; Cook 2008, Cook 2003</td>
</tr>
</tbody>
</table>
| Level 2 | It is plausible that measuring the size of metastases in sentinel nodes provides prognostically relevant information for melanoma. It is plausible that micro-anatomical location and invasion depth of the metastasis are also prognostically relevant.  
| Level 3 | There are indications that non-morphological methods of detecting melanoma metastases such as RT-PCR sometimes yield false-positive results that are not recognisable as such.  
B; Gutzmer 2002 |
| Level 2 | It is plausible that the use of RT-PCR for the detection of melanoma metastasis does not provide added prognostic value for the time being.  
B; Kammula 2004, Mangas 2006 |

**Considerations**
Alignment with the EORTC guideline and other European guidelines is partly an argument to advise halving a small sentinel node through the hilum. For larger nodes with a thickness > 4mm, the recommendation is to lamellate them parallel to this central cut.

### 8.5 Pathology analysis of lymph node dissection samples (consensus-based text)

**Recommendations**
It is recommended to include all lymph nodes where possible on the pathology request form, in which the clinician states the regions of the node dissection samples (neck, axilla or groin) and what side it is from.

It is recommended to state the following in the diagnosis text of the pathology report:
- the type of the lymph node dissection specimen, and what side it is from
- the number of positive nodes and total number of lymph nodes analysed, and the location of the positive nodes per region, where possible
- the presence or absence of capsule metastasis/extranodal tumour metastasis
- the presence or absence of extranodal tumour
- the presence of absence of melanoma in the surgical resection margins

**Considerations**

**Macroscopic analysis**
**Inspection:**
Dependent on the localisation of the primary tumour, it concerns a neck, axillary or inguinal node dissection specimen. The different regions of the sample are marked wherever appropriate; the axillary top node or deepest inguinal node is marked where possible.

In the macroscopic description, special attention is given to the following:
- the maximum dimension and location of any macroscopically abnormal lymph nodes
- the mobility of such nodes compared to the environment
- the minimum distance of such node(s) to the surgical margins of the sample

**Excision**
The specimen is carefully lamellated and inspected for lymph nodes and focal abnormalities. Each node is fully submitted, except when evident metastasis is present. In that case, reporting the diameter of the metastasis and removing one or several pieces suffices (confirmation of diagnosis and
evaluation of any extranodal metastasis; evaluation of surgical margin). Excised samples taken from the same region can be submitted using the same subdivision. The number of lymph nodes per region is noted. At location(s) where seemingly positive lymph nodes reach to less than 3 mm from an excision margin, pieces are taken after the outside surface of the sample is marked with ink.

Microscopic analysis
Attention is given to:

- the cell type (epithelioid, spindle cells, small cells)
- the presence of melanin
- any capsule metastasis / extranodal tumour growth

8.6 Pathology analysis of distant metastasis (consensus-based text)

**Recommendations**

It is recommended to compare the microscopic appearance of metastases with that of the primary tumour to assess if the histologic picture is similar.

It is recommended, if the tumour is entirely amelanotic, to confirm the diagnosis of (metastatic) melanoma by immunohistochemistry.

It is recommended to state the following in the diagnosis text of the pathology report:

- location of the metastasis
- the nature of the intervention
- the diagnosis melanoma metastasis
- a statement regarding the completeness of resection of metastases

**Considerations**

Macroscopic analysis
Inspection

The following should be paid attention to in the macroscopic description:

- dimensions of the total sample and nature of the tissue
- dimensions and colour of tumour foci and any other abnormalities
- minimum distance(s) of this lesion(s) to the excision margins

After fixation in its entirety, the lymph node is halved at the greatest diameter at the location of the hilum.

Excision

If the radicality of the excision is important (especially with a solitary metastasis), the sample is inked. After the sample is lamellated, the area where the tumour is closest to the margin is separately removed. Representative pieces are removed, including pigmented areas (if present).

Microscopic analysis

Attention is given to:

- the cell type (epithelioid, spindle cells, small cells)
- presence of melanin
- relation to pre-existing structures and surgical margins
CH9 AFTERCARE AND FOLLOW-UP

9.1 General (consensus based text)
In practice, the terms aftercare and follow-up are not always clearly distinguished from one another. The Health Council defines the terms aftercare and follow-up in its report ‘Aftercare in oncology’ (‘Nacontrole in de oncologie’, 2007). In this chapter, the elements of aftercare are used as per the definition by the Health Council.

‘Aftercare’ is defined by the Health Council as an essential part of individual patient care during and after treatment of cancer. It consists of three elements: the provision of information, guidance, addressing complaints and symptoms, detecting direct or late effects of disease and treatment and attention for social effects, detection of new manifestations of the primary treated cancer or newly associated malignancies, evaluation of medical procedure and its effects.

Aftercare is also precautionary care. Physical and psychosocial effects of cancer and cancer treatment may already occur directly after diagnosis and during treatment. Timely treatment of complaints through early screening, starting directly after diagnosis, may reduce disease burden and prevent worsening. The initiative for contact can be taken by both the general practitioner and the patient.

Aftercare has the primary objective of limiting disease burden by improving quality of life and extending the life span.

‘Follow-up’ is defined by the Health Council as the programmatic approach to aftercare that consists of return contact moments between the patient and his/her treating physicians and that relates to the treated form of cancer.

This chapter is based on The Dutch guideline ‘Cancer Survivorship Care’ and Cancer rehabilitation (Cancer Rehabilitation, ACCC, 2011), and Detection of psychosocial distress (ACCC, 2011). See the website www.oncoline.nl for these guidelines.

9.2 Effects and approach in the 1st year (consensus-based text)

Recommendations
Follow-up, medical content.
It is recommended to pay particular attention to the location of the original tumour and the relevant area from which the lymph drains to the same node region as the primary tumour. When taking the medical history, the patient is asked about specks and little lumps in this area. Such abnormalities are easily accessible for physical examination. The physician should be aware of the specific metastasis pattern of melanoma. With experience, dermal satellite metastases are often already recognised when they are barely one millimetre. In-transit metastases are common in the lymph ducts and it is therefore important to know where these are located. Local recurrence, satellite metastases and in-transit metastases are not always a dark colour. The lymph node area in which regional lymph nodes are most likely to be located is palpated [Roozendaal, 2000]. If findings on physical examination are doubtful, diagnostics can be expanded with ultrasound and thin needle punction of a suspicious space-occupying process for cytological analysis. (For further details see Chapter 10, Diagnosing a local and locoregional recurrence).

Individual aftercare plan (see example in Appendix 17)
It is recommended to register the aftercare plan of the patient with a thick melanoma (stage IB and higher) in electronic databases and files and to use this for interdisciplinary transfer, including to the general practitioner and to give the patient a copy of the aftercare plan.

Literature discussion
The Health Council (2007) concludes that many patients experience complaints after treatment of cancer with curative intent. These complaints may be limited or extensive, of either a physical or psychological nature and occur early or at a later point in time. It often concerns physical effects that are clearly associated with the specific nature of the cancer, treatment, psychosocial problems and general complaints.
There may be general problems in the area of relationships with partner and family, social contacts, problems with participation in society, participation in the work sphere and financial problems.

**Early effects**

Early effects are those effects that are experienced directly by the patient after diagnosis and during treatment or in the first period (up to one year) after treatment. The Health Council states that timely treatment through early detection may reduce the disease burden of early effects. This care in relation to early effects primarily falls under the responsibility of the treating specialist. Other health care professionals can of course be engaged to assist.

The operations that are performed are not so substantial and the consequences are therefore usually minor, but the patient feels unsure and may have questions about the prognosis, wound healing and self-examination.

Examples of early effects in the treatment of melanoma are pain in the wound or itchiness of the scar. If additional surgery is performed, such as the sentinel node procedure or a regional lymph node dissection, the abovementioned early effects are sometimes seen. Serious complications rarely occur if only a re-excision of the primary melanoma is performed. Postoperative complications may occur after a sentinel node procedure, such as wound infection, seroma, lymph fistula, haematoma, neuropraxia or cutaneous loss of sensation [Jansen, Nieweg 2000]. Sometimes there are complications with unpleasant effects in the long term. After the definitive excision, it may be a year before the scar settles down fully. It can then only be ascertained after a year what the situation is in terms of functional and cosmetic issues.

<table>
<thead>
<tr>
<th>Physical</th>
<th>Psychological</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>wound infection</td>
<td>fatigue</td>
<td>relationship with partner, family</td>
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<tr>
<td>seroma</td>
<td>concentration</td>
<td></td>
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<tr>
<td>lymph fistula</td>
<td>anxiety, depression</td>
<td></td>
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<tr>
<td>lymph oedema</td>
<td>anger</td>
<td></td>
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<tr>
<td>haematoma</td>
<td>sadness</td>
<td>work participation, resumption of work</td>
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<tr>
<td>haematoma</td>
<td></td>
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<td>lymph fistula</td>
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<td>neuropraxia</td>
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<td>cutaneous loss of sensation</td>
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<tr>
<td>fatigue/fitness</td>
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<tr>
<td>Limitations in activities of daily living</td>
<td>doubt about the prognosis</td>
<td></td>
</tr>
</tbody>
</table>

**Late effects**

Late effects are those effects that do not yet exist, or at least have not yet resulted in complaints, on completion of treatment. As long as it is unclear if detection of these late effects in an asymptomatic phase provides a health benefit for the patient, there is insufficient justification to keep all patients under long-term follow-up. It is important to provide patients and their general practitioner with good information and instruction about the possible late effects and how to deal with these. The patient must be informed which health practitioner should be contacted if these complaints occur. Especially in the case of melanoma where easily two or three healthcare providers are involved, it is important to have clarity as to who the primary healthcare provider is. Examples of late effects in the treatment of melanoma are lymphoedema (from mild to severe) or lymph fistula, which may occur after a sentinel node procedure or lymph node dissection.

**Screening**

Aftercare begins with systematic detection of complaints. A basis set of complaints detection should be applied as a standard with every patient. A measuring tool (the Distress Thermometer) was recommended in the guideline ‘Screening for psychosocial distress’ [IKNL 2010]. In addition, screening and diagnostic instruments may be utilised for specific complaints. Please see the guideline Cancer rehabilitation (IKNL, 2011) for these instruments.

**Self-management**

Renewed tumour growth is noticed by the patients themselves in half the cases [Jillella 1995, Garbe 2003; Poo-Hwu, 1999; Ruark 1993; Baughan1993; Hofmann 2002; DiFronzo 2001; Kittler 2002]. One of these studies reported that patients with a recurrence detected on follow-up by the physician, had a
survival percentage that was 5.8% better than when patients detected the recurrence themselves [Poo-Hwu, 1999]. However, a second study found the opposite trend [Ruark 1993]. Two other studies did not show a difference [Baughan 1993; Hofmann 2002]. A subsequent primary melanoma is also often detected by the patient [Garbe 2003], in which the Breslow depth is approximately half that of the first melanoma [DiFronzo 2001; Kittler 2002]. Perhaps patients would be able to detect their recurrence even earlier if they received instructions to this end. Healthcare professionals have the important task of supporting the patient in this self-management. Information about diagnosis and treatment is generally accessible, but information relating to psychosocial effects, long-term effects, lifestyle and financial consequences is often lacking. Healthcare providers can support the decision-making by patients with the use of aftercare plans (see Appendix 17, example melanoma aftercare plan) and referring patients to reliable sources of information (such as the patient brochure by the Melanoma Foundation and the Dutch Cancer Society (KWF) [Hoffman 2006]. Information about contact with fellow patients is provided by the patient association (www.stichtingmelanoom.nl).
Treatment

Aside from standard guidance, such as information, support and advice regarding self-management, different treatments for specific physical, psychological and social effects of cancer have been found to be effective. If lymphoedema occurs, the patient should be referred to a skin therapist for lymph drainage and fitting of a therapeutic elastic stocking if required.

Aside from treating specific complaints, psychological treatment and cancer rehabilitation can be employed for complaints and to improve quality of life. The guideline Cancer rehabilitation [IKNL, 2011] included decision trees for the referral and rehabilitation in case of specific complaints. The blueprint Cancer and Work [NVAB, 2009] provides recommendations for work integration.

Review after one year

On average, general complaints and complaints of distress decrease in the course of one to two years [Stanton 2006, Parker 2007]. It is therefore recommended to review, and finish where possible, the systematics of detection and aftercare in relation to residual complaints one year after completion of the primary cancer treatment. If necessary, this can lead to a sub-scenario: partial continuation of aftercare or referral.

Individual aftercare plan

After completion of cancer treatment for patients with melanomas stage IB and higher, the advice of the Health Council is to create an aftercare plan that becomes available to the patient, general practitioner and other parties involved. The aftercare plan contains at least information about:

- physical and psychosocial effects of disease and treatment
- desirability and content of the aftercare
- point in time of the review
- continuing points of attention

The individual aftercare plan has been made tumour-specific for melanoma and can be found in Appendix 17. Revision of the aftercare plan may be required if new information becomes available about the (late) effects of cancer and if new care demands arise. For example, the moment of reviewing the aftercare, a year after completing primary treatment.

9.3 Detection of new cancer manifestations

(Evidence-based text - clinical question 13.1: point in time at which new cancer manifestations develop)

Recommendations

For patients with melanomas through to stage IA, it is recommended to pay attention to the instruction for self-examination:

a one-off follow-up visit one month after treatment of a primary melanoma. At the time, the patient can raise any questions and be instructed in self-examination. It is explained to the patient that there is no evidence available that shows that regular follow-up leads to an improved chance of survival, but that an appointment can be made in the short-term at any time if there are complaints. Written instructions for self-examination and written contact information in case suspicious abnormalities are detected are given to the patient.

For patients with melanomas from stage B, it is recommended to follow the schedule below that best fits the underlying scientific evidence.

1st year: follow-up once every three months
2nd year: follow-up once every six months
3rd to the 5th year: follow-up once per year

Additional follow-up on indication.
Literature discussion
Melanoma recurrence (Evidence-based text, clinical question 13.1: point in time of occurrence)
A large (n=33,384) cohort study has calculated the number of patient years that is required to find one recurrence, at different points in time after primary treatment (table 1) [Leiter, Buettner2011]. For AJCC stage IA, the number of patient years required to find one recurrence was relatively constant over ten years follow-up and high (continuously above the 115 patient years). For AJCC stages IB, II and III, increasingly less recurrences were found as the follow-up time progressed, but the number of recurrences found per patient years remained high. (see the chapter TNM classification).

Table 1 Incidence of recurrences per patient years observation, at different points in time after primary treatment (Leiter, Buettner et al. 2011)

<table>
<thead>
<tr>
<th>AJCC stage</th>
<th>Number of years after primary treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>IA</td>
<td>1/152</td>
</tr>
<tr>
<td>IB</td>
<td>1/37</td>
</tr>
<tr>
<td>II</td>
<td>1/7</td>
</tr>
<tr>
<td>III</td>
<td>1/3</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC: American Joint Committee on Cancer

The study by Bernengo et al. reported that the incidence of distant recurrences was low (approximately 1/100 patients) and remained so during a follow-up of more than twenty years [Bernengo, 2005]. The incidence of local recurrences was high in the first year (approximately 1/6 patients) and reduced to approximately 1/20 patients in the fifth year and then remained at lower than 1/20 patients for more than twenty years. No distinction was made in this analysis on the basis of stage.

Four studies stated the percentage of recurrences that was found within a particular time period (Table 2) [Bernengo 2005; Francken. 2008; Romano 2010; Hohnheiser 2011]. These studies show that more than two-thirds of all recurrences were found within five years after primary treatment, except for AJCC stage IA. In one study evaluating patients with stage IA, half of all (rare) recurrences were found within five years after primary treatment and half from six to ten years after primary treatment [Francken, Accortt et al. 2008]. The recurrence percentage of all recurrences found within five years is an overestimation in studies with a relatively short follow-up [Francken 2008; Romano. 2010].

Table 2 Recurrence percentage (of all recurrences found) per time period after primary treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>N (% with a recurrence)</th>
<th>Follow-up</th>
<th>AJCC stage</th>
<th>% recurrences of all recurrences found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 years</td>
<td></td>
<td>≤5 years</td>
</tr>
<tr>
<td>(Bernengo, Quaglino et al. 2005)</td>
<td>3174 (43%)</td>
<td>Median 10 years</td>
<td>I 54%, II 46%</td>
<td>77%</td>
</tr>
<tr>
<td>(Francken, Accortt et al. 2008)</td>
<td>4748 (19%)</td>
<td>Median 6 years</td>
<td>IA 39%</td>
<td>50% #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IB 30%</td>
<td>68% #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIA 16%</td>
<td>74% #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIB 11%</td>
<td>83% #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIC 4%</td>
<td>88% #</td>
</tr>
<tr>
<td>(Hohnheiser, Gefeller et al. 2011)</td>
<td>2487 (21%)</td>
<td>Median 13 years</td>
<td>I 52%, II 23%, III 8% *</td>
<td>82%</td>
</tr>
<tr>
<td>(Romano, Scordo et al. 2010)</td>
<td>340 (100%)</td>
<td>Median 6 years</td>
<td>IIA 28%</td>
<td>92% #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIB 46%</td>
<td>98% #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIC 26%</td>
<td>100% #</td>
</tr>
</tbody>
</table>

# Data read from recurrence-free survival curves
* Figures from the Union for International Cancer Control (IUCC) staging
If percentages do not total %, this is due to rounding differences
Abbreviations: AJCC: American Joint Committee on Cancer
N.r.: not read due to the very small number of patients
One study reported the percentage of recurrences per time period with a primary tumour thickness ≤1 mm [Bernengo 2005]. Forty-three percent of all recurrences were detected through to the fifth year
after primary treatment, 14% from six to ten years, 21% from eleven to fifteen years and 21% from sixteen to twenty years.

In the two studies reporting on late recurrences (recurrences that occurred ten years or longer after primary treatment), late recurrences were found in 0.7-1.1% of patients [Leman 2003; Hansel 2010]. Only patients with a follow-up of ten years or longer were included in these studies; when the average follow-up was relatively short, e.g. eleven or twelve years, the stated percentages were an underestimation of the actual late recurrences. The average follow-up was not provided.

Second melanoma
The incidence of a second melanoma was described in three studies [McCaul 2008; Bradford 2010; Leiter 2011]. The incidence was relatively constant and low after the first year following primary treatment (always lower than 1/166 person years). The higher incidence found in the first year can be explained by the start of screening. See the chapter Treatment for treatment of a second melanoma.

Table 3 Incidence of a second melanoma per time period after primary treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>N</th>
<th>≤1</th>
<th>3</th>
<th>(1-5)</th>
<th>(5-10)</th>
<th>10-20</th>
<th>&gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Bradford, Freedman et al. 2010)</td>
<td>United States</td>
<td>89.515</td>
<td>1/158</td>
<td>-</td>
<td>1/261</td>
<td>1/287</td>
<td>1/310</td>
<td>1/299</td>
</tr>
<tr>
<td>(Leiter, Buettner et al. 2011)</td>
<td>Germany, Austria, Switzerland</td>
<td>33.384</td>
<td>1/122</td>
<td>1/769</td>
<td>1/526</td>
<td>1/1000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(McCaul, Fritschi et al. 2008)</td>
<td>Australia</td>
<td>52.997</td>
<td>1/79</td>
<td>1/166</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusions

Level 3 There are indications that the incidence of recurrence in AJCC stage IA melanomas is low and constant during follow-up, with less than a recurrence per 100 patient years.
C; Leiter 2011

Level 3 There are indications that the incidence of recurrence in AJCC stage IB, II and III is high (more than one recurrence per 40 patient years in the first year after primary treatment) and slowly decreases during follow-up.
C; Leiter 2011

Level 3 There are indications that more than two-thirds of all recurrences in the first five years after primary treatment are detected (except with AJCC stage IA).

Level 3 There are indications that the incidence of second melanomas, from the second year after treatment of a first melanoma is quite constant and low, with less than one detected second melanoma per 166 patient years.
C; McCaul 2008; Bradford 2010; Leiter 2011
9.3.1 Treatment

**Literature discussion**
See the chapter ‘Diagnosis and treatment of a local/locoregional recurrence’.

**Conclusions**
See conclusions in the chapter ‘Diagnosis and treatment of a local/locoregional recurrence’.

**Considerations**
See considerations in the chapter ‘Diagnosis and treatment of a local/locoregional recurrence’.

**Recommendations**
See recommendations in the chapter ‘Diagnosis and treatment of a local/locoregional recurrence’.

9.3.2 Early detection

(Evidence-based text, clinical question 13.2: effectiveness of treatment in early detection)

**Literature discussion**
Treatment of early detected new cancer manifestations, e.g. based on strict follow-up, were not compared in a randomised study with treatment of late detected new cancer manifestations, e.g. based on clinical signs or symptoms. Six observational studies have been published since 2002 that provide an idea of the difference in survival between early and late detected new cancer manifestations.

One prospective study [Francken 2007] and two retrospective studies [Hofmann 2002, Meyers 2009] did not find a survival advantage between new cancer manifestations detected by the patient themselves on the one hand and the physician or imaging on the other, or between symptomatic and asymptomatic new cancer manifestations. However, these three studies showed important methodological limitations, so that the findings are not so reliable. None of these studies reported the exact survival figures or conducted a risk correction. Lead-time bias was not taken into account. In addition, widely varying inclusion and exclusion criteria were used. For example, Meyers et al. only included stage II and III patients [Meyers 2009], while Francken et al [Francken 2007] and Hofmann et al [Hofmann 2002] also included a substantial number of stage I patients. Hofmann et al. did not provide a clear definition of the different detection methods.

Three studies did find significant differences in survival, but compared different patient groups each time. This makes comparison between these three studies difficult.

In a prospective study, Garbe et al. followed patients with stage I-IV melanoma for twenty-five months [Garbe 2003]. A second primary tumour or recurrence was determined in 46 and 112 patients respectively with a stage I-III melanoma. Early detection was defined by the authors on the basis of disease characteristics: organ or lymph node metastases of 2 cm at the most, less than ten affected lymph nodes, and an indication for surgery with curative intent. The 3-year survival was significantly better in patients with an early detection (stage I/II: 76% versus 38%, p<0.0001; stage III: 60% versus 18%, p<0.0001) [Garbe 2003]. The 10-year survival was significantly better in the group with early detection, also after correction for lead-time bias (41% vs. 26%) [Leiter 2010]. Nonetheless, selection bias cannot be excluded in this study. In patients followed intensively with imaging, a proportion of the recurrences may have been detected in an early stage.

Two other retrospective studies were published by researchers of the Memorial-Sloan Kettering Cancer Center. Moore Dalal et al. followed 1,062 patients with a stage I and II melanoma who underwent a sentinel node biopsy [Moore Dalal 2008]. Of these, a recurrence was determined in 203 patients. Patients in whom a recurrence was determined through self-examination had a significantly better survival (median 37 months) than patients in whom the recurrence was determined based on symptoms (7 months), on physical examination by a physician (29 months), or through imaging (9 months). Romano et al. followed 340 patients with a stage III melanoma who developed a recurrence after curative treatment [Romano 2010]. Patients with a symptomatic recurrence (new tumour determined by the patient or new symptoms) had a significantly poorer survival than patients in whom
the recurrence was determined through physical examination by a physician or imaging (RR 0.67, 95% CI 0.50-0.88, p=0.004).

**Conclusion**

<table>
<thead>
<tr>
<th>Level 2</th>
<th>There is no convincing evidence for a survival advantage associated with early detection of distant metastases after treatment of a primary melanoma.</th>
</tr>
</thead>
</table>

**9.3.3 Diagnostics** (editorial update)

Which diagnostics are the most suited to diagnosing treatable new cancer manifestations at an early stage in an accurate manner?

**Literature discussion**

See the literature discussion in the chapter ‘Diagnosis of a local/locoregional recurrence’.

**Conclusions**

See conclusions in the chapter ‘Diagnosis of a local/locoregional recurrence’.

**Considerations**

See considerations in the chapter ‘Diagnosis of a local/locoregional recurrence’.

**Recommendations**

See recommendations in the chapter ‘Diagnosis of a local/locoregional recurrence’.

**9.4 Evaluation of medical procedure** (consensus-based text)

**Recommendations**

<table>
<thead>
<tr>
<th>The quality of medical care can be evaluated under certain conditions and with explicit information provision to, and consent by, the patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The efficacy and quality of oncological care can be evaluated in a systematic manner with scientific associations and other parties involved.</td>
</tr>
</tbody>
</table>

**Literature discussion**

The report by the Health Council [2007] outlines that evaluation of medical care is often stated as the objective of aftercare. This objective only benefits the individual patient indirectly. The quality of medical care can be evaluated under conditions. The guideline Cancer rehabilitation [IKNL 2011] recommends that if aftercare is used for the evaluation of medical procedure, this only occurs with explicit information to and informed consent by the patient. In doing so, a systematic approach is recommended for the evaluation of medical procedure. Effectiveness and quality of oncological care can be systematically evaluated together with scientific associations, the parties involved and available databases. Indicators for the testing of, and improvement in, the quality of oncological care should be made on a national level.
9.5 Pregnancy, hormonal contraceptives and hormonal substitution agents

(editorial update)

**Literature discussion**

Melanomas that occur during pregnancy are on average thicker than those occurring outside it [Travers 1995]. Causes of this mentioned are changing hormonal balance and the influence of growth factors that occur during pregnancy. It also appears that melanomas are detected later during pregnancy. However, there are no indications that pregnancy negatively influences the prognosis of patients with melanoma, as long as a correction is made for thickness [Mackie, 1991; Daryanani, 2003]. As a result, pregnancy does not need to be advised against. The same applies to the use of hormonal contraceptives and hormonal substitution agents [Holly 1994; Holly 1995].

Advice in the case of a patient with a desire to have children (either a woman or a man) who has been treated for a melanoma does not differ, in principle, as appears from the abovementioned, from that which you would give in the case of other malignancies. It is based on the chance of survival, which can be calculated on the basis of the (micro)stage of the treated melanoma; the interval between removal of the melanoma and pregnancy also plays a role here. In these cases it is up to the patient or couple, often in consultation with the physician, to decide which chance of death they are consciously willing to carry.
CH10 ORGANISATION OF CARE

10.1 Maximum acceptable waiting times (consensus-based text)

General recommendations

The guideline development group is of the opinion that if the general practitioner suspects melanoma, the patient should be seen by a dermatologist or surgeon within two weeks. The extent to which melanoma is suspected is also important, a clear/advanced melanoma must be seen by a dermatologist or surgeon within a few days.

The guideline development group is of the opinion that the conversation about the diagnosis should preferably take place within two after the diagnostic excision; if earlier is possible, this is recommended for patient-friendliness.

The guideline development group is of the opinion that it is preferable for the excision and re-excision (in combination with the sentinel node procedure if indicated) to take place within six weeks after the first visit, but preferably earlier for psychological reasons.

The guideline development group is of the opinion that it is preferable for Screening for psychosocial distress/care needs (recommended instrument: the Distress Thermometer) to take place approximately six weeks after the conversation about the diagnosis but may coincide with the first follow-up visit after three months. (See the guideline Screening for psychosocial distress, www.oncoline.nl).

Additional recommendations for patients with melanoma from stage III

The guideline development group is of the opinion that agreements need to be made about the task division for aftercare offered in the hospital, first- or third-line institutions.

The guideline development group is of the opinion that on completion of primary treatment for aftercare, a fixed contact should be appointed for each patient and that the patient receives the contact data for this contact person. Update the general practitioner.

The guideline development group is of the opinion that the patients should be informed who the fixed contact person is for them in relation to aftercare. Ensure there is regular (interdisciplinary) transfer of information, certainly also in regard to the general practitioner; for example, via the aftercare plan of the patient.

Considerations

The Melanoma Foundation has formulated a document with criteria for quality healthcare from the patient perspective. This document says that patients with a suspected mole are preferably seen within five working days by a dermatologist. One of the other criteria for quality healthcare by the Melanoma Foundation states that general practitioners do not remove moles. The guideline development group is of the opinion that general practitioner are allowed to remove moles, as long as this takes place according to the guideline and the general practitioner sends the tissue for histological analysis.

The conversation about psychosocial effects (screening using the Distress Thermometer) could be conducted by a nurse specialist, dermatology nurse or oncology nurse. It is recommended to create an individual aftercare plan for patients with stage IB and higher (see example in Appendix 17).
10.2 Multidisciplinary consultation for stage III and IV melanoma (consensus-based text)

Recommendations

The guideline development group is of the opinion that melanoma patients with stage III and IV should be discussed in multidisciplinary consultation or in a separate multidisciplinary team for melanoma patients or at the general oncology consultation, but then after consulting a melanoma expert who works in a melanoma centre. The intention is to arrive at optimal treatment results and provide patients with the possibility of participating in clinical trials.

The guideline development group is of the opinion that it is preferable for multidisciplinary consultation or general oncology consultation to take place once per week and at least once every two weeks. This multidisciplinary consultation involves the definitive staging, the choice of treatment fitting the stage as well as decisions are made regarding (possible) follow-up treatment. The following items should be covered in succession during the multidisciplinary consultation: general medical history, specific history, physical examination, additional examination/tests: radiology, laboratory and possible PET and other isotopes research (such as bone scintigraphy); evaluation whether further diagnostics are necessary, if that is important for the decision regarding treatment; staging, when this is complete a) recommended treatment fitting the melanoma in the stage found, b) proposed plan for this patient; any deviations from the treatment guideline and the reasons for it, c) relevant clinical research and any participation in this.

The guideline development group is of the opinion that the treating physician and all relevant specialist should be present in any case during the multidisciplinary consultation. A (oncological) surgeon and clinical oncologist should always be present and preferably an oncology nurse or nurse specialist, who may act as case manager for the patient (potentially instead of the treating physician).

Considerations

An ENT specialist or plastic surgeon is sometimes needed in the multidisciplinary consultation or the patient is discussed in a head/neck team. Consultation with a radiotherapist is sometimes necessary. In principle, the general practitioner of the patient is invited to be present during the consultation.

It is preferable for the multidisciplinary consultation for patients with stage III and IV to take place in or with a ‘melanoma expertise centre’. Teleconferencing is possible for this purpose. Melanoma centres for advanced melanoma could be existing centres: the university medical centres, the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI/AVL) and Erasmus MC Daniel den Hoed.
10.3 Organisation of aftercare (consensus-based text)

Aftercare is collaborating and requires coordination

Recommendations

The guideline development group is of the opinion that agreements need to be made about the task division for aftercare offered in the hospital, first- or third-line institutions. Consider a greater role for the general practitioner in aftercare.

The guideline development group is of the opinion that there should be a fixed contact person for the aftercare for each patient on completion of primary treatment. Arrange this in a multidisciplinary manner with the team and with the general practitioner.

The guideline development group is of the opinion that the patients should be informed who the fixed contact person is for them in relation to aftercare. Record this in the aftercare plan for the patient.

The guideline development group is of the opinion that there should be regular interdisciplinary transfer of information, certainly also to the general practitioner, e.g. via the aftercare plan of the patient.

Literature discussion

Cancer care is pre-eminently multidisciplinary care; for the recovery phase it is offered partly by clinical practice and partly in the first- or third-line institutions. There does not seem to be clear evidence for the best task division (aftercare offered by the specialist, a nurse specialist or general practitioner) and approach in aftercare (personal and telephone consults). The needs of the patients also appear to be diverse. In the report ‘Cancer aftercare: the role of the first-line’ (‘Nazorg bij kanker: de rol van de eerstelijn’, 2011), the Dutch Cancer Society (KWF) argues for the general practitioner to have a greater role in cancer aftercare. The thought is that a generalist approach prevails above a specialist approach for many comorbidities in the (increasingly aging) cancer patient. The Health Council indicates that aftercare after treatment for cancer should be better coordinated. This is in line with the recommendations by the Health Care Inspectorate (IGZ) for the quality of the cancer chain care [IGZ 2009]. On completion of the tumour-specific treatment, the treating physician and other health care professionals agree amongst each other and with the patient who will take responsibility for coordination of (the continuity of) the aftercare. The aftercare plan for the patient can function as a means of transferring care between health care professionals involved in the oncological care path.

Restructuring provides opportunities

Recommendations

In improving aftercare, the guideline development group is of the opinion that a restructure of the entire cancer care process should be considered with an eye for effectiveness.

Literature discussion

The Health Council [2008] states that there are opportunities in cancer aftercare for improved effectiveness by combining the rearrangement of tasks with a change in structure of the care process.
CH11 DIAGNOSIS OF A LOCAL/LOCOREGIONAL RECURRENCE  (editorial update)

**Recommendations**

| It is recommended not to perform imaging or laboratory testing/examination for recurrences and metastases when no suspicious findings are made during physical examination. |
| If a radical intervention is being considered, the guideline development group is of the opinion that it is desirable to confirm the diagnosis by means of pathology analysis. |

**Literature discussion**

**Incidence and diagnosis (editorial update)**

Local recurrence, satellite metastases and in-transit metastases each occur in a few percent of patients. The chance of lymph node metastases is approximately 20%. Treatment with curative intent is possible in these situations. Patients are therefore instructed to search for these metastases. It is recommended in particular to pay attention during any check-up visits to the location of the primary tumour and the relevant area from which the lymph drains to the same node region as the primary tumour. When taking the medical history, the patient is asked about specks and little lumps in this area. Such abnormalities are easily accessible for physical examination. The physician should be aware of the specific metastasis pattern of melanoma. With experience, dermal satellite metastases are often already recognised when they are barely one millimetre. In-transit metastases are common in the lymph ducts and it is therefore important to know where these are located. Local recurrence, satellite metastases and in-transit metastases are not always a dark colour. The lymph node area and other locations where regional lymph nodes may be found are palpated [Roozendaal, 2000]. If findings on physical examination are doubtful, diagnostics may be expanded with ultrasound and thin-needle puncture of a suspicious space-occupying process for cytological analysis.

While laboratory testing and imaging is recommended by the World Health Organisation and in guidelines of countries surrounding the Netherlands, no research has been performed on the benefit of radiological examination of the chest, abdominal ultrasound, computed tomography of the abdomen and brains and lymph node ultrasound on survival [Orfanos 1994; Bassères 1995; Mackie WHO; Newton Bishop2002]. The yield is generally low and false-positive findings that may unnecessarily worry patients are common [Hoffman 2002].

**Conclusion**

<table>
<thead>
<tr>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no indications that laboratory analysis and imaging for recurrences and metastasis lead to an improved chance of survival.</td>
</tr>
<tr>
<td>C Baughan, 1993; Ruark, 1993; Po Hwu, 1999; Hofmann, 2002</td>
</tr>
</tbody>
</table>

**Considerations**

Confirmation of the diagnosis by means of pathology analysis is desirable if a radical intervention is being considered.

Examination/testing for haematogenous metastasis is usually not necessary. After all, even in the case of haematogenous metastasis, a local recurrence or regional tumour manifestation will often be removed to prevent problems such as ulceration, bleeding or nerve innervation at the location. The value of an S-100 determination and of the polymerase chain reaction on circulating tumour cells in serum is still unclear.
Recommendations

The guideline development group is of the opinion that local recurrence, satellite metastases, in-transit metastases and regional lymph node metastases can be treated with curative intent.

12.1 Treatment (editorial update)

Literature discussion

The preferred treatment of locoregional disease is surgical. Local recurrence, satellite metastases and in-transit metastases are, where possible, excised with a margin of 1 cm. Isolated regional perfusion may be considered for tumour manifestations on extremities with a large risk of recurrence. Extensive locoregional disease of an extremity is also preferably treated by means of isolated regional perfusion. Please refer to the relevant chapter for a more detailed description of indications, technique and results of this treatment.

Radiotherapy is an option if surgery is not possible due to medical or technical reasons. Addition of hyperthermia to radiotherapy improves local control of a local recurrence or skin metastasis [Overgaard 1995]. Cryosurgery, electrocoagulation, laser, intrallesional application of Bacille Calmette-Guérin (BCG) or dinitrochlorobenzene (DNCB) may be applied in the palliative treatment of numerous (sub)cutaneous metastases [Strobbe 1998]. With palpable regional lymph node metastases, there is a chance of 80% that non-palpable nodes are also affected. A therapeutic regional lymph node dissection is therefore performed, in which the regional node area is removed in its entirety. It is incorrect to only remove the palpable node(s). Radiotherapy is an option if surgery is not possible. Radiotherapy after lymph node dissection significantly improves regional control and is considered if there is doubt regarding radicality (see adjuvant radiotherapy after lymph node dissection).

Surgical technique (editorial update)

Therapeutic treatment of the neck may consist of the removal of submental and submandibular nodes (level I), the high, middle and low jugular nodes (level II-IV) and the nodes in the posterior cervical triangle (level V), called a modified radical cervical node dissection. Depending on the extent of the metastases, this may be expanded to include the sternocleidomastoid muscle and/or the internal jugular vein and/or the accessory nerve. This is called a formal radical cervical node dissection, but is rarely indicated [Robbins 2002]. Depending on the location and extent of metastases, a selective cervical node dissection may be sufficient for the melanoma, in which not all levels are removed in the neck. If the lymph nodes in and around the parotid gland are part of the drainage area of the primary tumour, a superficial parotidectomy should be performed ‘en bloc’ with the dissection while sparing the facial nerve. For facial melanomas with metastasis in the parotid only, a superficial parotidectomy and selective cervical node dissection of levels II and III may suffice [Ch’ng S 2012]. In melanomas localised on the back of the head and in the neck, the retro-auricular and suboccipital nodes are removed, together with the nodes of level II, III, IV and V (posterolateral cervical node dissection).

A complete node dissection is always performed in the axilla (level I, II, III). To this end, the medial pectoral nerve, the long thoracic nerve, the thoracodorsal nerve and the arteries and subcapsular arteries and veins are almost always spared. If node metastasis in the axilla is extensive, the minor pectoral muscle may be removed along with the sample. Metastasis to the supraclavicular area occurs via the nodes located ventral and dorsal of the axillary vein. These may also be partially removed. During a complete pelvic node dissection, the femoro-inguinal nodes as well as the nodes along the external iliac arteries and veins (to the iliac bifurcation and the aorta bifurcation if necessary) are removed (supported by preoperative imaging, such as a CT or PET scan), together with the nodes along the arteries, veins and obturator nerve. If imaging does not show metastases in deeper located nodes in the pelvis, an alternative to an extensive node dissection may be chosen [van der Ploeg, 2011].
Conclusion

**Level 4**

Treatment with curative intent is possible for a local recurrence, satellite metastases, in-transit metastases and regional lymph node metastases.

D; Expert opinion

**Considerations**

If there is limited life expectancy, less extensive surgery or a wait-and-see approach may be considered.

**12.2 Adjuvant radiotherapy after lymph node dissection** (consensus-based text)

**Recommendation**

It is recommended to give patients with a high risk of a regional recurrence and relatively favourable prognosis adjuvant radiotherapy, after performing a lymph node dissection, to improve the disease-free survival.

**Indication for adjuvant radiotherapy after lymph node dissection**

**Literature discussion**

In a retrospective study over a period of 26 years with 338 patients who underwent a lymphadenectomy without radiotherapy, the chance of regional recurrence was 30% after a follow-up period of ten years. The recurrences occurred especially within two years after node dissection [Lee, 2000]. Multiple non-randomised studies suggest a better regional control with adjuvant radiotherapy after a therapeutic lymph node dissection in node-positive melanomas [Agrawal, 2009; Ballo 2006, Ballo 2002, Bibault, 2011; Strojan, 2010]. Regional control after radiotherapy was 78-89% after radiotherapy compared to 56-70% control after surgery only. The advantage is probably the greatest in patients with a high risk of a regional recurrence. Most studies did not show a difference in survival. The radiotherapy schedules used in post-lymph node dissection series varied from 5 x 6 Gy to 30 x 2 Gy. The doses used were usually greater than the biological equivalent of 50 Gy in 2 Gy. A retrospective analysis of 86 lymph node dissection patients with a high risk of a regional recurrence showed an improvement in regional control of 35% to 80% at doses of < 50 Gy and > 50 Gy respectively [Bibault, 2011].

In a recent phase III study, the role of adjuvant radiotherapy was researched in patients with a high risk of a regional recurrence after a regional lymph node dissection. Criteria for a high risk were: more than 1 parotid node, more than 2 neck or axillary nodes, more than 3 pelvic nodes, extracapsular metastasis, nodes greater than 3 cm, or greater than 4 cm in the pelvis. In this study, 250 patients were randomised between observation versus regional radiotherapy with a dose of 48 Gy in 20 fractions of 2.4 Gy. The study confirmed that irradiation significantly improved disease-free survival (HR 1.77, p=0.041), but without effect on survival.[Henderson, 2009]

**Conclusions**

**Level 3**

There are indications that radiotherapy improves regional tumour control after performing a lymph node dissection in high risk patients.

A2; Henderson, 2009

**Level 3**

There are indications that adjuvant regional radiotherapy after a lymph node dissection does not affect survival.

A2; Henderson, 2009

**Level 2**

There are indications that doses >50 Gy are necessary to reduce the chance of a regional recurrence after a lymph node dissection.

B; Bibault, 2011; Henderson, 2009; Ballo, 2002
Considerations
Application of adjuvant regional radiotherapy only appears to be appropriate if the patient does not have an unfavourable prognosis and/or does not have distant metastasis in the short-term.

12.3 Regional isolated perfusion (editorial update)

Literature discussion
Regional perfusions in the Netherlands are performed in four clinics (University Medical Center Groningen, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (Amsterdam), Erasmus MC-Daniel den Hoed Oncological Centre (Rotterdam) and University Medical Centre St Radboud (Nijmegen). The indication for perfusion is the same in all clinics.

Technique
During perfusion, the blood circulation of an arm or leg is isolated and connected to an extracorporeal circuit (heart-lung machine) with oxygenation and temperature regulation. The extremity is subsequently flushed for 60 to 90 minutes with one or two drugs. High doses of these drugs can be used because of the isolation; vital organs are not affected. A radio-pharmacon injected into the extracorporeal circuit controls the isolation. Any leakage to the systemic circulation is measured above the heart.

Indications
There is no role for adjuvant perfusion in a primary melanoma of the extremity [Schraffordt Koops, 1998]. An indication for therapeutic perfusion is extensive tumour growth in an extremity, such as satellitosis and in-transit metastases. Amputation of an extremity can usually be prevented in these situations. The chemotherapeutic agent melphalan was initially used in perfusion. Complete remission was achieved in approximately 50% of patients using this agent; the remission was maintained for longer than three years in a bit more than half of patients. Partial remission was achieved in approximately 25% of patients, while a temporary stabilisation of the tumour process was seen in the remaining 25% of patients [Klaasse, 1994]. The addition of the cytokine tumour necrosis factor-alpha (TNF-a) to melphalan is preferable with large recurrences. A complete remission percentage of approximately 70% can be achieved with this combination. The remission duration is probably no different to perfusion with melphalan only. [Fraker, 2002; Eggermont, 2003]
In the meantime it has become known that TNF-a does not increase locoregional toxicity. Systemic toxicity on leakage is more serious however, than with a perfusion with melphalan only. Some patients have fever and chills within four hours after treatment following perfusion in which TNF-a is administered. Hypotension can be resolved using extra addition of infusion fluids. Admittance to an intensive care department is sometime necessary.

Conclusion
Level 4
The guideline development group is of the opinion that there is no indication for adjuvant regional isolated perfusion in patients with a primary melanoma of an extremity. Regional isolated perfusion with melphalan is the first choice for irresectable metastases of an extremity. In the case of so-called ‘bulky disease’, the preference is a perfusion in which melphalan is combined with TNF-a.

D: Expert opinion
**Literature discussion**

In the palliative phase, screening for psychosocial distress and providing psychosocial care where required may (also) improve quality of life. In the guideline Screening for psychosocial distress (NVPO (Dutch Society for Psychosocial Oncology), 2009), a screening instrument (the Distress Thermometer) is recommended. It is preferable for screening of complaints to take place every three months. See the guideline Screening for psychosocial distress for further details. To determine if cancer rehabilitation is a suitable intervention for the patient with complaints, the Distress Thermometer can be supplemented with the Visual Analog Scale (VAS) fatigue list and the Patient Specific Complaints Questionnaire (PSK). There are special cancer rehabilitation programmes aimed at disease-focused and symptom-focused phases of palliation. The personal goals and preferences of the patient (and their family) are central in the rehabilitation programme. In doing so, one can strive to prevent and treat symptoms on the one hand, and optimise the quality of life on the other. Striving to maintain physical functions such as walking stairs may be essential to this. For patients that gradually ‘fall out of the programme’ as a result of a progressive illness, it is recommended a more limited version of the programme is facilitated at home, in order to be able to benefit from the effects of what is still possible (empowerment) in the terminal phase. See the guideline Cancer rehabilitation (IKNL 2010) for further details.

See www.pallialine.nl for palliative care guidelines.