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Melanoma – investigation and primary treatment

CLINICAL REVIEW

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Melanoma is a relatively common diagnosis, both in the primary and specialist health service. Ongoing research and new evidence base means that the recommendations for investigation and treatment are continually changing. This can lead to uncertainty among doctors who do not treat this patient group regularly. In this clinical review we give a summary of the latest recommendations, primarily aimed at general practitioners, dermatologists and doctors in local hospitals.

Melanoma is one of the most common forms of cancer in Norway, and its incidence has been rising sharply since the 1960s. After breast and testicular cancer, it is the second most common form of cancer in women and men aged 25–49 years (1). Metastatic melanoma was previously considered to be incurable with a relatively short life expectancy, but developments in treatment in the last decade have led to patients now living considerably longer.

The aim of this article is to give a brief summary of investigation and treatment based mainly on the Norwegian action programme for malignant melanoma (2), a search for relevant articles in PubMed and the authors' own clinical experiences.

Epidemiology

A total of 2,770 new cases of melanoma were recorded in Norway in 2020, with 1,439 cases in men and 1,331 in women. In the same year, 295 people with the diagnosis died (3). The high mortality is largely due to late diagnosis and a more advanced stage of the disease at the time of diagnosis (4). Damage caused by ultraviolet radiation from sun exposure is the largest risk factor, and people with fair skin (Fitzpatrick skin types 1 and 2) are particularly at risk due to low levels of melanin in the skin and thus less sun protection. Other risk factors are a family history of melanoma and the number of moles (common and atypical). People with a mutation in the genes *CDKN2A* and *CDK4* have a significantly increased risk of melanoma (2,5). We recommend that these patients, as well as patients with a strong family history of melanoma, be offered annual check-ups with a dermatologist, using digital dermatoscopy where possible in those with the abovementioned gene mutation (5).

A meta-analysis from 2012 concluded that the use of sunbeds significantly increased the relative risk of developing melanoma, and that this risk increased with the number of sunbed sessions as well as first use of sunbeds before the age of 35 years (6).

Prevention

Preventative work is important. Since the 1980s, Australia, which has the highest incidence and mortality rates for melanoma in the world, has run an active information campaign about sun protection. This has led to a decrease in incidence and mortality in the under-40s age group (7). Basic sun safety knowledge as well as self-examination and early contact with a doctor in the event of changes in moles are simple measures that improve prognosis.

Diagnostic evaluation

CLINICAL ASSESSMENT

It is important to take a thorough case history, including family history and sun exposure, as well as examine skin type in patients who present to their general practitioner with a skin lesion. Most cases of melanoma occur de novo in melanocytes in normally pigmented skin, but around 30 % occur in existing moles (8). Characteristics of melanoma are asymmetry, irregular borders and pigmentation, dimensions and changes (growth, bleeding and itching). Some melanomas are unpigmented. The presence of one or more criteria of the ABCDE rule can be used to identify pigmented lesions that may be malignant. Nodular melanomas often have different characteristics and can be identified using the EFG rule (Figure 1).

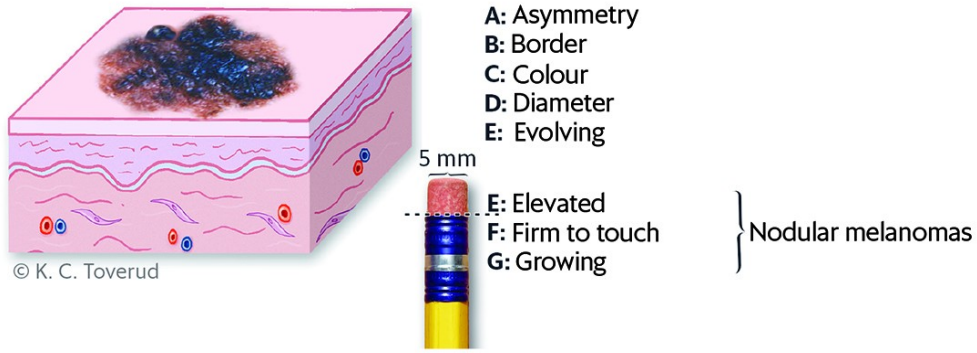

Figure 1 The ABCDE/EFG rule.

The most common location of melanomas is the torso in both men and women, as well as the lower extremities in women (3). If melanoma is suspected, lymph nodes should be palpated for metastases. The sensitivity of clinical diagnosis of melanoma by experienced dermatologists is approximately 70 %, which increases somewhat with the use of dermatoscopy (9).

EXCISION OF SUSPECTED MELANOMA

Excision is carried out primarily by a general practitioner or dermatologist with a 2–5 mm margin and cuff of underlying fat (2). The skin incision in extremities should run in a vertical direction, which reduces the tension in any subsequent wide excision (Figure 2). Punch or shave biopsies should not be taken. Punch biopsy is acceptable for large tumours where excision with direct closure is not possible or would result in major cosmetic consequences. Laser removal should not be performed for moles.

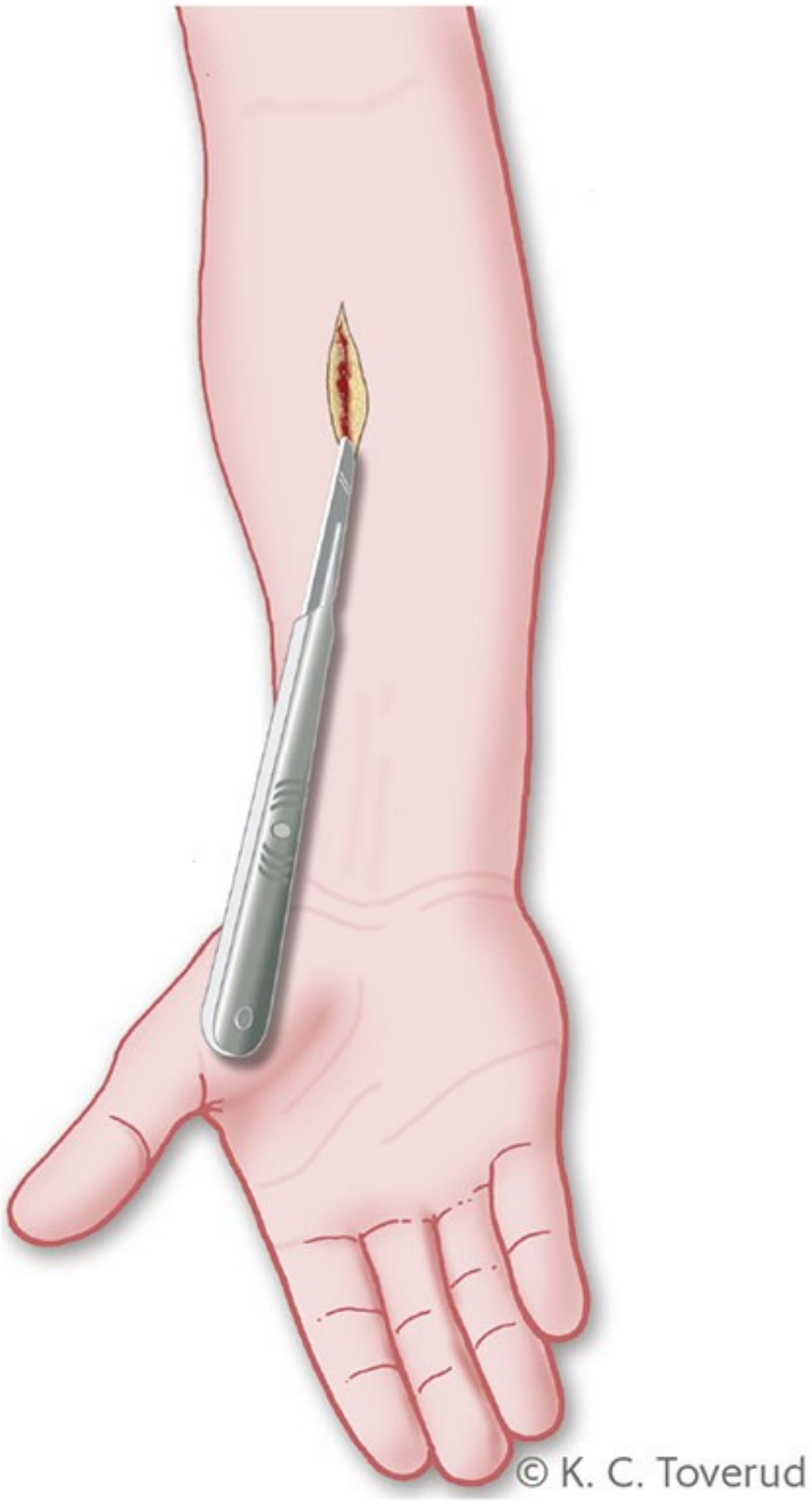

Figure 2 The incision should run in a vertical direction for excision biopsies in extremities to reduce the tension in the scar, particularly if subsequent re-excision is required.

The specimen is fixed on formalin and sent to a pathology department labelled 'cancer pathway'. The pathology referral should contain information about the location (preferably with a diagram), degree of suspicion of malignancy and whether the patient has had melanoma previously. The latter is important in assessing whether it is a new melanoma or metastasis.

SPECIFIC LOCATIONS

Assessment of subungual pigment changes requires experience with taking samples and diagnostic evaluation. Melanoma can cause pigmented bands in the nail, with or without accompanying pigmentation of the proximal skin (Hutchinson's sign), thickened nail with destruction, nail lifting, ulceration and pain (10). Suspect subungual pigment changes, as well as moles on the soles of the feet or palms of the hand (acral nevi), should be referred to a surgeon for excision.

Melanoma can also occur in the mucous membranes and eye. These lesions are rare, difficult to treat, have a poor prognosis and should be treated and followed up by an ophthalmologist, surgeon or oncologist with special knowledge related to melanoma treatment (2).

PATHOLOGY

Microscopic examination of a tumour by a pathologist is the gold standard for diagnostic evaluation, including, where appropriate, immunohistochemical examination and mutation analyses (11). Melanoma is classified into several subtypes, the main groups being superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral melanoma. The WHO classification by frequency of cumulative sun damage and oncogenic mutations is not used in Norway today (2, 12).

The pathology report should contain histological subtype, any in situ changes, growth phase, any ulceration, depth of invasion (Clark's level 1 - 5), tumour thickness (Breslow thickness), mitotic rate per mm^2, any vascular or nerve invasion, regression, tumour-infiltrating lymphocytes, microscopic satellites or in-transit metastases, as well as distance to resection margins for melanoma in situ and melanoma (2, 11, 13).

Surgery for detected melanoma

If melanoma is detected, the patient is informed about the pathology report and referred to a surgical department under the 'cancer pathway'. The patient is assessed and investigated based on the thickness, subtype and location of the primary tumour. Then a wide excision is performed with 1–2 cm free macroscopic margins, down to underlying muscle fascia (Table 1) (14). The national action programme for melanoma still contains the recommendation for margins of up to 3 cm, but this is being revised at the time of writing (2). Excision margins of 5 mm are recommended for melanoma in situ (2). The stated margins are not absolute. Account must be taken of the type of tumour growth and adjacent critical structures and aesthetics, particularly in the face.

Table 1

Excision margins according to Curti and Faries (14).

Tumour type and thickness	Margin
Melanoma in situ	0.5 cm
Melanoma ≤ 2 mm	1 cm
Melanoma > 2 mm	2 cm
Desmoplastic melanoma	2 cm

In case of re-excision, the specimen must be marked for orientation, and the pathologist must be informed about the melanoma's subtype, location, tumour thickness and whether or not the tumour was removed with clear margins initially. Histological findings for desmoplastic melanoma may resemble scar tissue, and residual tumour may be overlooked if information is not provided about this subtype (13). If residual tumour is detected, assessment of whether this entails a change in tumour thickness is required.

Sentinel lymph node diagnostic evaluation

Sentinel lymph node diagnostic evaluation is currently offered for tumours over 1 mm in thickness and performed at the same time as wide excision (9). It is reported that 20 % of patients with tumour thickness 1–4 mm have sentinel lymph node metastasis. Of these patients, 15–20 % have spread to further lymph nodes in the same regional lymph node basin (15).

The rate of finding positive sentinel lymph nodes is low with tumour thickness below 0.8 mm (pT1a), and the procedure should not be offered to this patient group. Young patients with tumour thickness of 0.8–1.0 mm with ulceration or mitoses can be assessed for sentinel lymph node diagnostic evaluation by a multidisciplinary team (2).

Wide excision and sentinel lymph node diagnostic evaluation are generally performed as day surgery with preoperative lymphoscintigraphy and single-photon emission computed tomography (SPECT)-CT the day before. A gamma probe and, if appropriate, patent blue are used peroperatively to locate sentinel lymph nodes, which can be challenging to find, particularly in the neck. Therefore, patients with melanoma in the head/neck region can be referred to a university hospital for this diagnostic evaluation. If the sentinel lymph nodes are not accessible for surgery, the patient can be referred for ultrasound examination, if necessary with fine needle aspiration cytology if suspect lymph nodes are found. The specimen(s) are sent to a pathologist for diagnostic evaluation.

If sentinel lymph node metastasis is found, adjunctive treatment may be appropriate. These patients are discussed by a multidisciplinary team. Factors such as the aggressiveness of the primary tumour (Breslow thickness, ulceration, mitotic rate), as well as the size of metastatic foci in the lymph node and comorbidities, determine further follow-up and treatment.

Completion lymph node dissection was previously the standard treatment to prevent regional recurrence and further spread of the disease. This is no longer routinely recommended today (16, 17).

Follow-up and adjuvant treatment

Adjuvant treatment is not currently offered for patients with melanoma in stages I and II (18). Internationally, there are several phase III studies for patients with melanoma in stages IIB and IIC (19), and immunotherapy is approved for these patients in the USA (20).

The patient's first check-up should take place with a dermatologist three months after resection. This is the only check-up recommended for patients with stage IA melanoma and melanoma in situ. Further check-ups for low-risk patients (i.e. stage IB–IIA) can take place with their general practitioner every six months for five years. These check-ups will entail examination of the scar following previous excision, examination of regional lymph node basins and a general inspection of the skin.

Patients at higher risk of recurrence (i.e. stage IIB–IIC) should be followed up by a dermatologist every six months for five years. In addition, locoregional ultrasound examination is recommended every six months for three years and positron emission

tomography (PET)-CT after 12, 24 and 36 months. An MRI scan of the head is taken if there is a clinical suspicion of brain metastases (2).

Adjuvant treatment with immunotherapy or signal inhibitors (BRAF and MEK inhibitors) are approved for use in stage III–IV melanoma (21–23). Treatment should be initiated within twelve weeks following the date of surgery and administered for up to one year after complete resection of melanoma in stages III and IV. The treatment of these patients is followed up by an oncologist with specialist experience in melanoma.

Local recurrence and metastases

Local recurrence is defined as tumour growth in or under the scar following primary excision. Tumours located < 2 cm from the primary scar are known as satellite metastases, while in-transit metastases are located between the primary scar and regional lymph node basin (2).

Melanoma can recur several decades after the primary diagnosis. A new tumour or enlarged lymph node in a patient with a history of melanoma should always be investigated with a cytological sample, and a general practitioner can make this referral. Surgical treatment is the first choice for locoregional recurrence. Adjuvant treatment by an oncologist is often also initiated.

Summary

Melanoma is a serious cancer that can metastasize to all organs. In Norway, the incidence of this form of cancer is rising, and mortality is relatively high. Improved treatment provision means that more patients are living longer with the diagnosis. Surgery is still the first choice of treatment for primary melanoma and locoregional recurrence. Pathologists require appropriate information to make the correct diagnosis. Adjuvant treatment is offered to patients with stage III and IV melanoma to reduce the risk of recurrence. Prevention, early diagnosis and appropriate primary treatment are key in reducing incidence and mortality.

The article has been peer-reviewed.

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