Cutaneous Melanoma

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Contents

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13.1 Introduction

13.1.1 Epidemiology

Melanoma is a relatively rare tumour, arising from the melanocyte in the basal layer of the skin, but can sporadically also arise in the squamous epithelium and in the neuroepithelium, i.e. the retina of the eye.

The incidence of melanoma is more than doubled in the past 20 years. For example, in the Netherlands, the incidence has increased from 10 to >25 per 100,000 persons; the incidence is lower in Southern European countries and somewhat higher in the Northern European countries but two- to threefold higher amongst Caucasians in Australasia. The incidence increases with age.

As a consequence of the higher incidence rate, also the absolute mortality rate from melanoma increased from 2.2 to 3.6 per 100,000 persons [1]. However, the 5-year survival rate improved slightly to about 88 % and is strongly dependent of the tumour stage (Table 13.1) [2].

A genetic predisposition, particularly a Nordic Caucasian family trait with a white skin, fair or red hair and dimples, is the most important risk factor, a risk which is exaggerated by exuberant UV exposure, i.e. sunbathing and sun bench (Fig. 13.1).

13.1.2 Staging and Prognosis

See Tables 13.1 and 13.2.

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Table 13.1 Melanoma stage [TNM, 7th edition, 2010] [35], relative incidence and 5-years survival by stage

Stage	Description				5-year survival (%)
		T	N	M	
I	A	Clinical T1a	N0	M0	~100
	B	Clinical T1b or T2a		M0	95
II	A	Clinical T2b or T3a	N0	M0	85
	B	Clinical T3b or T4a	N0	M0	77
	C	Clinical T4b N0 M0	N0	M0	65
III	A	Any clinical T Pathological T1-4a	N1-3 N1a or N2a	M0	78
	B	Pathological T1-4a Pathological T1-4b	N1b, N2b or N2c N1a, N2a, or N2c	M0	62
	C	Pathological T1-4b Any T	N1b or N2b N3	M0	50
IV		Any T	Any N	M0	12
All stages					88

Source: Netherlands Cancer Registry [1]

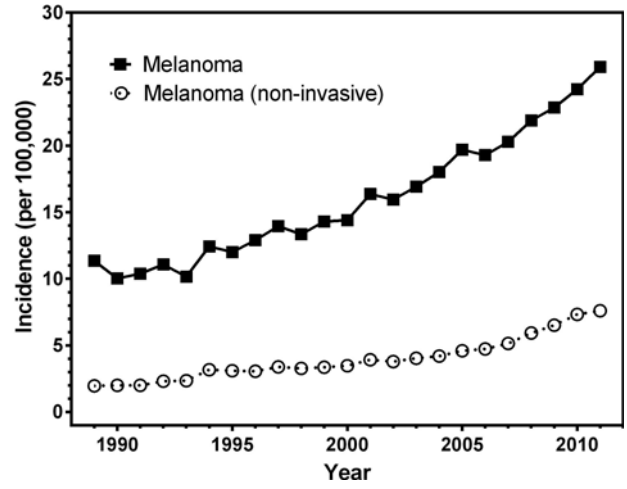

Fig. 13.1 Incidence of invasive and non-invasive melanoma in the Netherlands from 1989 until 2011 (*ESR* European Standardized Rate per 100,000 persons per year, adjusted for age and sex) (Source: Netherlands Cancer Registry [1])

Table 13.2 Melanoma stage [TNM, 7th edition, 2010] [35]

Clark level	Description
I	Melanoma confined to the epidermis (melanoma in situ)
II	Invasion into the papillary dermis
III	Invasion to the junction of the papillary and reticular dermis
IV	Invasion into the reticular dermis
V	Invasion into the subcutaneous fat

13.2 Clinical Diagnosis

The diagnosis of a melanoma starts with a critical inspection of the patient. A popular mnemonic to remember signs and symptoms of melanoma is 'ABCDE' [3, 4]:

- *A*symmetrical skin lesion.
- *B*order of the lesion is irregular.

- *C*olour: melanomas usually have multiple colours.
- *D*iameter: moles greater than 6 mm are more likely to be melanomas than smaller moles.
- *E*volving, i.e. changing in shape, size or aspect.

Particularly for the identification of the aggressive nodular melanoma, the 'EFG' acronym may better apply [5]:

- *E*levated
- *F*irm to touch
- *G*rowing progressively for more than a month

13.3 Surgery

13.3.1 Surgery (Diagnosis)

Radical surgical excision is the cornerstone of both diagnosis and treatment. For a diagnostic excision, usually a 2 mm tumour-free margin is recommended. A wider excision is not advised for primary diagnosis, since in more than one third of cases, the histological diagnosis is not a melanoma. Furthermore, the prognosis is less dependent of radial extension and more from tumour depth, expressed by the Breslow thickness, which is difficult to assess by clinical observation.

If satellite or in transit metastases are present, a biopsy of one of these lesions should be taken for histological verification. If distant metastases are suspected, the diagnosis should be made by the most simple method, which usually is an incision biopsy or a fine-needle aspiration.

13.3.2 Re-excision

For a therapeutic (re-)excision, the following margins are recommended: 0.5 cm for in situ melanoma (pTis), 1 cm if the Breslow thickness ≤2 mm (pT1 and pT2) and 2 cm for Breslow thickness >2 mm (pT3 and pT4).

13.3.3 Sentinel Node Procedure and Lymph Node Dissection

The value of the sentinel node procedure in melanoma is not yet established and is not recommended beyond a clinical study.

Dissection of regional lymph node is not recommended as an elective procedure, but is indicated if regional lymph nodes are involved, i.e. inguinal, axillary or neck nodes. There is debate if such dissections should be radical or can be limited to superficial dissection or involved palpable nodes only.

13.4 Radiotherapy

The radiosensitivity of melanomas is heterogeneous, and the variation in radiation response amongst melanomas is almost as large as that reported for other human cancers differing in histological type [6]. However, based on very few clinical studies, it is mistakenly held that melanoma always is a radioresistant tumour and that the sensitivity is not much different from that of the normal skin [7, 8]. This suggests that there would only be a marginal advantage of fractionated irradiation, and the authors therefore recommended to use hypofractionated radiotherapy, i.e. the use of few but high fractions.

However, the assumption that there is only a minor fractionation effect of conventional schedules using 2.0–3.0 Gy per fraction was based on very few direct observations and was predominantly based on extrapolation of radiobiological modelling from melanoma patients that received high fraction doses (≥5 Gy) anyway and, moreover, an insufficient total doses (mostly ≤50 Gy). Further clinical studies that addressed the question of optimal fractionation, including a prospective clinical study, did not provide convincing evidence that hypofractionation is superior to conventional dose fractionation [9–14].

In hindsight, the shallow dose-response effect of melanoma radiotherapy may be biased on one hand by the fact that radiotherapy is usually reserved as palliation for patients with inoperable bulky tumours, with widespread metastases, and on the other hand by the large field sizes and inconvenient tumour sites frequently precluding the delivery of a biologically adequate dose (≥60 Gy).

13.4.1 Primary Curative Radiotherapy

Curative radiotherapy is an alternative for patients with a primary melanoma or lentigo maligna (M. Dubreuilh) unfit for surgery. This may also include patients with nodal metastasis. Many radiation schedules are being used, such as [9, 11, 14–16]:

- Conventional 2 Gy per day fractionation schedule of ≥60 Gy in microscopic disease and ≥70 Gy in macroscopic disease
- 45 Gy in 9 fractions of 5 Gy, 2 fractions per week
- 36 Gy in 6 fractions of 6 Gy, 2 fractions per week

13.4.2 Adjuvant Radiotherapy

Although the role of adjuvant radiotherapy, especially after dissection of nodal metastases, is debated, recent studies suggest an improvement of loco-regional control from ~60 % after surgery alone to ~80 % after surgery plus adjuvant radiotherapy, provided that a sufficient dose is being given (≥60 Gy, conventionally fractionated) [14, 17]. However, radiotherapy does not seem to improve survival in patients with N+ disease, since distant metastasis is the major cause of tumour relapse and death in this stage [18].

13.4.3 Recurrent Melanoma

Recurrent melanoma in the scar, or in previously resected in transit metastases or lymph node stations are dreaded for pain and the risk of ulceration. Usually, a second resection is technically not feasible. As argued above, tumour localisation, metastatic spread and a poor patient condition usually preclude high-dose curative radiotherapy. Palliative radiotherapy alone therefore results in few enduring complete remissions, but a partial response resulting in worthwhile palliation of pain, ulceration or obstruction is very common [19, 20].

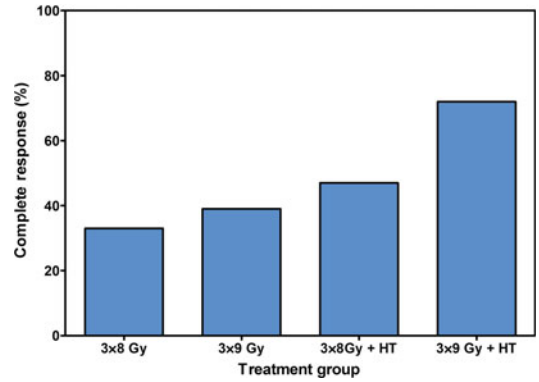

Fig. 13.2 Complete response in malignant melanoma treated with radiation alone or combined with hyperthermia as a function of radiation dose, yielding a 1.4- to 1.8-fold enhancement ratio of hyperthermia (Overgaard et al. [21])

Radiotherapy with hyperthermia improves local control. In the four-armed randomised trial by Overgaard et al. [21], patients received either 3×8 Gy or 3×9 Gy, 1 fraction per week, with or without hyperthermia [21]. Complete or partial response was 80 %. Complete response was >70 % in patients receiving 3×9 Gy plus hyperthermia, compared to <40 % in patients receiving radiotherapy alone. Hyperthermia was particularly more effective in smaller tumours (tumour size <4 cm, response >70 %) than in larger tumours. In larger tumours, one might consider to use a higher dose, i.e. 7–9×5 Gy, twice a week combined with weekly hyperthermia. Hyperthermia makes tumour cells more sensitive to irradiation; however, hyperthermia may induce the so-called thermal tolerance, which requires larger time intervals (>2 days) between each hyperthermia treatment (Fig. 13.2).

13.4.4 Brain Metastasis of Melanoma

Brain metastasis is a common and usual fatal complication of melanoma, sometimes as the only manifestation occurring many years after first diagnosis.

Surgical resection is usually performed for operable single metastasis, both for diagnosis and swift palliation [22]. Post-operative whole brain radiotherapy (30 Gy in 10 fractions of 3 Gy) is usually recommended for patients with a single metastasis, without extraneous disease and in a fair or good general condition (Karnofsky performance status ≥70).

For patients without extracranial disease, with one to three brain metastases, stereotactic radiotherapy alone gives comparable control rates as surgery, with a median survival up to 9 months [23].

For patients with multiple brain metastases (>3), with extracranial disease and in a poor condition, a short fractionation schedule (20 Gy in 5 fractions of 4 Gy) is probably as effective as more prolonged schedules. The median survival is less than 3 months.

13.4.5 Extracutaneous Melanoma

Extracutaneous melanomas are rare tumours, between 8 and 11 new cases per million citizens, compared to 120–160 cases of cutaneous melanoma per year [24]. Melanoma of the eye is the most common extracutaneous localisation. The prognosis of extracutaneous melanoma is worse than that of cutaneous melanoma.

13.4.6 Melanoma of the Eye

Choroidal melanoma is the most common primary malignant tumour of the eye. Until the introduction of plaque brachytherapy in the 1960s, enucleation was the standard treatment. From that time on, various eye-conserving treatment modalities such as ruthenium-106 (Ru-106) or iodine-125 plaque brachytherapy, proton beam radiotherapy, stereotactic radiotherapy, transscleral or transretinal local resection and phototherapy (photocoagulation or transpupillary thermotherapy, TTT) have been developed with the aim of preserving useful vision without increasing the risk of metastatic spread [25]. A randomised trial comparing iodine-125 brachytherapy with enucleation did not find a difference in survival, but vision could be saved in 40 % of patients [26]. In a recent study of patients treated by Ru-106 brachytherapy, the 5-year local tumour control was 96 %, a functional vision could be retained in 50 % of patients, and 4.4 % required enucleation for tumour recurrence or radiation complications [27]. The dose to the scleral surface was 600–800 Gy in 6–8 days.

Conjunctival melanoma is a rare melanoma localisation, which, unfortunately, is frequently treated with mutilating surgery alone, harbouring a high recurrence rate, and with meagrely effective treatments for palliation [28]. The recommended treatment is local excision followed by brachytherapy, with either a high dose rate strontium-90 (Sr-90) or a low dose rate Ru-106 plaque applicator [29, 30]. Recommended doses vary between 60 Gy in 6 fractions of 10 Gy high dose rate Sr-89 to 100 Gy and continuous low dose rate Ru-106 at 1 mm depth. Tumour control is well over 90 % in tumours of the lateral conjunctiva, but both local recurrences and distant metastasis are high (>50 %) when the medial eye and caruncula are involved. For larger tumours, surgery plus interstitial brachytherapy can be considered [31].

13.4.7 Melanoma of Squamous Epithelium

Melanoma of the squamous epithelium usually presents as multiple superficially extended disease of the mucosa, for instance, of the oral or vaginal mucosa. The tumour is usually not amenable for radical surgical resection. If palliative radiotherapy is indicated, we recommend combination with hyperthermia, which may yield durable local control [20].

13.5 Recent Developments in Melanoma Treatment

13.5.1 Activation of the Immune System

For metastatic melanoma, alkylating cytostatic drugs, such as DTIC and temozolomide, were the only demonstrated effective chemotherapy. Immunotherapy, although promising, is

usually reserved for patients in clinical studies. Ipilimumab is an antibody that activates the body's immune system by inhibiting the cytotoxic T-cell lymphocyte antigen-4 molecule. In a randomised study in patients with stage III or IV melanoma, the median survival was improved to 10 months for patients treated with ipilimumab compared to 6.4 months in the control groups [32]. Treatment-related mortality was about 2 %. These findings fuel further research for targeted therapy and combination with chemotherapy and radiotherapy.

13.5.2 PARP Inhibition and Hyperthermia

Radiotherapy works by causing DNA breaks. These DNA breaks are less well repaired by tumour cells than by normal cells. Hyperthermia is a tumour-selective sensitiser of radiotherapy by selectively inhibiting the DNA repair in (hypoxic) tumour cells and not so much in healthy (normoxic) cells. The molecular mechanism of hyperthermia was, until recently, poorly understood.

For some time, it is known that the BRCA2-protein is an essential DNA-repair molecule involved in the repair of DNA double-strand breaks by homologous recombination. Fong et al. [33] found that patients with congenital BRCA2 deficiency and with metastasised breast cancer respond well by additionally inhibiting DNA single-strand break repair by inhibition of PARP [33]. Recently, we found that hyperthermia blocks the production of the BRCA2 protein. Next, hyperthermia did sensitise tumour cells proficient in BRCA, but not in BRCA-deficient cells [34]. Next, we found, both in vitro and in vivo, that the inhibition of PARP sensitises tumour cells for hyperthermia and delays tumour growth. These results are presently translated in to early clinical studies.

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