

Clinical features and classification

Subtypes of melanoma

Clinicopathologic subtypes

Clark et al [1] were the first to divide melanoma into subtypes depending on clinical and histologic features, criteria that were later used by other researchers [2]. The majority of all melanomas fall into the following four subtypes (the World Health Organization [WHO] classification of melanoma) (Table 2.1) [1–5]:

- Superficial spreading
- Nodular
- Lentigo maligna
- Acral lentiginous

Precursor lesions with no penetration of the basal membrane but with a high risk of transforming into melanoma are called “melanoma in situ” or “lentigo maligna.” The superficial cells of the primary lesion, either intraepidermal or just below the basal membrane, determine the classification of melanoma. Lesions without pigment are classified as “amelanotic” [1]. Nodular and acral lentiginous melanomas have the poorest 5-year survival rates among all histological subtypes (69.4% and 81.2%, respectively), mainly because of their higher tumor thickness at the time of diagnosis [6].

The WHO classification includes further subtypes listed in Table 2.2 [7]. One rare melanoma subtype is the desmoplastic melanoma that is often amelanotic and can be difficult to diagnose. Histopathologically, perineural invasion is an atypical feature of this desmoplastic melanoma

Overview of the four major melanoma subtypes



Superficial spreading melanoma is the most common subtype [3]. It frequently presents with diffused borders, a combination of several colors such as brown, black, red, white, or others, and an irregular and elevated surface. It is characterized by laterally spreading melanocytes within the epidermis, making the assessment of the lateral extent of the melanoma difficult [1,2].



Nodular melanoma is another common subtype. In contrast to the superficial spreading melanoma, the nodular melanoma presents with a relatively sharp border as the melanocytes extend vertically rather than horizontally [1,2].



Lentigo maligna or Lentigo maligna melanoma usually develops on sun-damaged skin (eg, on the head and neck area of elderly patients). Lentigo maligna is a melanoma in situ and a precursor lesion for the lentigo maligna melanoma. Distinction from “actinic melanocytosis” (increased intraepidermal melanocytes secondary to chronic sun exposure) can be difficult [2]. Contrary to the melanoma in situ, lentigo maligna melanoma invades the dermis.



Acral lentiginous melanoma is rare in the white population but appears in higher proportions in other races (in particular in Blacks, Asians, and Pacific Islanders) [4]. It is found on acral regions, such as the palms of the hands, the soles of the feet, within nail beds, or under nail plates [2,5]. Diagnosis is often delayed due to the hidden location or because it can be mistaken for an ulcer or a plantar wart with hemorrhage.

Table 2.1 Overview of the four major melanoma subtypes. Adapted from Clark et al [1], Smoller et al [2], Kaatsch et al [3], Bradford et al [4], and Glud et al [5].

Melanoma subtypes according to the WHO classification

Melanoma subtypes	ICD-O-3 codes
Malignant melanoma – major subtypes	M8720/3
Superficial spreading melanoma	M8743/3
Nodular melanoma	M8721/3
Lentigo maligna melanoma	M8742/3
Acral lentiginous melanoma	M8744/3
Other	
Desmoplastic melanoma	M8745/3
Melanoma arising from a blue nevus	M8780/3
Melanoma arising in a giant congenital nevus	M8761/3
Melanoma in childhood	
Naevoid melanoma	M8720/3
Melanoma, NOS	

Table 2.2 Melanoma subtypes according to the WHO classification. ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; NOS, not otherwise specified; WHO, World Health Organization. Adapted from the World Health Organization [7].

that leads to higher rates of local relapses. In some cases (<10%) desmoplastic melanomas also display components of a nondesmoplastic melanoma (so-called mixed desmoplastic melanoma in contrast to pure desmoplastic melanoma) [8].

Take-home message

Different melanoma subtypes can be distinguished. The four major subtypes (according to the WHO classification and on the basis of clinical and histological features) are:

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Acral lentiginous melanoma

Genetic alterations in melanoma subtypes

Cutaneous melanoma is a heterogeneous disease with different clinico-pathologic subtypes. However, in clinical practice, a substantial number of melanomas do not fit into the classic subtypes. More recently, mutation analyses showed that melanomas can also be classified according to

distinct genetic alterations in different pathways, which also helps to better understand why melanomas develop and explains some of the biologic features [9]. These findings served as the foundation for the development of the first targeted therapies in melanoma. The different subtypes are summarized in Table 2.3 [10].

Another approach for a genetic classification of melanomas, proposed by Bastian et al, relates to their preferential body site of occurrence and exposure to ultraviolet (UV) radiation [11]. Mutations in BRAF and chromosomal losses (chromosome 10) were shown to occur significantly more often in melanoma of intermittently sun-exposed skin, while mutations in NRAS were mostly found in melanoma in sun-protected areas (eg, acral lentiginous melanoma) [11]. The role of sun exposure or sun damage to the skin in the development of acral lentiginous melanoma is assumed to be of lesser importance [9].

Principal melanoma molecular subtypes				
Detailed subtypes	Pathway(s)	Key gene/ biomarker(s)	Diagnostic technologies	Potentially relevant therapeutics
1.1	MAPK	BRAF	Targeted sequencing	BRAF inhibitors, MEK inhibitors, Hsp90 inhibitors
1.2		BRAF/PTEN	Targeted sequencing and IHC	(BRAF inhibitors) and (PI3K, AKT, or mTOR inhibitors)
1.3		BRAF/AKT	Targeted sequencing and copy number	(BRAF inhibitors) and (AKT or mTOR inhibitors)
1.4		BRAF/CDK4	Targeted sequencing and copy number/CGH	BRAF inhibitors and CDK inhibitors
2.1	c-KIT	c-KIT	Targeted sequencing	Imatinib and other c-KIT inhibitors
3.1	GNAQ, GNA11	GNAQ	Targeted sequencing	MEK inhibitors
3.2		GNA11	Targeted sequencing	MEK inhibitors
4.1	NRAS	NRAS	Targeted sequencing	MEK and PI3K inhibitors and farnesyltransferase inhibitors
5.1	MITF	MITF	Copy number	HDAC inhibitors

Table 2.3 Principal melanoma molecular subtypes. CGH, comparative genomic hybridization; HDAC, histone deacetylase; IHC, immunohistochemistry. Adapted from Vidwans et al [10].

Despite the many investigations in this field and a rapidly growing knowledge base, classification according to specific mutational profiles is not yet validated. Further investigations are required for validation and refinement, and to possibly identify additional factors.

Take-home message

Different key molecular pathways are involved in melanoma disease onset and progression. Classification of different melanoma subtypes on the basis of genetic factors (in contrast to traditional clinical pathologic subtypes) has been proposed but requires validation.

American Joint Committee on Cancer staging and classification

Melanoma staging is based on the American Joint Committee on Cancer (AJCC) TNM classification system (T=tumor, N=nodes, M=metastases), which was developed in 2009 on the basis of long-term follow-up data of more than 38,000 patients (Table 2.4) [12]. The anatomic stage groupings for cutaneous melanoma are based on the TNM staging (Table 2.5) [12]. Compared to previous classification systems (eg, AJCC 2002) [13], mitotic rate has been added as a prognostic factor in low-risk melanoma, replacing the level of invasion (Clark level). According to the TNM classification, the Clark level is only used for the subdivision between T1a and T1b if the mitotic rate was not assessed. Sentinel node biopsy is required for the correct N-classification [12].

Patients with melanoma of unknown primary should be allocated to stage III (in case of skin and/or lymph node metastases) or IV disease, depending on the site(s) of metastases.

Prognostic factors and course of disease

Melanoma is the most serious form of skin cancer because it metastasizes so readily. The clinical course of cutaneous melanoma can be severe and depends on several prognostic factors. The Individualized Melanoma Patient Outcome Prediction Tool website (www.melanomaprognosis.org), found at the AJCC Melanoma Database, allows the provider to enter all

AJCC TNM staging categories for cutaneous melanoma (2009)		
Classification	Thickness (mm)	Ulceration status/Mitoses
Tis	Not applicable	Not applicable
T1	≤1.00	a: without ulceration and mitosis <1/mm ² b: with ulceration or mitoses ≥1/mm ²
T2	1.01–2.00	a: without ulceration b: with ulceration
T3	2.01–4.00	a: without ulceration b: with ulceration
T4	>4.00	a: without ulceration b: with ulceration
Classification (N)	Number of metastatic nodes	Nodal metastatic burden
N0	0	Not applicable
N1	1	a: micrometastasis* b: macrometastases [†]
N2	2–3	a: micrometastasis* b: macrometastases [†] c: in-transit metastases/satellites without metastatic lymph nodes
N3	4+ metastatic lymph nodes, or matted lymph nodes, or in-transit metastases/satellites with metastatic lymph nodes	
Classification (M)	Site	Serum LDH
M0	No distant metastases	Not applicable
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated

Table 2.4 AJCC TNM staging categories for cutaneous melanoma (2009). *Micrometastases are diagnosed after sentinel lymph node biopsy. [†]Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically. AJCC, American Joint Committee of Cancer; LDH, lactate dehydrogenase; M, metastases; N, nodes; T, tumor. Reproduced with permission from Balch et al [12].

of these factors to calculate the 5- and 10-year survival probability at the time of primary diagnosis [14].

Anatomic staging groups for cutaneous melanoma

Clinical staging*				Pathologic staging [†]			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
IIA	T2a	N0	M0		T2a	N0	M0
	T2b	N0	M0		T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
IIC	T4a	N0	M0		T4a	N0	M0
	T4b	N0	M0		T4b	N0	M0
III	Any T	N> N0	M0	IIIA	T1-4a	N1a	M0
				IIIB	T1-4a	N2a	M0
					T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
					T1-4b	N1b	M0
					T1-4b	N2b	M0
				T1-4b	N2c	M0	
				Any T	N3	M0	
				IV	Any N		IV

Table 2.5 Anatomic staging groups for cutaneous melanoma. *Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases. †Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception as they do not require pathologic evaluation of their lymph nodes. M, metastases; N, nodes; T, tumor. Reproduced with permission from Balch et al [12].

Prognostic factors

The following risk factors [12] are described and incorporated into the 2009 AJCC classification system:

- **Tumor thickness** is the most important prognostic factor. In patients with melanomas with tumor thickness ≤ 1.00 mm, the 10-year survival rate was shown to be about 92%, compared with 80% in patients with melanomas of 1.01–2.00-mm

thickness, 63% in patients with melanomas of 2.01–4.00-mm thickness, and 50% in patients with melanomas of >4.00-mm thickness [12].

- **Ulceration** has an important influence on survival. Patients with an ulcerated T4 melanoma (pT4b) have a 5-year survival rate of 53%, while the survival rate for patients with a nonulcerated T4 primary (pT4a) ranges around 71% [12].
- The **mitotic rate** is a marker for the proliferation of the primary melanoma. A highly significant correlation between increasing mitotic rate and declining survival rates was demonstrated. The most significant correlation with survival was identified at a threshold of at least 1/mm². Survival rates of patients with an ulcerated primary or elevated mitotic rate are lower than those of patients with a nonulcerated melanoma of equivalent T-category [12].
- **Nodular involvement**-related survival rates differ due to heterogeneity. Tumor burden at the time of staging (microscopic versus macroscopic) was shown to be a further prognostic factor. Five-year survival rates within stage III were 78%, 59%, and 40% for patients with stage IIIA, IIIB, and IIIC melanoma, respectively (Figure 2.1) [12].
- Prognosis is worse in patients with distant metastases. **Lactate dehydrogenase** (LDH) is a highly significant predictor of survival or outcome in stage IV patients, independent of other factors (Figure 2.2) [12]. When elevated LDH levels are found, patients are classified as M1c regardless of the location of distant metastases. One-year survival rates are approximately 62% (M1a), 53% (M1b), and 33% (M1c), respectively. Survival rates after 10 years range between 5% and 20% [12].

Other clinical factors of prognostic importance for survival include gender (males with poorer prognoses than females), increasing patient age, and location of the primary tumor (trunk and head sites have poorer prognosis than extremities) [13,15,16]; however, these factors are not included in the 2009 AJCC classification system [12,13].

Take-home message

Staging of patients is based on the 2009 AJCC classification, a TNM staging system that accounts for important prognostic factors:

- Tumor thickness
- Ulceration
- Mitotic rate (in melanoma with a tumor thickness <1 mm)
- Nodular involvement
- LDH levels (in stage IV)
- Additional known prognostic factors such as gender, age, and localization of the primary melanoma

Rate of growth

Early detection of melanoma before metastatic spread is of great importance. Diagnostic delay can have severe consequences, particularly in cases of rapidly growing melanomas. The spectrum of the growth rate varies widely, and growth rates from 0.03 mm/month in a slowly growing lentigo maligna melanoma and up to 1.48 mm/month in a rapidly growing nodular melanoma have been reported [17].

The assessment of clinical factors related to rapidly growing melanomas demonstrated the following associated factors [17]:

- Tumor thickness
- Mitotic rate
- Male sex
- Older age (≥ 70 years)
- Fewer melanocytic nevi and freckles ($n < 50$)
- Atypical clinical features (eg, asymmetry, elevation, amelanosis, border irregularity, presence of symptoms)

Take-home message

When melanoma is suspected, rapid diagnosis and treatment are mandatory.

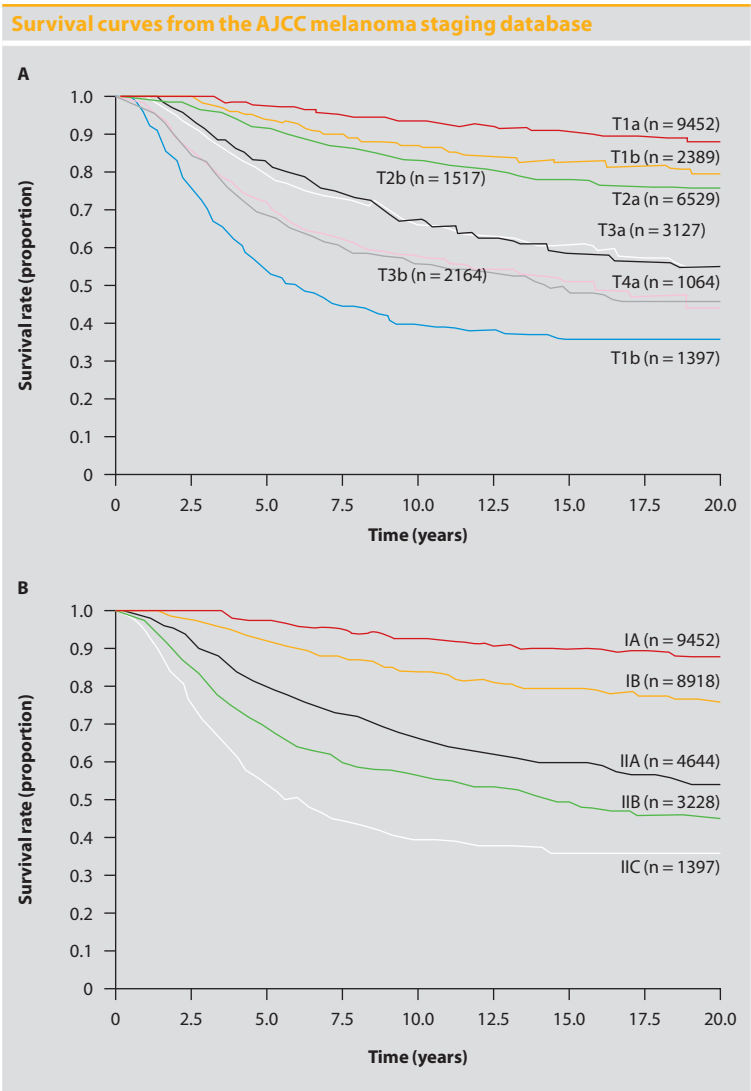


Figure 2.1 Survival curves from the AJCC melanoma staging database (continues overleaf).

Survival curves from the AJCC melanoma staging database (continued)

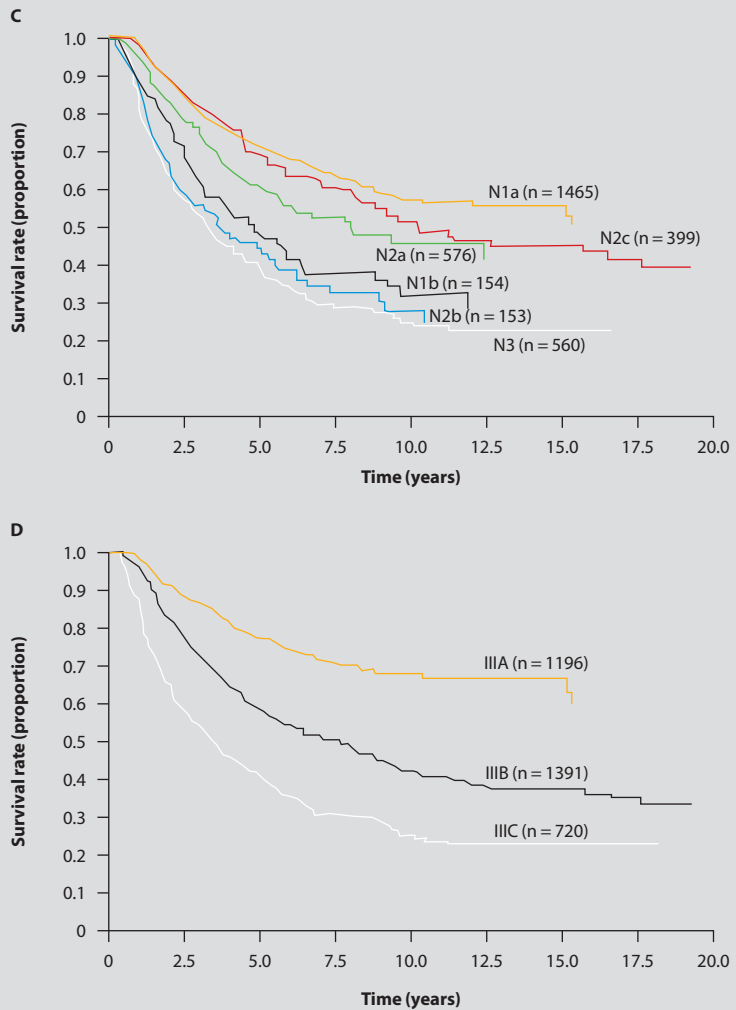


Figure 2.1 Survival curves from the AJCC melanoma staging database (continued).

The graphs above compare (A) T categories and (B) the stage groupings for stages I and II melanoma. For patients with stage III disease, survival curves are shown comparing (C) the different N categories and (D) the stage groupings. AJCC, American Joint Committee of Cancer; M, metastases; N, nodes; T, tumors. Reproduced with permission from Balch et al [12].

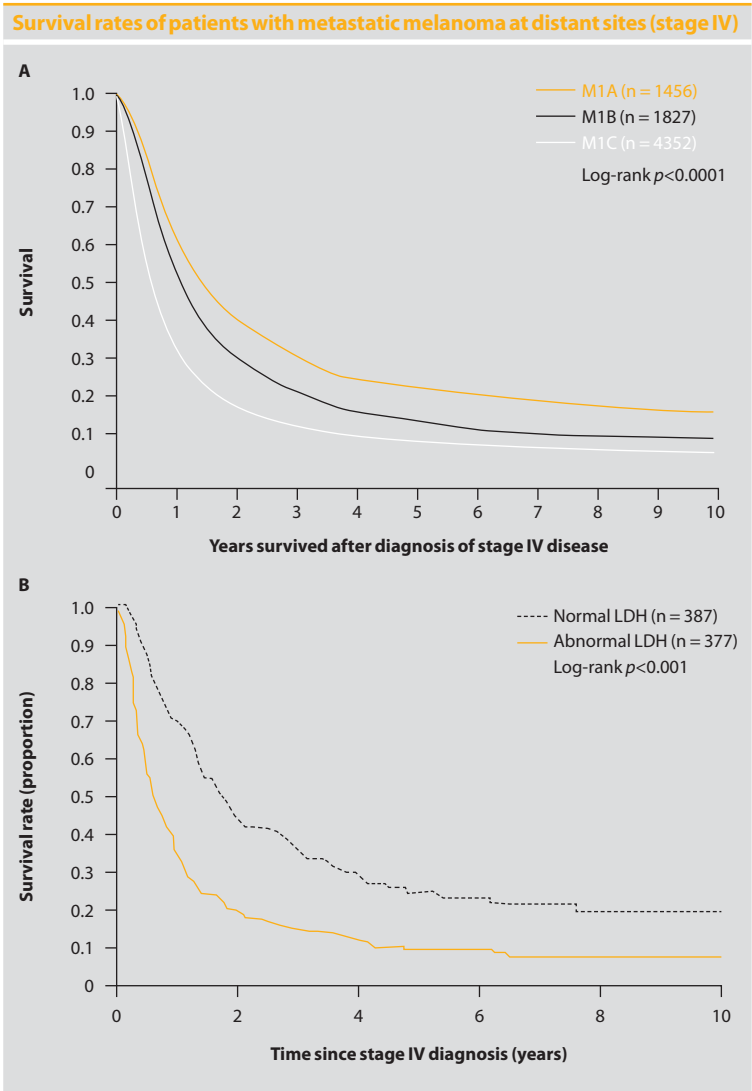


Figure 2.2. Survival rates of patients with metastatic melanoma at distant sites (stage IV). Subgrouped by (A) the site of metastatic disease and (B) serum LDH levels. LDH values are not used to stratify patients. Curves in (A) are based only on site of metastasis. The number of patients is shown in parentheses. LDH, lactate dehydrogenase SQ, subcutaneous. Reproduced with permission from Balch et al [12].

Metastatic pathways and clinical course of melanoma

Metastases may arise from very small tumor masses that can circulate by two different metastatic pathways:

- **Lymphogenic** (mainly responsible for locoregional lymph node, in-transit, and satellite metastases), which accounts for around 80% of first dissemination; or
- **Hematogenic** (frequently responsible for distant metastases).

In about two-thirds of cutaneous melanoma cases, metastatic spread develops primarily as the local recurrence and/or locoregional metastases, while in about one-third of cases primary development of distant metastases is observed [15,18]. The majority of patients with metastases ($\approx 50\%$) develop regional lymph node metastases. In about 21% of patients, metastases appear as in-transit or satellite metastases [15,18,19] as, for example, shown in Figure 2.3.

Generally, time to appearance of first metastases is shorter for locoregional metastasis (≈ 16 or 17 months) than for distant metastases (≈ 24 – 30 months), irrespective of whether locoregional metastases

Satellite and in-transit metastases of a primary melanoma located on the sole of the right foot

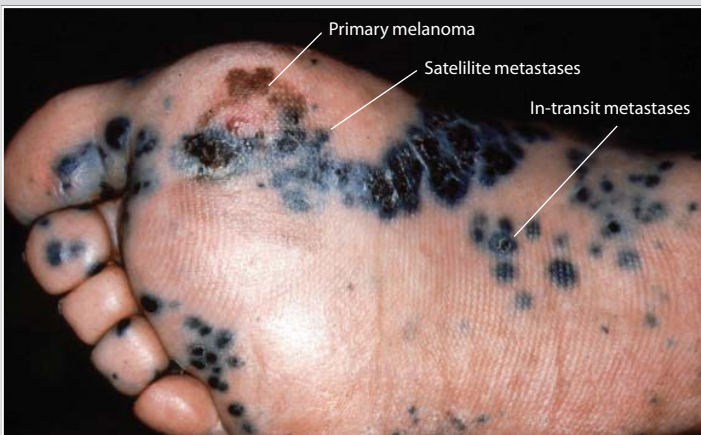


Figure 2.3 Satellite and in-transit metastases of a primary melanoma located on the sole of the right foot.

appeared first [15]. The risk of recurrence is highest within the first 3 years after melanoma diagnosis [19,20] (see Chapter 3, page 47).

Patients with distant metastatic disease have poor survival rates as depicted in the survival curves in Figure 2.2.

Late recurrences (ie, after ≥ 10 years after diagnosis) are described in rare cases (about 1–7%) and comprise patients with all stages of disease [21]. There are no specific predictors for the risk of late recurrence [20].

Take-home message

Metastatic spread occurs via the lymphogenic system in three quarters of affected patients leading to locoregional disease. Visceral dissemination occurs via the hematogenic system. Once melanoma has metastasized, survival rates are poor. Patients with distant metastases have a 10-year survival rate of only 5–20%.

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Handbook of Cutaneous Melanoma

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