CHAPTER 8

# HISTOLOGY OF MELANOMA AND NONMELANOMA SKIN CANCER

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**Abstract:** Incidence of skin tumors is increasing among elderly patients, and the multi-morbidities which occur in the elderly are a great challenge for dermatologists. Basis of every treatment of skin cancer patients is a reliable diagnosis. Therefore, histopathology serves as the gold standard in clinical dermatooncology and dermatologic surgery. This chapter provides a comprehensive review on the main types of melanoma and nonmelanoma skin cancers, including precursor lesions.

## INTRODUCTION

Incidence of skin tumors is increasing among elderly patients, and the multi-morbidities which occur in the elderly are a great challenge for dermatologists. Basis of every treatment of skin cancer patients is a reliable diagnosis. Therefore, histopathology serves as the gold standard in clinical dermatooncology and dermatologic surgery.

Histopathology of melanoma is a challenging subject as borders between benign and malignant are not clearly defined. Malignant melanoma is very well known for the wide range of histological variability and the ability of mimicking a variety of other malignancies. Besides classical forms of melanoma there are a lot of different variants described, accountable for the often difficult recognition, even by expert dermatopathologists. Actually, the existence of melanocytic lesions with a low malignant potential is regarded as highly probably, but diagnostic possibilities still are insufficient for these kinds of neoplasms.

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Pathology of epithelial tumors is well defined and precursor lesions as actinic keratosis and Bowen`s disease are well described. Hence, there is still controversial eponymical discussion ongoing denomination of these lesions as "carcinomata in situ" or "keratinocytic intraepidermal neoplasia" as progression to invasive carcinomata is seen in a small percentage of cases.

## ACTINIC KERATOSIS (AK)

According to the WHO classification of skin tumors from 2006 actinic keratoses are very common intraepidermal neoplasm of sun-damaged skin with variable atypia of the epidermal keratinocytes. Main cause of these changes is chronical exposition to ultraviolet B (UVB) light, but AKs are also observed following long-term PUVA-treatments as well as exposure to arsenic.[1] The AK can be considered to represent early squamous cell carcinomas in situ,[2,3] respectively possess a striking potential to progress to fully developed neoplasms.[4] But only small portions of AK will develop into an invasive squamous cell carcinoma. Regression of some cases of AK have been reported, most likely as a result of immune mechanisms.[5] Metastases after transformation of AK into invasive squamous cell carcinomas are very rare except for those tumors that arise on the ear, lip, anus and vulva, which have been reported to be often associated with a more aggressive behavior.[6] It has been widely accepted, that actinic keratoses are a clinical manifestation of ultraviolet (UV)-induced neoplastic transformation of keratinocytes representing a continuum with progress to a fully developed squamous cell carcinomas.[7] Cockerell observed the same cytological features of keratinocytic atypia in actinic keratoses than in epidermal or metastatic SCCs.[8] Like current nomenclature of cervical intraepidermal neoplasia (CIN) Cockerell therefore recommends the use of the term "keratinocytic intraepidermal neoplasia" to illustrate the biological nature of these lesions.[7]

### Morphology

Histopathologically, the actinic keratoses are classified into several groups: hypertrophic, atrophic, bowenoid, acantholytic, pigmented, and lichenoid (see Table 1). All of these subtypes collective is a partial thickness atypia of crowded keratinocytes with overlying parakeratosis and sparing of acrotrichia and acrosyringia extensions with overlying orthokeratosis. This characteristical pattern of alternating ortho- and parakeratosis is often referred to as "flag sign" or "pink and blue pattern"[7]. The cytologic atypia include nuclear enlargement and prominence, hyperchromasia, pleomorphism, mitotic activity and dyskeratosis. Constantly associated dermal changes are solar elastosis and a sometimes dense lymphocytic infiltrate and an increased vascularity.

## BOWEN`S DISEASE

Clinically Bowen`s disease represents a slow growing malignancy which most often arises in sun-damaged skin of the elderly.[12,13] In Bowen`s disease, the epidermis usually shows localized full thickness atypia resembling carcinoma in situ and it is seen as a distinct clinicopathologic entity of the skin and the mucocutaneous junction. Typically, a completely disordered architechture, abnormal mitosis, dyskeratoses, involvement of the pilosebaceous unit with an intact epidermal junction is seen.[14] Synonyms of the same

**Table 1.** Summery of distinct types of actinic keratosis[9-11]

| Type of Actinic Keratosis | Clinical Features | Morphology |
|---|---|---|
| Hyperplastic/ hypertrophic AK | Dorsum of hands and forearms, sometimes appearing as *cornu cutaneum* | Hyperplastic epidermis probably due to chronic itching and scratching |
| Pigmented | Brown patch or plaque, centrifugally spreading at cheeks ore forehead | Pigmented basal keratinocytes |
| Atrophic | No distinct clinical features | Severe epidermal atrophy, less hyperkeratosis |
| Bowenoid | No distinct clinical features | Morphologic changes similar to Bowen's disease |
| Acantholytic | No distinct clinical features | Acantholysis predominantly in periadnexal epidermis |
| Lichenoid | No distinct clinical features | Differential diagnosis: lichen-planus-like keratosis |

entity are: squamous carcinoma in situ, intraepidermal carcinoma, bowenoid dysplasia and bowenoid squamous carcinoma in situ. The most common causation of Bowen's disease is, likewise for the actinic keratoses, chronic exposition to UVB-light.

## Morphology

Main changes in morphology are seen in Figure 1A. Histopathologically characteristical, hyperkeratosis, parakeratosis, hypo- or hypergranulosis and plaque-like acanthosis with an increased cellularity is seen, as well as a complete loss of epidermal polarity and keratinocytic maturation are found. Typically, crowding of atypical keratinocytes with pleomorphism, multinucleated or vacuolated cells with hyperchromatism and dyskeratosis appear. In addition, very large atypical cells and bizarre mitoses are usually found. In Bowen's disease typically the follicular epithelium is involved. Morphological variants have been described, including clear-cell and pigmented forms.[15] As in actinic keratoses dermal changes are composed of solar elastosis, a lymphocytic and plasma cell- rich infiltrate in the papillary dermis and ectatic vessels. Intriguingly, in actinic keratosis intraepidermal proliferation of atypical keratinocytes starts in the basal layer of the epidermis. In contrast, in Bowen's disease basal layer remains intact (see Fig. 1B).[16] Additionally, there is a different staining pattern of proliferative markers (Mib1) as well as cell cycle regulatory marker (p53) in actinic keratosis sompared to Bowen's disease, indicating that both entities derive originally from distinct epithelial cell.[16]

## Types of Disease

- Erythroplasia of Queyrat: mucosal Bowen's disease on genital and oral areas.[17] The histologically features of lesions on the glans or shaft of the penis are identical to those at other sites of the skin.[14]
- Pagetoid Bowen's disease: cluster of atypical keratinocytes are found in pagetoid intraepidermal spread

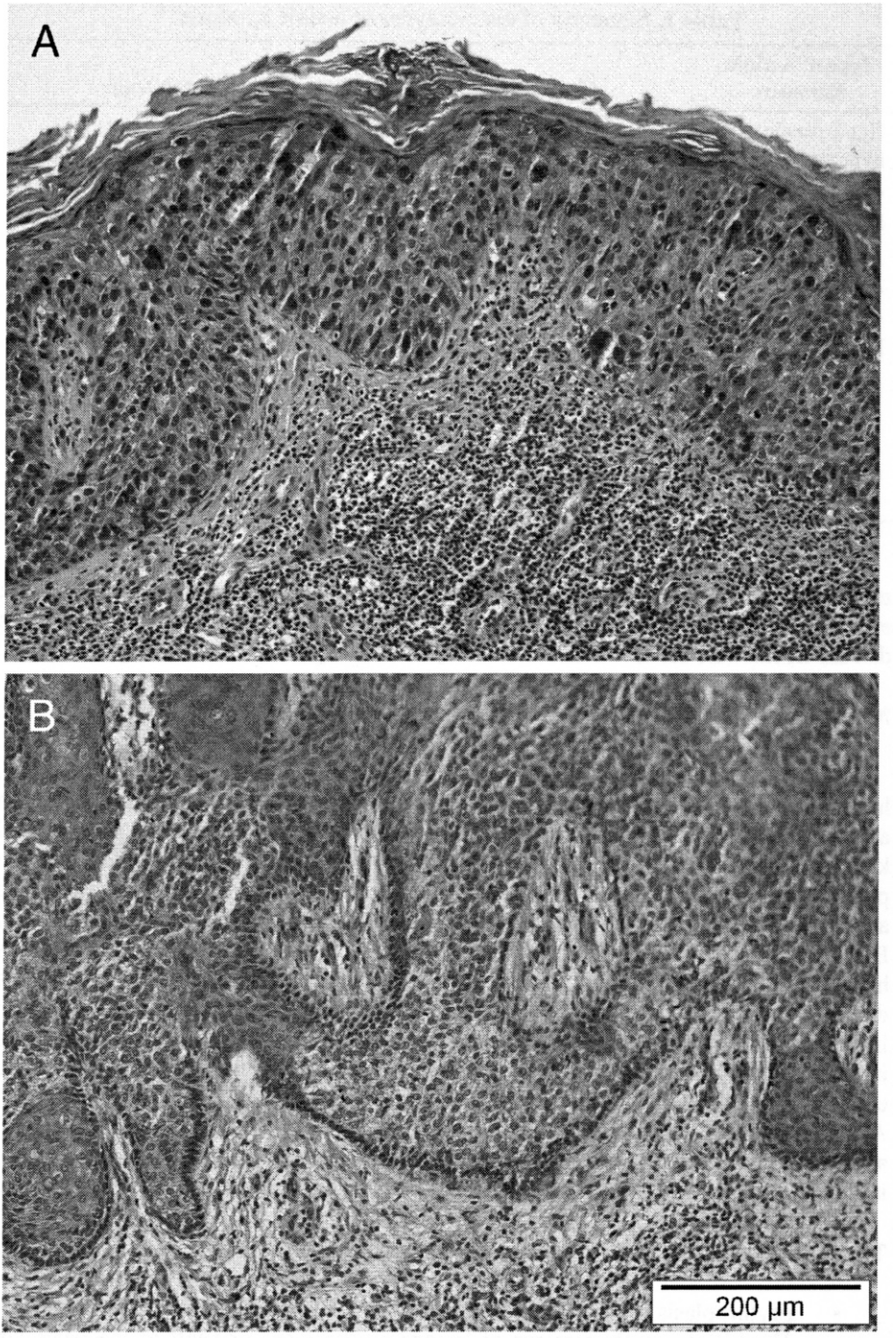


**Figure 1.** Bowen's disease. A) Transepidermal dysplasia and cytologic changes. HE. 400x. B) Note, that basal keratinocytes are not affected. HE.

## INVASIVE SQUAMOUS CELL CARCINOMA (SCC)

SCCs are the most frequent form of skin cancer among blacks and the second one in the white population. The average age of patients is about 70 years and males are more frequently affected than females.[18] Even genodermatoses such as Xeroderma pigmentosum, albinism and Epidermodysplasia verruciformis are at increased risk for SCCs.[18] Main factors associated with an increased risk of developing an invasive squamous cell carcinoma are UVB-exposition, viral HPV-infections, therapeutic immunosuppression for allogenic organ transplants, arsenic exposure, ionizing radiation and chronic dermatoses, e.g., lichen sclerosus genitalis.[14]

By definition a SCC is a malignant neoplasia of epidermal (and mucous membrane) keratinocytes in which the component cells show variable squamous differentiation[15] and the ability of local infiltration and tissue destruction.[18] Mostly seen in elderly people, they arise on chronically sun-damaged skin sites.

### Morphology

Histologically SCCs are composed of nests, sheets or strands of squamous epithelial cells arising from the epidermis and extending into the dermis in a variable degree (Fig. 2). Initially developing as carcinoma in situ, they later become invasive, infiltrating dermis, subcutis, musculature, cartilage or bone and may also lead to regional lymph node disease

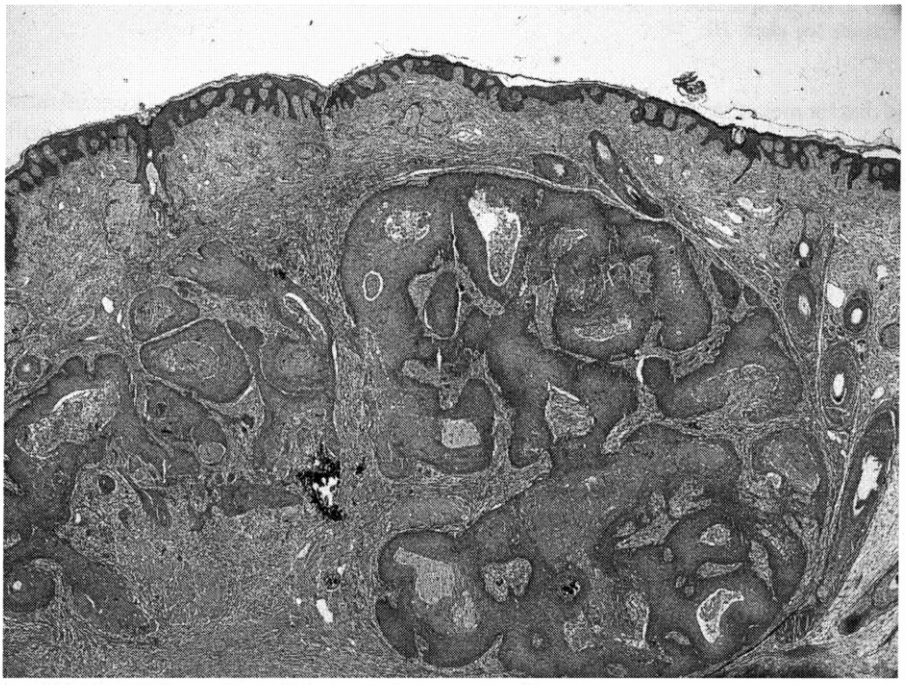

**Figure 2.** highly differentiated squamous cell carcinoma of the skin mainly proliferating within then dermis. HE. 100x.

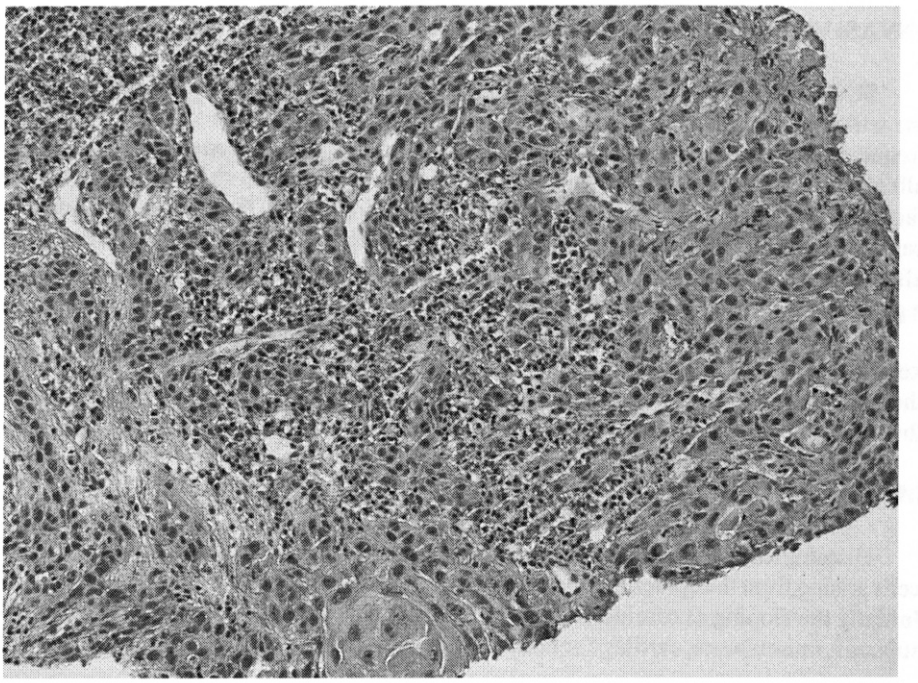

**Figure 3.** Biopsy specimen of a poorly differentiated epithelial carcinoma of the skin presenting clinically as chronic leg ulcer. HE. 400x.

and distant metastatic spread.[18] Typically, horn pearl formation and central keratinization are seen, depending on the degree of differentiation of the tumor. Immunohistochemically these atypical cells are positive for epithelial membrane antigen (EMA) and cytokeratins.

Actually, multiple classification systems exist, mostly historically developed:

- Classification into "well," "moderately" and "poorly" differentiated types (Fig. 3).
- Broder`s system of classification, based on four grades of differentiation
  grade 1: 75% or more of the lesion is well differentiated
  grade 2: 50–75% or more well differentiated
  grade 3: 25–50% well differentiated tumor cells
  grade 4: less than 25% well differentiated tumor cells.[19]
- WHO classification system distinction between in situ carcinomas and invasive carcinomas with the following variants: SCCs with horn pearl formation, spindle cell SCCs, lymphoepithelial carcinoma, acantholytic SCCs, SCCs arising from Bowen`s disease and the verrucous carcinoma.[18]
- Additionally, there are a lot of rare variants of SCCs known, including clear-cell, signet-ring, pigmented, basaloid, inflammatory, infiltrative, desmoplastic, verrucous and rhabdoid types.[18,20]

Though there are numerous classification systems, only little is known about the behavior with respect to local recurrence and metastasis. In general, poorly differentiated tumors recur and metastasize more frequently than well differentiated variants.[21] Neurotropism is

associated with high recurrence and metastasis rate. Perineural spread is particularly common in tumors arising on head and neck, especially lips and mid-face. The clinical outcome of SCCs of the skin depends on the microscopic parameters of thickness and histologic grade. Additional, attention should be paid to the histologic subtype, because the individual SCCs forms vary considerablely in prognosis. Based on a proposal of Cassarino et al. the above mentioned forms of SCCs should be classified upon their malignancy behavior and prognostic factors into four groups: low behavior (less than 2% metastatic rate), intermediate (3–10%), high (greater than 10%) and the intermediate behavior.[13]

- Low risk SCCs: actinic keratoses, HPV associated SCCs, tricholemmal carcinomas, spindle cell SCCs not associated with radiation.
- Intermediate risk SCCs: acantholytic SCCs, intraepidermal epithelioma with invasion, lymphoepithelioma-like carcinoma of the skin.
- High risk SCCs: de novo SCCs, SCCs arising in association with radiation, burn scars, immunosuppression, invasive Bowens diseasem, adenosquamous carcinoma, malignant proliferating pilar tumors.
- Intermediate behavior SCCs: singnet-ring-cell, follicular and papillary SCCs, SCCs arising in adnexal cysts, eccrine ductal carcinomas, clear-cell SCCs.

Additional all the above mentioned classification systems prognostic relevant factors such as tumor size, differentiation, depth of invasion, perineural invasion should be announced when diagnosing a squamous cell carcinoma.[13]

## KERATOAKANTHOMA (KA)

Clinically, keratoakanthomas appear as usually solitary dome-shaped nodules with a central keratin plug, fastly growing and often spontaneously regressing. Severel clinical subtypes are known, as the giant KA, keratoakanthoma centrifugum marginatum or subungual types. Even multiple and eruptive cases are described, occurring mostly in immunosuppressed patients and within the Muir-Torre syndrome as well as at posttraumatic sites.[15] Rare cases of perineural invasion[22] and intravascular spread[23] have been reported, often occurring in the facial region. In most cases, these tumors affect sun-exposed hair follicle bearing skin of elderly individuals and they mimic clinically and histopathologically well-differentiated squamous cell carcinomas. Keratoakanthomas can therefore be considered as a histologic variant of squamous cell carcinoma with distinct clinical and pathologic attributes.[24]

### Morphology

Histologically, they are exophytic squamoproliferative nodules with central keratin plug. Typically, the lesion appears symmetrical and a mixed inflammatory cell infiltrate, including eosinophils and neutrophils, with exocytosis of inflammatory cells.[15] The center of the tumor presents as a crater filled with eosinophilic laminated orthokeratotic scales. This central crater is mostly partially encoled by a well defined lip that forms the superficial border of the neoplasm. The epithelium of this lip may be hyperplastic, but there is usually no evidence of dysplasia or actinic keratosis in the epithelium adjacent to th tumor.[24-26] Nearly impossible is the differential diagnosis of squamous cell carcinoma in superficial shaves or punch biopsies.[15]

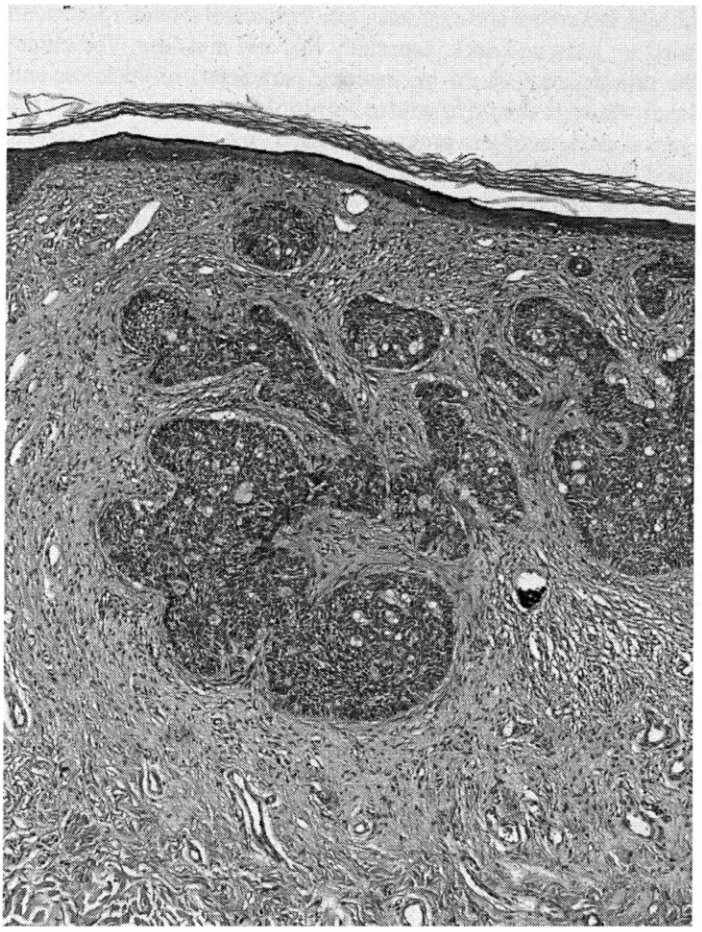

**Figure 4.** Basal cell carcinoma, solid type. Note the characteristic feature of peripheral palisading. HE. 100x.

## BASAL CELL CARCINOMA

Basal cell carcinomas are tumors with in general non-metastasizing behavior that derive from undifferentiated pluripotent epithelial stem "germinative" cell. They are typically characterized by a fibrous stroma surrounding islands of dependent tumor cells that resembles keratinocytes of the basal layer of the epidermis or hair follicle. Usually, these tumor cells are fairly regular with rounded hematoxiphilic nuclei and little cytoplasm. Typically, the proliferating cell component of the tumor is found predominantly in so called peripheral "palisades" of cells around the margin of each tumor nest (Fig. 4) . It has been shown that this phenomenon corresponds to the way, in which basal cell carcinomas grow by slow progressive, local invasion.[27] Basal cell carcinomas show a

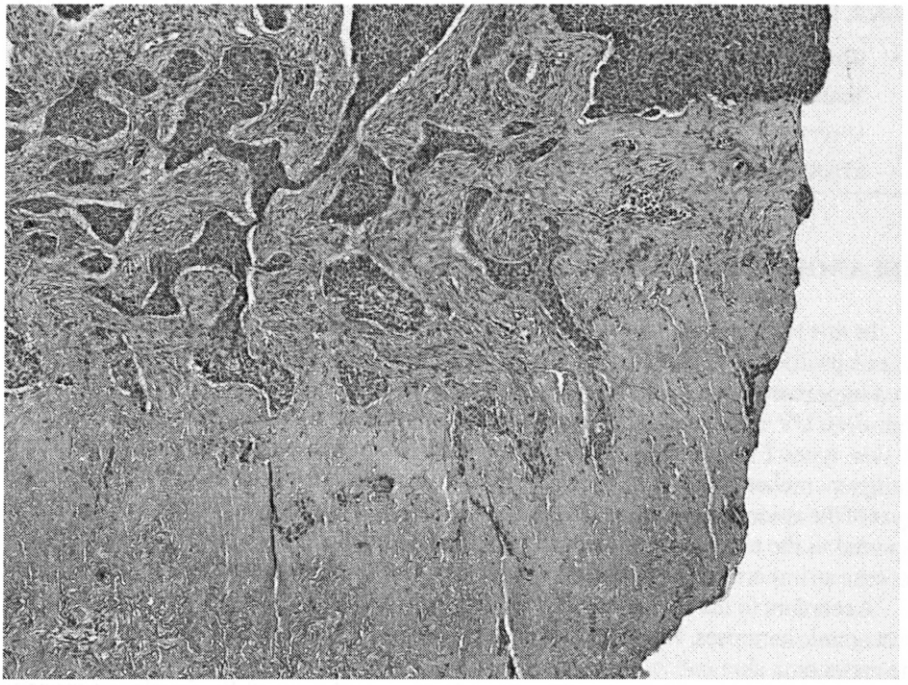

**Figure 5.** Basal cell carcinoma, sclerotic type. Note the dissecting tumor nests invading the surrounding dermis with severe sun damage. HE. 200x.

distinct tumor stroma, that is usually loose and mucin-rich (predominantly hyaluronic acid). A very typical sign of basal cell carcinoma is the presence of a constant retraction artifact; the seperation of the tumor cells from the underlying stroma. Five variants of basal cell carcinomas can be distinguished: nodular/ulcerative (solid) with 45–60%; diffuse (infiltrating, sclerosing) 4–17% (Fig. 5), superficial multicentric 15–35%, pigmented varaients 1–7% and the fibroepithelioma of Pinkus. Rare basal cell carcinomas have been referred to as metatypical carcinomas.[26]

Immunophenotype of basal cell carcinoma is consistent with that of the outer root sheet of hair follicles: expression of cytokeratin 5 and 14 as well as 15 and 17 is typically observed. No expression of CK1 and 10 (characteristic for simple epithelia) and CK8 and 18 (typically found in secretory epithelium) is seen. Epithelial membrane antigen (EMA), S100 or carcinoembryogenic antigen (CEA) are negative.[28]

**Differential Diagnoses (Morphologically)**

- Squamous cell carcinoma
- (desmoplastic type of) trichoepithelioma
- Sebaceous carcinoma
- Eccrine carcinoma

**Table 2.** Summary of the four most important prognostic parameter of malignant melanoma

- Breslow tumor thickness
- Sentinel lymph node status
- Ulceration
- Mitotic rate

## MELANOMA SKIN CANCER

In this topic a great variety of neoplasms with distinct clinical, morphological and genetic profiles are included. Because of their often fatal biological behavior they are the most important group of skin cancer. The major environmental risk factor is intermittant high-dose UV radiation, aggravated by the combination with endogenous factors, such as skin types I and II or genetic susceptibility.[15] Most important prognostic factor in malignant melanoma is Breslow`s tumor thickness measured from the top of the granular layer of the epidermis to the deepest point of invasion in the dermis. Recently, mitotic rate, reported as the number of mitosis per high-power-field or per 10 high-power-fields, has become an important prognostic parameter, even in thinner melanomas.[29-33] (See Table 2.)

Accordant to the sequence of development of invasive epithelial neoplasias starting with actinic keratoses, Bowen`s disease and finally, fully developed invasive carcinoma, the melanoma skin cancer also does show an evolutionary sequence with early lesions, as melanoma in situ or historically named lentigo maligna to fully developed invasive malignant melanomas.

## IN SITU MELANOMA (SYN. LENTIGO MALIGNA)

Clinically these early melanomas present as flat, pigmented macules, mostly seen in chronically light-exposed skin sites. The clinical differential diagnoses include lentigo simplex, junctional melanocytic nevus as well as non-melanocytic lesions, as seborrhoic keratoses and basal cell carcinomas. Changes in preexisting melanocytic lesions or development of a new pigmented lesion later in life should be a striking hint to development of an early melanoma.

Histologically, a melanoma in situ is characterized by linear and nested proliferations of atypical melanocytes predominantly along the dermo-epidermal junction and extending the adnexal epithelium.[15] Later on, single atypical melanocytes can be found in higher layers of the epidermis.[34] Characteristically, in early melanomas the neoplastic melanocytes are localized within the epidermis. Dermal changes such as severe solar elastosis, ectatic vessels and a lymphocytic infiltrate but also epidermal atrophy are seen. The lentigo maligna is broadly accepted as in situ variant of the lentigo maligna melanoma, in which the dermis is infiltrated by atypical melanocytes.

## INVASIVE MELANOMA

Based on historically proposals by Clark and Mc Govern[19] the clinicopathological classification of malignant melanoma has evolved into 4 main groups that are used

even today in daily routine work: the lentigo maligna melanoma, the superficial spreading melanoma, the nodular and the acral lentiginous melanoma. The relative incidence of these subtypes varies in different areas of the world. The concept of the radial and vertical growth phase of melanomas is mainly accepted. A progressive centrifugal spread of flat pigmented areas characterized by intraepidermal proliferating melanocytes labels the radial growth phase. In most cases of lentigo maligna, superficial spreading and nodular melanoma the radial growth phase precedes the vertical growth phase, where the dermis gets infiltrated by melanocytic tumor cells. Associated with the development of the vertical phase is angiogenesis and the expression of vascular endothelial growth factor.[15,35]

- Superficial spreading melanoma
  Proliferating single or nested melanocytic cells with cytological atypias in all levels of the epidermis characterizes this type of melanoma. The superficial adnexial structures usually are involved. Dermal tumor masses contain lymphoid, epithelial, spindle-shaped melanocytic tumors cells with variable degree of pigmentation. Typically, maturation of melanocytic tumor cells in the deeper compartments is missing. Clinically superficial spreading malignant melanomas appear on any part of the body as wells as at any age. Not uncommon are areas of regression mostly caused by immune mechanisms.[35]
- Lentigo maligna melanoma
  Basal proliferations of atypical melanocytes, singly or nested, focally aggregating to crowding conglomerates characterizes this type of melanoma. The deep adnexial epithelium is regularly involved and heavy cellular pleomorphism and cellular atypia are seen. Often there is a moderate to severe solar elastosis of the papillary dermis, but this is not a prerequisit of the lentigo maligna melanoma. Only little pagetoid spreading of atypical cells into higher levels of the epidermis is seen and there are quite often multinucleated tumor cells. Microinvasive foci are strikingly ignored, in those cases highlighting these areas with S100, HMB45 and Melan A is a useful tool (Fig. 6). Most of the lentigo maligna melanomas appear in the face and other sun-exposed areas of elderly people.[35] Of special interest is a potential disastrous pitfall using immunohistochemistry with Melan A: in the context of chronically sun-damages skin, Melan A is able to stain "pseudomelanocytic nests," simulating nests of a malignant melanoma. These "pseudomelanocytic nests" are characterized by presence of necrotic keratinocytes melanocytes and inflammatory cells. Therefore, in this setting Melan A has to be used in conjunction with other melanocytic and non-melanocytic markers to avoid misdiagnoses with terrible outcome for the patient.[36]
- Nodular melanoma
  These melanomas do not have any radial growth phase,[35] but show exclusively an vertical proliferation direction. The clinical feature is therefore nodular, polypoid and sometimes pedunculated amelanotic and ulcerated variants do exist (Fig. 7). Typically, there is mostly no or little intraepidermal component of atypical melanocytes. Mostly the tumor cells in the dermal part are round to oval with hyperchomatic nuclei[35] and an often epitheloid feature. The cell population mostly appears monomorphous[15] Failure of deep dermal maturation is a strong hint to the malignant behavior of this type of melanoma. Characteristically, S100, HMB45 and Melan-A as the typical melanocytic markers are expressed here (Fig. 8).

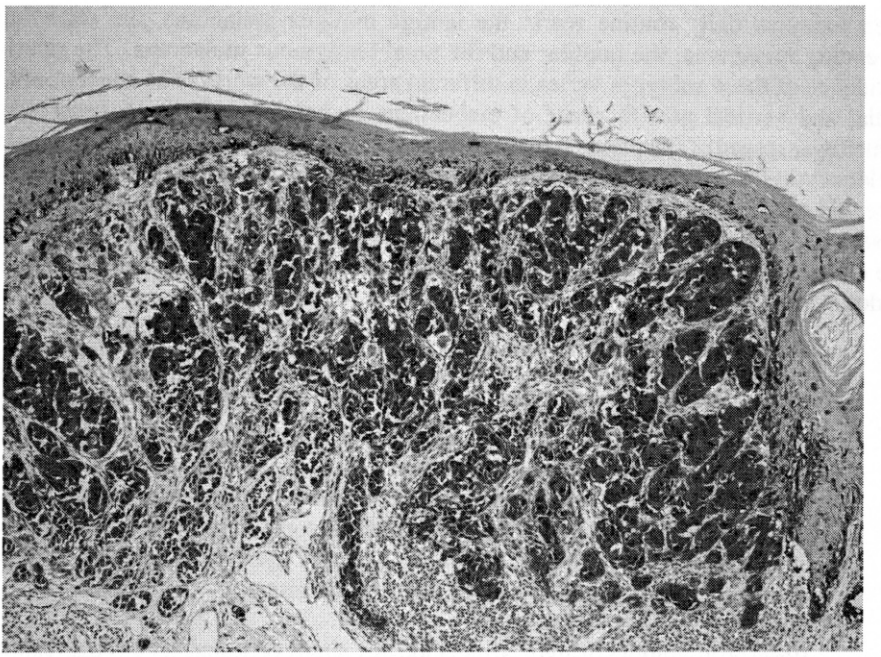

**Figure 6.** Immunohistochemistry of an invasive malignant melanoma with Melan A. Note discrete pagetoid spread of atypical dendritic melanocytes and lymphatic invasion (arrow). 200x.

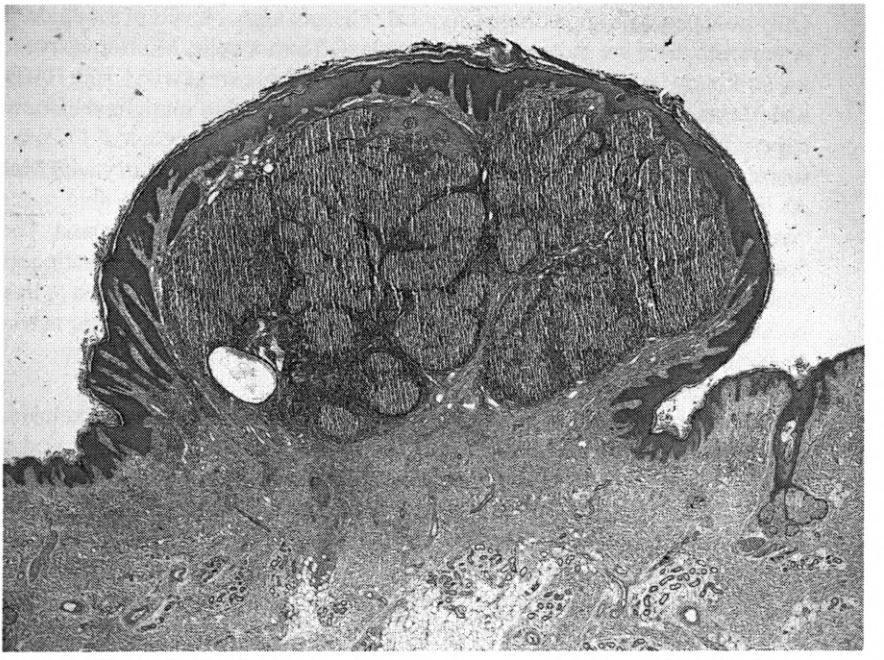

**Figure 7.** malignant melanoma, nodular "polypoid" type. HE, 100x.

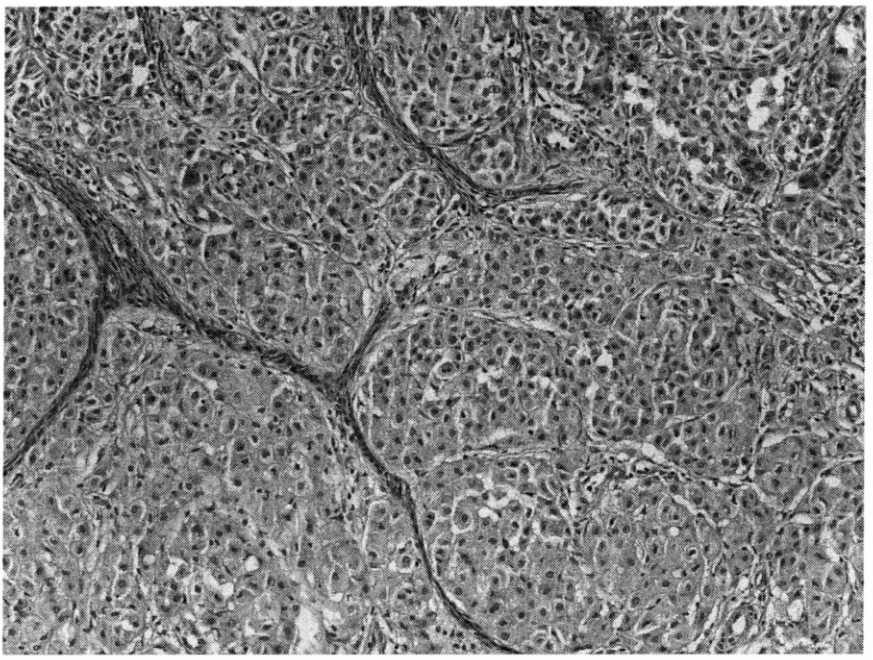

**Figure 8.** HE section of a malignant menaoma, balloon cell type. 200x.

- Acral lentiginous melanoma
  The acral lentiginous melanomas arise on non-hair bearing palmar, plantar and subungual skin sites.[15] It has a characteristical but not distinct histology with marked acanthosis, expanded cornified layer, elongated rete ridges and a lentiginous proliferation of atypical melanocytes in the radial growth phase, with a dominant intraepidermal component. In the vertical growth phase mostly spindle-shaped tumor cells and a desmoplastic stroma form a nodular tumor.[35]

Main morphologic criteria for diagnosis of malignant melanoma (according to ref. 37):

- Overall symmetry
- Poor lateral circumscription
- Predominance of single melanocytes over nests
- Pagetoid spread
- Lack of maturation
- Skip areas and regression
- Cytologic atypia
- Deep mitosis

## VARIANTS AND SPECIALTIES

Malignant melanoma is very well known for the wide range of histological variability and the ability of mimicking a variety of other malignancies. Besides the above mentioned classical forms there are a lot of different variants described, accountable for the often

difficult recognition, even by expert dermatopathologists. Smoller and Rongiolette favor a classification of these melanoma variants into four groups corresponding to the architectural patterns, cytologic features, stromal changes and combinations of these three.[38] This description is not only suggestive for pedogogic and nosologic values, but also important for the possible prognostic correlations. So espeacilly desmoplastic melanomas tend to local recurrance after surgery, angiotropic and ballon cell melanomas tend to skin metastasis whereas signet ring cell melanomas are of poor prognostic sign (Fig. 8). In the following the most important variants of malignant melanomas concerning to the above mentioned classification are accounted.

- Architectural patterns
  Here polypoid, verrucous, angiomatoid, *angiotropic*, primary dermal bullous and pseudopapillary/ adenoid- cystisc melanomas are outlined. The polypoid malignant melanoma is marked of a distinct exophytic growth pattern with a nodule connecting the underlaying skin by a pedicle. Bulky proliferations of atypical melanocytes filling the nodule. Later on infiltration of these melanoma cells through the pedicle in the underlying skin is seen. The verrucous melanoma is often been misdiagnosed clinically as benign lesions, such as dermal nevus or seborrhoic keratoses. Histologically strikingly at scanning magnification is the prominent papillomatous epidermal component, e.g., hyperkeratosis, parakeratosis and pseudoeptheliomatous pattern. The other mentioned variants of architectural forms of melanomas are extremely rare entities, e.g., only 2 cases of bullous melanomas, with floating melanoma cells in a pigmented epidermal blister are described.[39] In contrast it is not that uncommenly to see subepidermal blistering within classical melanomas.
- Stromal features
  In this fraction the desmoplastic or neurotropic melanoma is the most common representative. Among the classical forms desmoplastic melanomas are only seen in 3% of all melanomas.[38] But also the myxoid and ossifying/ chondroid melanoma has to be mentioned here. The myxoid pattern is often observed in elderly people and clinically presents as pigmented nodules on the trunk and extremities. Strikingly other mucin-containing neoplasms can be misdiagnosed. A strong positivity for S100 and NSE is observed, whereas Melan A or HMB45 are commonly negative. The osteocartilagineous metaplasia is a very rare histological phenomenon in melanomas.[40] Especially in akral and primary mucosal melanomas this pattern is seen.[41]
  Clinically desmoplastic melanomas present as indurated, pigmented or non-pigmented plaques, often associated to lentigo maligna.[42] Histologically, spindle cell proliferations diffusely infiltrating the dermis and/ or subcutis associated with a abundent stromal collagen are seen. In the conventional H&E stain these lesions mimick a scar or dermatofibroma. At higher magnification cytologic atypias are observed. The overlaying epidermis often shows lentiginous proliferations of atypical melanocytes. The spindled cells are mostly amelanotic. Concerning to an often strong neurotropism frequently recurrence of demsoplastic melanomas is a common feature after surgery.[43]
- Cytological features
  A great variety of melanomas subforms are condensed in this fractions: ballon-cell, spindle-cell, signet-ring-cell, small-cell, animal-type, amelanotic,

spitzoid, rhabdoid, schwannoid, ganglioblastic, plasmacytoid, merkel-cell-like and actin-rich melanoma. Mostly they have no distinct clinical features, but are very often difficult not to be misdiagnosed histologically. It shows the capacious spectrum of morphological variants of melanocytes and their atypical forms.

- Variants of combined patterns
  Sometimes the above mentioned architectural and cytological features are associated and form histologically arrestingly melanoma variants. The malignant blue nevus, malignant peripheral nerve sheth tumor like melanoma, clear cell sarcoma (melanoma of the soft parts), the nevoid and minimal deviation melanoma are summarized here. Confusingly is the nomenclature spectrum of the so called nevoid melanomas: Reed 2000 called them minimal deviation melanoma, but also pseudonevoid, small diameter and small cell melanomas often mean the same histological entity.[44] All these forms and terms in commen is the feature that tumor cells mimic nevus cells, with the broad morphological spectrum of nevus cells. Clinically preferential sites are lower extremities and the trunk of middle- aged men and women.[38]

## CHILDHOOD MELANOMA

Childhood melanoma is a very rare and fatal entitiy, with only 1–3% of all childhood malignancies[45] occurring with a slight female predominance. Per definition, these melanomas occur in individuals prior to puberty and can be further subcategorized as:

- Congenital melanomas (onset in utero to birth)
- Infantile melanomas (birth- to one year of age)
- Childhood melanoma (one year to onset of puberty)
  They must be further distinguished from simulants of melanomas, as Spitz naevi and atypical nodular proliferations developing in congenital naevi in infants and young children. Childhood melanomas can be further subcatagorized into three principal groups:[15]
- Conventional melanomas
  In about 40 to 50% of childhood melanomas are similar in histology to those in adults. The lentigo maligna melanomas are not seen in this age group, but pagetoid spreading of atypical cells intraepidermal and nested or lentiginous proliferations of melanocytes are seen.[45]
- Small cell melanomas
  They are composed of monomorphous small cells reminiscent such cells as in lymphomas or melanocytic nevi. These cells are arranged in sheets or organoid configurations and they usually appear de novo or develop in congenital naevus. Striking Breslow index and a poor prognosis with a fatal outcome are often seen.
- Melanomas simulating Spitz naevus
  These melanomas exhibit features strongly suggesting a Spitz naevus. Characteristically, wedge-shaped configuration, epidermal hyperplasia, epidermal clefting about intraepidermal nests with large epitheloid cells and spindle cells are seen.

Approximately 50% of childhood melanoma arise in association with preexisting lesions (congenital melanocytic nevus but also other aquired melanocytic nevi).[45] Criteria

for distinguishing childhood melanomas from nevi or Spitz naevus are: ulceration, high mitotic rate of more than 4 mitosis/ $mm^2$, large size of more than 7 mm asymmetry, poorly demarked lateral borders, lack of maturation and marked nuclear polymorphism. It is suggested that melanocytic lesions that cannot be classified sufficient as melanomas should be designated as biologically intermediate.

## THE "GRAY ZONE" IN MELANOMA DIAGNOSTIC

In recent years the traditional "black and white" approach to the diagnosis of melanocytic neoplasms has become less popular. A lot of special settings exist with diagnostic difficulties in melanocytic lesions e.g., unrecognized melanoma on partial biopsies, nevoid melanoma vs. "common" or "congenital" nevus, spindle cell melanoma vs. spindle cell nevus and a lot more.[37] This is followed from the adoption of "provisional" terms:

- SAMPUS (superficial atypical melanocytic proliferation of uncertain significance)
- MELTUMP (melanocytic tumor of uncertain malignant potential)
- Melanocytoma: describes a group of melanocytic lesions with a nevus/ melancytoma/ melanoma classification scheme reflecting the existence of a true morphobiologic spectrum of benignity to malignancy.[37,46] Atypical Spitz tumors, atypical dermal dendritic melanocytic proliferations and deep penetrating nevus are main representatives of this group.[46]

Actually, the existence of melanocytic lesions with a low malignant potential is regarded as highly probably, but diagnostic possibilities still are insufficient for these kinds of neoplasms.

Therefore, diverse techniques for mutational analysis on paraffin embedded tissue found its way into daily routine of dermatopathology trying to decrease diagnostic uncertainty in these "gray zone neoplasms":

- comparative genomic hybridization (CGH)
- array- CGH (a-CGH)
- fluorescence in situ hybridization (FISH)
- polymerase chain reactions techniques

CGH and aCGH is able to detect genome-wide DNA copy number changes and can be performed on formalin fixed and paraffin embedded samples. Different studies have shown that chromosomal copy number changes are typical for melanoma with distinct features in Spitz nevi. However, CGH is limited to highly qualified and specialized centers and is not a useful tool in daily practice.[37,47-49]

FISH technique (four-probe panel) can be used in several difficult but classical settings, e.g., distinction between nevoid melanoma and mitotically active nevi or between cellular blue nevi and blue nevus-like melanoma and much more and there is potential applicability for routine diagnostic. At present, FISH can be useful as ancillary diagnostic tool but is not a replacement for light microscopy.[37]

With PCR technique detection of point mutations are possible, that are beside chromosomal aberrations usually found in malignant melanocytic lesions. Several pathways have been found in malignant melanomas with increasing impact on therapeutic strategies:

Mitogen-activated protein kinase pathway (MAPK) - has been found in 80% of primary malignant melanomas, resulting from mutations within the RAS-RAF-MEK-ERK pathway.[37,50,51] Distinct mutations are usually seen in all subtypes of melanoma:[37]

- cutaneous melanoma: 50% v-raf murine sarcoma viral oncogene homologB1 [BRAF], 15% neuroblastoma RAS viral [v-ras] oncogene homolog [NRAS], 17% cKIT.
- Mucosal melanoma: 11% BRAF, 5% NRAS, 21% tyrosine-protein kinase Kit [cKIT]
- Uveal melanoma: GNAQ

These mutations can be detected on formalin fixed and paraffin embedded samples or using fine-needle aspirates from metastatic melanoma in patients with advanced-stage melanoma as rapid, minimally invasive and effective diagnostic option.[52] Dependent of the underlying mutation distinct molecular-based therapies are possible, so dermatopathologist has to include these molecular findings into pathological report.

## CONCLUSION

This chapter provides a comprehensive summary on histopathologic features of nonmelanoma skin cancer and melanoma and its current molecular based aspects with impact on daily routine work of a dermatopathologist.

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