Non-Melanocytic Skin Cancers

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(with clinical comments by Olivia Dolan)

Introduction

In the UK and Ireland non-melanoma skin cancer (NMSC) is the most common cancer group accounting for 20% of all new malignancies and 90% of all registered skin cancers. The incidence is increasing rapidly and is higher in males. Squamous cell carcinoma and basal cell carcinoma (previously referred to as epithelioma) are the commonest solar induced non-melanocytic cutaneous lesions. Other skin malignancies are relatively rare. Actinic keratosis and squamous cell carcinoma *in situ* (Bowen's disease) are extremely common non-invasive lesions. All the aforementioned lesions may present as red, scaly patches or non-healing sore nodular lesions on the sun exposed head and neck areas and hands of fair skinned people, who have a 10–20 fold increased risk over people with dark skin. Approximately 75% of NMSCs are basal cell carcinomas with the remaining proportion mostly squamous cell carcinomas. A mixed group of rare skin cancers of which Merkel cell carcinoma is the commonest, account for <1% of cases. The majority of these arise on the head and neck areas with exposure to ultraviolet irradiation a key aetiological factor. Almost 50% of new cases are in people aged over 75. A minority are associated with genetic disorders, or areas of chronic scarring and ulceration, e.g. Marjolin's ulcer of the leg. Patients who are immunocompromised due to long term immunosuppressive therapy, e.g. following solid organ transplantation, are at a much higher risk of developing NMSC. Delay in presentation of cutaneous carcinoma is associated with increased tumour growth with potential for local tissue destruction (e.g. spread to the orbit requiring exenteration), and, with squamous cell carcinoma potential for lymphovascular metastases.

Regarding the nature of specimen type, curettage, shave, and punch biopsies are often small, processed intact and embedded *in toto*. Curettage removes the lesion in fragments and is followed by electrothermal cautery to its base (C&C). Diathermy excision distorts the tissue, potentially rendering accurate histological assessment problematic. Shave biopsy is often used to excise benign surface lesions. Punch biopsy material can be either diagnostic (incisional) or therapeutic (excisional) in intent, and the submitting clinician should indicate this clearly on the request form. They can also be deep if it is necessary to visualise the subcutaneous fat. Slightly larger shave or punch biopsies may be bisected and similarly all processed. In general, margins are not marked when the intent is purely diagnostic. Excisional biopsies attempt to remove the lesion with clear margins of normal skin. Assessment, in these cases, is aided by painting the deep and

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peripheral limits and use of serial transverse slices or quadrant (cruciform) blocks tailored to local protocols. Attached orientation sutures aid assessment of specific anatomical margins: orientation and inking during gross examination should be recorded in the final report. This is particularly useful when it is only feasible to achieve minimal clearance, e.g. on the face, ear, lip, nasal or periorbital areas. Thus, cases are handled individually according to the specimen size, type of lesion and its size and position within the specimen. If initial histological sections fail to reveal a tumour when an experienced clinician strongly suspects that one is present, the pathologist must always be prepared to take extra blocks or carry out many further levels for examination: a day's delay is preferable to a missed diagnosis. This most often occurs in small punch biopsies submitted intact that contain a centrally placed or off centre lesion not revealed in initial sections. Additional histological clues can be evident e.g. epidermal dysplasia, dermal inflammation/hyalinisation or retraction artefact that could suggest the possibility of an adjacent carcinoma. This is particularly so for recurrences which can be small and difficult to demonstrate.

Tumours arising in facial anatomic sites and in particular eyelids, medial canthus, nasal tip and ala, preauricular area, ears, and lips (H-zone) are more difficult to treat with a tendency for wider subclinical spread and a higher incidence of local recurrence and metastasis. A more specialised dermatological surgical technique may be required combining serial excisions with intraoperative frozen section checking of the entire circumferential surgical margin (Mohs micrographic surgery). The wound is then repaired after histologic confirmation of tumour clearance. Sometimes primary or secondary excision specimens are submitted with a central circular deficiency to aid excision or due to prior sampling for diagnosis or research by the clinician. Care must be taken in orientation of the specimen as accurate assessment of tumour diameter and margin distances can be somewhat problematic. In secondary excision for scar recurrence the tumour may be small or macroscopically difficult to define and eccentrically located within the specimen. Serial slices and total processing of the tissue may be required.

In general, treatment of cutaneous carcinoma is by wide local excision, or if indicated Mohs micrographic surgery. Mohs micrographic surgery is reserved for high risk primary and recurrent facial lesions with poorly defined margins, usually but not exclusively basal cell carcinoma. Other modalities are: radiotherapy, photodynamic therapy, topical imiquimod (an immune response modifier mediating cell death), curettage and cautery, cryotherapy and laser. Choice of therapy is determined by patient age and preference, comorbidities, tumour type, site, size, and whether it is a primary or recurrent lesion. Depending on local practice and knowledge or familiarity with referring clinicians, it is occasionally necessary to prompt the clinician to refer a case for local multidisciplinary team discussion, e.g. squamous cell carcinoma excised by general practitioner.

Gross description

Specimen

- Cytology/curettage/shave biopsy/punch biopsy/incision biopsy/excisional biopsy which may be immediately preceded by curettage of the lesion/re-excision/Mohs' surgery.
- Size: length x width x depth (mm).

Tumour

Site

- Anatomical site: limbs/trunk/head/neck/perineum/epidermal/dermal/subcutaneous.
- Sun exposed areas of the head and neck, scalp and back of hands are the most frequent sites for the common cancers. The central face, periorbital areas, lips and ears are clinical high risk anatomical sites prone to local recurrence due to difficulties in obtaining adequate primary margins.

Size

- Length x width x depth (mm) or maximum dimension (mm).
- Tumour size ≤2 cm or >2 cm is a pT1/pT2 stage determinant for many skin cancers (including squamous cell carcinoma, basal cell carcinoma, adnexal carcinomas and Merkel cell carcinoma). This is the clinical dimension but the macroscopic pathologic dimension can be used in lieu of an absent clinical measurement. Deep invasion defined as tumour thickness of >6 mm, invasion of an anatomically named nerve (or a nerve ≥0.1 mm diameter, or extradermal nerve), or minor bone erosion upstages pT1 and pT2 tumours to pT3. Prognosis of Merkel cell carcinoma >5 mm in thickness is poor. Cutaneous adnexal carcinoma >2 mm in thickness is a high risk feature.

Appearance

- Verrucous/warty/nodular/exophytic/sessile/ulcerated/invaginated/cystic/plaque/ haemorrhagic/necrotic/pigmented.

Edge

- Circumscribed/irregular.

Histological Type

Squamous Cell Carcinoma

- Forehead, face, ears, scalp, lip, neck, back of hands.
- Keratinising/non-keratinising.
- *80% are well to moderately differentiated and keratinising*.
- Although tumour location, stage, depth of invasion, differentiation and immunosuppression may be more important in terms of prognosis, particular histologic subtypes are associated with more aggressive behaviour: variants with adverse prognosis and higher rates of local recurrence and/or metastasis:
  - *Desmoplastic:* >30% of the tumour area is desmoplastic.
  - *Small cell* or *basaloid: associated with in situ disease and must be distinguished from basal cell carcinoma.*
  - *Spindle cell (sarcomatoid):* accounts for over 30% of metastatic squamous cell carcinomas. Those cases associated with radiation run an aggressive course while de novo examples may be no more aggressive than conventional squamous cell carcinoma.
  - *Post traumatic (de novo)*: not related to sun exposure and occur in the setting of chronic injury (often burns, i.e. Marjolin's ulcer). Paradoxically, may be moderate to well differentiated but not associated with actinic keratosis or dermal damage.
  - *Squamous cell carcinoma associated with adjacent in situ change (Bowen's disease).* Incidentally, Bowen's disease terminology was originally applied to *in situ* neoplasia in sun-protected skin but is now used interchangeably with *squamous cell carcinoma in situ* at both sun exposed and non-sun exposed areas.
  - *Acantholytic (pseudoglandular or adenoid):* there is conflicting evidence regarding risk and this subtype may be more indolent than previously reported when usual histologic factors are compared. It occurs more frequently in immunosuppressed patients.
  - *Adenosquamous* (mixed differentiation) arising from pluripotential acrosyringium cells.
- Others:
  - *Verrucous:* locally destructive but with little potential for metastases, this subtype may recur particularly on the foot and at the anal margin. Association with HPV infection. Superficial samples may resemble keratoacanthoma and verruca vulgaris. Ki67 and p53 expression in the lower third of epidermis in contrast to confluent epidermal expression in squamous cell carcinoma may help in diagnosis: distinguishing these may be important given the higher likelihood of nodal metastasis and

variation in treatment in squamous cell carcinoma.

- *Clear cell* (elderly, head and neck): differential diagnoses include metastatic renal cell carcinoma, clear cell acanthoma, sebaceous neoplasms and trichilemmoma. Many tumour types have a clear cell variant.
- *Lymphoepithelial* (elderly, head and neck): squamous differentiation may not be morphologically apparent.
- *Keratoacanthoma:* rapid clinical growth over a few months with potential for involution and even complete regression with variable histology depending on sample timing. It is crateriform with a central keratin plug and collarette of hyperplastic squamous epithelium. It may be difficult to distinguish from a well differentiated squamous cell carcinoma and in such cases may be best considered as the latter: the term invasive squamous cell carcinoma of keratoacanthomatous type has been proposed. A designation of keratoacanthoma is excluded by adjacent in situ change, desmoplasia, significant cellular pleomorphism, an inappropriate clinical history and should be avoided in immunocompromised patients.
- *Follicular variant of squamous cell carcinoma*: there is increasing recognition of a variant of squamous cell carcinoma with both in situ and invasive counterparts. Lesions are defined histologically by abrupt connections of the tumour with the epidermis at the site of follicular infundibula, presence of infundibular and/or tricholemmal differentiation, malignant cytological and/or architectural features and absence of bowenoid dysplasia or features of keratoacanthoma. Most lesions show relatively mild cellular atypia and clear cell change may occur. Additionally, there may be subtle peripheral cellular palisading as well as central acantholytic spaces containing mucin but in contrast to basal cell carcinoma, there is generally no mucin in stromal retraction artefact spaces. Recognition of the invasive form may have implications on prognosis and follow-up: in particular depth of invasion measurement may be problematic as it may not be appropriate to measure from granular cell layer of the surface epidermis in a tumour arising from a hair follicle as this could overestimate risk.

Basal Cell Carcinoma

- *The commonest non-melanocytic cutaneous carcinoma* comprising a proliferation of basaloid/germinative cells and characterised by slow growth and *local tissue infiltration* and *destruction*. Metastases are exceedingly rare and morbidity results from local tissue invasion and destruction, particularly on the face, head and neck. The morphoeic, infiltrative, micronodular and basosquamous types are associated with the highest risk of recurrence as they may be more pervasive microscopically than apparent clinically and more likely to exhibit perineural invasion. In contrast, circumscribed, local or expansile tumours and particularly those with a superficial or nodular growth pattern have a lower risk of local recurrence. More than one growth pattern may be apparent in any given lesion and the level of clinical risk is determined by the highest risk growth pattern present. Morphologic subtyping is an important facet in determining therapy options as some lower risk lesions may be treated by non-surgical means such as imiquimod or photodynamic therapy.
- *Nodular*: the commonest subtype (60–80% of cases, often head and neck area) with nodules of varying size, ± tumour necrosis and cystic spaces (nodulocystic), peripheral palisading, mitoses and dermal retraction artifact. Includes adenoid, (trabecular/ribbons of cells), keratotic (horn cysts, squamous metaplasia), pigmented, fibroepithelial (Pinkus tumour) variants, and, those with adnexal (follicular, sebaceous or eccrine) differentiation. Care should be exercised not to interpret squamous

metaplastic foci or keratocystic areas as representing basosquamous differentiation.

- *Superficial*: 10–20% of cases. Sometimes called multifocal given its apparent discontinuous nature when viewed on histologic sections, it comprises multifocal nests of tumour budding off the epidermal or hair follicle basal layer. Buds should be confined to papillary dermis and less than 1 mm thickness. It remains unclear whether this represents in situ or truly invasive disease. Recurrence is due to inadequate primary excision of peripheral margins. Often occur on the trunk.
- *Infiltrative/morphoeic*: small, irregular infiltrating groups in a fibrous, scirrhous or hyaline stroma in a poorly circumscribed lesion. The pattern resembles a tree trunk with spreading roots which can be deeply infiltrative, more often reaching subcutis and compromising the deep margin. Usually occurs on the upper trunk or face.
- *Micronodular*: multiple discrete small round nests less than 0.15 mm diameter (or approximately 25 cells in diameter), with an asymmetrical, infiltrative growth pattern. It is the infiltrative growth that confers high risk status to this subtype and can result in margin compromise that is not clinically apparent. Tumours comprising small nodules but with a well circumscribed edge, best appreciated on low power examination, and with no other high risk attributes are more appropriately categorised as nodular.
- *Basosquamous carcinoma*: tumours with moderately to severely atypical or malignant squamous cell differentiation. Tumours may have focal squamous areas or squamoid cells scattered throughout with transition areas containing intermediate cells. This is an intermediate tumour between basal cell and squamous cell carcinomas of usual type with potential for local recurrence (4.5% rate) and metastatic spread (nodal metastases in 5%). It is currently categorised a high risk variant of basal cell rather than squamous cell carcinoma. Basosquamous is the variant most likely associated with vascular invasion and has the greatest metastatic potential. Perineural invasion is found in approximately 10% of cases. It is recommended that the poorly defined term "metatypical" be avoided as it is probably a variant of basosquamous carcinoma with no robust discriminating histologic characteristics or appreciable differences in clinical outcome.
- Metastasis in basal cell carcinoma is extremely rare. *Low risk primary tumours* may be treated in *primary care* by suitably trained personnel, whereas *high risk tumours* are dealt with in *secondary care.* Features of low risk basal cell carcinoma include sites below the clavicle and size <20 mm. High risk lesions prone to local recurrence are characterised by: *anatomical site* (face, eyes, nose, lips, ears), *growth pattern* (infiltrative/morphoeic/micronodular), *cellular differentiation* (basosquamous), the presence of *perineural or lymphovascular invasion*, *Clark level V invasion,* and *stage ≥ pT2.*

Adnexal Carcinoma

- Adnexal tumours are relatively infrequently encountered in general practice. These comprise a diverse group with morphologic differentiation towards one or mixtures of adnexal epithelium: follicular epithelium, sebaceous, apocrine and eccrine glands. Whilst the majority will be benign, the rare malignant counterparts have potential for locally aggressive growth, nodal involvement and distant metastases with poor outcome. Correspondingly, these *tumours* are best dealt with by a pathologist with dermatopathological expertise in the context of a multidisciplinary meeting.

Diagnostic clues to malignant behaviour include asymmetry, cellular atypia, necrosis, mitoses, perineural or lymphovascular invasion and an unusually deep and infiltrative margin. Low power patterns are solid-cystic, papillary-tubular or sclerosing. Low-grade carcinomas show considerable cellular differentiation, uniform cell size with infrequent mitoses and little pleomorphism: they do well if small and

completely excised. Examples are microcystic adnexal carcinoma, syringoid eccrine carcinoma, adenoid cystic carcinoma and mucinous eccrine carcinoma. High-grade cancers show poor differentiation, necrosis and mitoses, and they can metastasise widely. Examples are malignant hidradenoma, malignant spiradenoma/cylindroma, aggressive digital papillary adenocarcinoma and porocarcinoma.

- Hair follicle differentiation: follicular differentiation is recognised by basaloid germinative cells, peripheral nuclear palisading and papillary mesenchymal cells. Ghosted epithelium and attachment to normal follicular structures are additional features. Examples include tricholemmal carcinoma, malignant pilomatrixoma and malignant proliferating trichilemmal cyst.
- Sebaceous differentiation: these tumours may have bubbly vacuolated cytoplasm and jagged irregular nuclei. Examples include sebaceous carcinoma and basal cell carcinoma with sebaceous differentiation.
- Ductal differentiation: this represents the most diverse group and includes apocrine and eccrine tumours—including syringoid carcinoma, microcystic adnexal carcinoma, malignant chondroid syringoma, hidradenocarcinoma, porocarcinoma, mucinous carcinoma, aggressive digital papillary adenocarcinoma and adenoid cystic carcinoma. EMA and CEA immunochemistry can be helpful in highlighting ductular structures. In some cases a precise diagnosis may not be possible and a management label of malignant cutaneous sweat gland tumour may suffice. Consideration should be given to cutaneous metastatic disease with more common mimics including carcinoma from thyroid, breast, salivary gland and kidney: clinical history and judicious immunochemistry may be beneficial.

Paget's Disease

- Extramammary sites include apocrine rich areas of vulva, perineum, scrotum, axillae. This may be associated with occult visceral malignancy (in about 15% of cases) and should be accurately differentiated from pagetoid squamous cell carcinoma in situ and melanoma in situ. A useful immunopanel to differentiate these includes CK7, CK20, CEA, EMA, CAM5.2 (expressed in extra-mammary paget's disease), p63 (expressed in squamous cell carcinoma in situ) and S100, SOX10 and melan-A (expressed in melanoma in situ).

Neuroendocrine Carcinoma: Merkel Cell or Small Cell Neuroendocrine Carcinoma of Skin

- On the head/neck, extremities, in the elderly, it is a poorly differentiated/high-grade neuroendocrine carcinoma comprising small blue cells with increased apoptosis and a high mitotic rate.
- Chromogranin/synaptophysin/CD56 and paranuclear or perineuclear dot CAM 5.2, AE1/3, CK20 positive. Ki67, CD117, CD99 and FLI1 positive, but TTF-1 and CD45 negative.
- May be associated overlying basal or squamous cell carcinoma (in situ or invasive) in >30% of cases although this may not necessarily confer a worse prognosis. Rarely the tumour can also show components of squamous cell or eccrine differentiation. Chronic lymphocytic leukaemia is the most common second extracutaneous malignancy.
- *Clinically exclude secondary small cell carcinoma of lung* (CK 20 negative/TTF-1 positive). *Histologically exclude malignant lymphoma* (CD45 positive) and *small cell variant of malignant melanoma* (S100, melanA positive). Polyoma virus is positive in 80% (molecular and immunochemical techniques available). Positive cases tend to have a better prognosis while negative cases may have greater cellular atypia and a greater association with UV light exposure. Cases with a second malignancy also tend to be negative.
- Treatment is *primary excision with wide margins and consideration for adjuvant radiotherapy. Adverse indicators* are: size >20 mm,

thickness >5 mm, mitoses >10 per high power field or Ki-67 >50%, an infiltrative border, subcutaneous fat invasion, lymphovascular or lymph node involvement or positive primary excision margins. Approximately 10% of Merkel cell carcinomas present as metastatic disease of unknown origin possibly related to primary tumour regression.

Metastatic Carcinoma

Skin metastases occur in up to *9% of malignancies* and can *predate, occur synchronously, or after the primary lesion*. *Clinical presentation* with a skin metastasis (2% of cases) is seen particularly with lung, kidney and ovarian cancer. *Late metastases* (at 10 years or more) come from breast carcinoma, malignant melanoma, kidney, bladder, colon and ovarian cancers. Some metastases are by *direct local extension* to overlying skin, e.g. breast carcinoma, others by *distant vascular spread,* e.g. kidney carcinoma and malignant melanoma. Although melanoma has a higher propensity to metastasise to skin, breast cancer is the most frequently encountered type as it is much more common. Other common sources of skin metastases in females are colon, ovaries and lung. In males: lung, colon and the oral cavity.

- Single/multiple nodule(s) commonly on the trunk and head and neck regions (especially umbilicus and scalp), sometimes *in the vicinity of the primary lesion*.
- Some metastases can be epidermotropic and *simulate a primary lesion,* e.g. malignant melanoma. Most are dermal and show nodular, interstitial and intravascular patterns necessitating distinction from primary adnexal carcinoma. *Previous clinical history, comparative morphology* and relevant *immunohistochemical profiles* are important in this respect.
- Immunochemistry should be judiciously applied. Primary adnexal tumours may commonly mimic skin metastases and in the case of breast, since this is a modified apocrine gland, immunochemical markers may be unhelpful: both show expression with markers such as GCDFP-15, GATA3, ER and PR. Adnexal tumours and metastatic lung adenocarcinomas are both usually CK7+/CK20 − .
- Secondary small cell carcinoma of lung or gastrointestinal tract can mimic Merkel cell carcinoma although both are CK20 negative.

Differentiation

Squamous cell carcinoma differentiation has been based on Broders' 4 tier classification but in practice this is difficult to apply. A modified 3 grade classification which assimilates additional cytologic and mitotic features is favoured with grading based on the worst area regardless of proportion involved.

Well differentiated tumours are easily recognised as squamous with abundant keratinisation, intercellular bridging and relatively infrequent mitoses usually basally located. At the other end of the spectrum, *poorly differentiated* tumours may only have extremely focal intercellular bridging or keratin formation and an overlying dysplastic epidermis may hint at the correct diagnosis. Such tumours may require immunochemistry to reveal their true nature. *Moderately differentiated* tumours will have an intermediate degree of differentiation. They exhibit greater architectural and cytonuclear atypia than well differentiated tumours but are still relatively readily recognised as squamous. Tumours showing no keratinization or intercellular bridging are regarded *anaplastic* and require immunochemistry for diagnosis. As a general rule of thumb, in the absence of morphologic prompts and if immunochemistry is required for the diagnosis then differentiation is likely to be at least poor.

Grading is not formally applied to basal cell carcinomas. These are subtyped according to low or high risk growth patterns with comment made on any unusual cellular differentiation features e.g. basosquamous carcinoma.

Grading of adnexal tumours broadly utilises the same approach to squamous cell carcinoma: well-differentiated tumours readily reveal their adnexal subtype with few mitoses and minimal cytonuclear atypia. The adnexal lineage is difficult to recognise in poorly differentiated tumours and there is

significant cytonuclear atypia with numerous atypical mitotic figures. Moderately differentiated tumours will have an intermediate degree of differentiation. Again, it is recommended that grading is based on the worst rather than predominant morphology although it may be useful to comment on relative proportions if the worst area is very focal.

Primary Tumour Staging

The following TNM8 classification applies to any skin carcinoma (except Merkel cell carcinoma) and to any site except eyelid, vulva, penis, non-hair bearing lip or non-hair bearing perianal skin (within 5 cm of the perianal margin). Staging (of all skin carcinomas including Merkel cell carcinoma) is based on the clinical measurement provided but the macroscopic pathologic measurement can be used if the former is unavailable.

pTis	Carcinoma in situ
pT1	Tumour ≤20 mm or less in maximum dimension
pT2	Tumour >20 mm to ≤40 mm in maximum dimension
pT3	Tumour >40 mm in maximum dimension
pT4a	Tumour with gross cortical/marrow invasion
pT4b	Tumour with axial skeleton/skull base/foraminal invasion

pT1 and pT2 tumours can be upstaged to pT3 by one or more high-risk clinical or pathological features including deep invasion (tumour thickness > 6 mm), bone erosion that does not fulfil pT4 criteria or perineural invasion defined as follow: invasion of an anatomically named nerve detected clinically or radiologically or involved nerves at least 0.1 mm diameter and any extradermal nerve involvement.

Clinical high risk factors for skin carcinomas include ear and hair bearing lip sites, recurrent or persistent lesions, reduced immunity, origin in non-exposed sites (e.g. sole of foot, perineum) and arising in areas of chronic injury. This information may be unavailable to the pathologist at the time of reporting.

Pathologic high risk factors for **squamous cell carcinoma** include high risk morphologic subtypes, poor differentiation, perineural invasion, thickness > 4 mm (squamous carcinomas of this size have a significantly increased metastatic potential, those >10 mm are very high risk with potentially high mortality), extradermal invasion, >pT1 stage and close margins (usually <1 mm). For **basal cell carcinoma** high risk factors are similar although >6 mm thickness is required and lymphovascular invasion is most important in the basosquamous type.

Tumour thickness (perpendicular distance from granular cell layer to deepest point of tumour invasion) may be difficult to measure in exophytic and ulcerating/endophytic or cup shaped lesions. The measurement is essentially similar to Breslow as used for melanoma with the acknowledgement that the granular cell layer may be lost in squamous cell carcinomas: therefore is may be advisable to take the measurement in relation to the granular cell layer of adjacent normal epidermis. This avoids overestimating risk in very exophytic lesions confined to superficial portions of the skin and, conversely, recognises the higher risk status of deeply ulcerating tumours that may appear rather thin if measuring from base of ulceration to base of tumour. In the case of a very exophytic tumour where the entire invasive portion is above the granular cell layer of adjacent normal epidermis and in the absence of other high risk factors, it may be appropriate to record thickness as <2 mm rather than stating a somewhat confusing negative value (Fig. 20.1).

The greater the number of clinical and pathologic risk factors, the higher risk the lesion is for local recurrence, nodal metastases and poorer outcome and survival. Overall assessment may only be possible by the referring clinician or through MDT discussion. A pragmatic approach to tumour thickness measurement should be taken and placed in the context of the overall lesion: any difficulties can be expanded in reports or discussed through MDT.

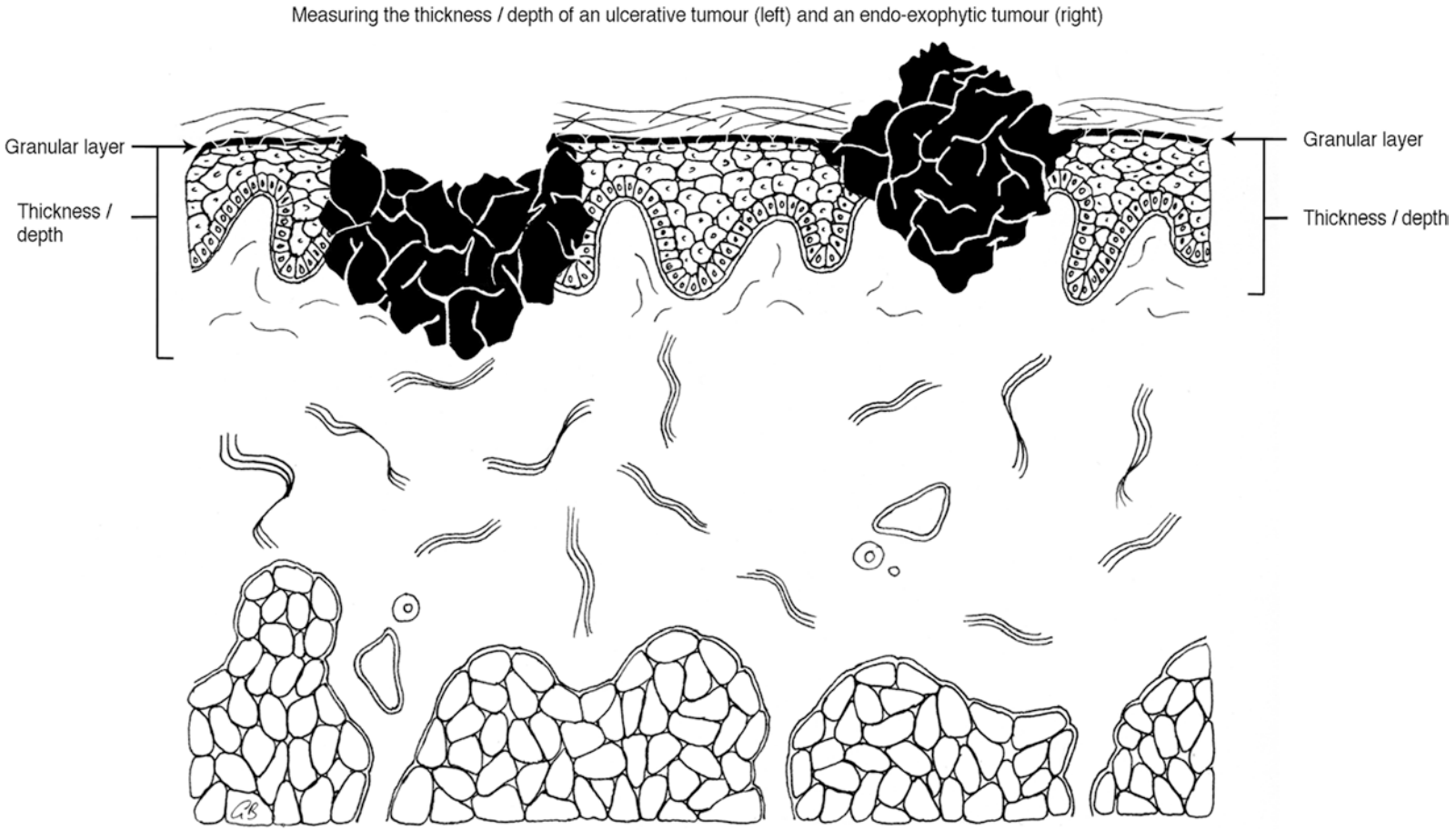

Fig. 20.1 Measuring tumour thickness in ulcerating and exophytic tumours. A modified and pragmatic approach is required in tumours from sites where adjacent skin is not flat or the tumour is cup shaped and not ulcerated

Merkel Cell Carcinoma

The staging of Merkel cell carcinoma includes all sites except the eyelid, non hair-bearing lip and non hair-bearing perianal skin:

pT0	No evidence of primary tumour (e.g. nodal/metastatic presentation without associated primary)
pTis	In situ primary tumour
pT1	≤20 mm maximum clinical dimension of tumour
pT2	>20 mm to ≤50 mm maximum clinical dimension of tumour
pT3	>50 mm maximum clinical dimension of tumour
pT4	Primary tumour invades fascia, muscle, bone or cartilage (i.e. beyond subcutaneous fat)

Lymphovascular Invasion

Perineural and lymphovascular invasion are not commonly seen (sometimes in squamous cell carcinoma, rarely in high risk basal cell carcinoma) but when present correlate with higher rates of local recurrence and metastases. This correlates most strongly with sentinel lymph node positivity and poor outcome in Merkel cell carcinoma and must be extratumoural. Lymphovascular invasion can be highlighted with D2–40 immunostaining.

Lymph Nodes

Site/number/size/number involved/extranodal extension.

Regional nodes are those appropriate to the site of the primary tumour:

Head and neck (preauricular, submandibular, cervical and supraclavicular).

Thorax and upper limb (axillae).

Abdomen, loins, buttocks, lower limbs, perianal/anal margin (all inguinal nodes: lower limbs also includes popliteal).

The following nodal staging refers to all carcinomas (except Merkel cell carcinoma) with ipsilateral nodes (contralateral nodal involvement represents distant metastatic spread: M1) and applies to all sites except eyelid, head and neck, perianal, vulval, and penis. In this case a regional lymphadenectomy should include at least 6 lymph nodes.

pN0	No regional lymph node metastasis
pN1	Metastasis in a single regional lymph node ≤30 mm in greatest dimension
pN2	Metastasis in a single regional lymph node >30 mm but <60 mm, or multiple ipsilateral nodes all ≤60 mm
pN3	Metastasis in a lymph node >60 mm in greatest dimension

Head and neck cutaneous carcinomas (excluding the eyelid and again excluding Merkel cell carcinoma) utilise a different nodal staging system. This will ordinarily include at least 10 lymph nodes in selective neck dissection and at least 15 in radical or modified neck dissection specimens.

pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral lymph node ≤30 mm in greatest dimension, without extranodal extension.
pN2a	Metastasis in a single ipsilateral lymph node, more than 30 mm but <60 mm in greatest dimension, without extranodal extension.
pN2b	Metastasis in multiple ipsilateral lymph nodes, all ≤60 mm in greatest dimension, without extranodal extension.
pN2c	Metastasis in bilateral or contralateral lymph nodes, all ≤60 mm in greatest dimension, without extranodal extension
pN3a	Metastasis in a lymph node, more than 60 mm in greatest dimension, without extranodal extension
pN3b	Metastasis in a lymph node with extranodal extension

Extranodal extension may be reported pathologically as the presence of skin involvement or soft tissue invasion with deep fixation or tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement as clinical extranodal extension.

Merkel Cell Carcinoma

pN0	No regional lymph node metastasis
pN1a	Microscopic (occult) involvement (sentinel or node dissection)
pN1b	Macroscopic involvement (clinically apparent)
pN2	In-transit metastasis without nodal involvement
pN3	In-transit metastasis with nodal involvement

In-transit metastasis refers to discontinuous tumour distinct from the primary lesion and located distal to the primary or between the primary and draining regional lymph nodes. In practice this is taken to mean discontinuous nests >0.05 mm diameter and separated by completely normal dermis from the main tumour by ≥1 mm.

Distant metastasis is: pM1 beyond regional nodes, pM1a distant skin, subcutaneous tissue or non-regional nodes, pM1b lung and pM1c other visceral sites.

Excision Margins

Distances (mm) to the nearest painted deep and peripheral excision margins, either of serial transverse slices (bread sliced) or quadrant blocks according to local protocols with pragmatic modifications based on closest grossly assessed edges. Comment should also be made on the presence of other benign lesions and of dysplasia or in situ change at the margins.

Adequate treatment is based on successful *complete primary excision* or, if there is initial margin involvement, on *secondary re-excision*. Clinically intended margins may not correspond to pathologic measurements due to specimen handling, tissue fixation and on occasion unexpected pathology. Pathologic involvement is tumour at (=0 mm) a margin; clear but close to is <1 mm; clear of is >1 mm. Quantification of margins to 1 decimal place is recommended particularly for lesions with "close" margins and may aid in subsequent treatment decisions. This information is often requested at MDM if a margin is quoted as "close" or <1 mm. Providing this degree of detail precludes any misunderstanding of the subjective term close which may vary depending on the tumour type. For example: with respect to clinical margins a 95% clearance rate may be expected with a 4 mm clinical margin for a low risk basal cell carcinoma. However, the same degree of confidence of clearance for a morphoeic basal cell carcinoma may necessitate a 13–15 mm clinical margin. It may be helpful to provide a further qualitative assessment of involved margins in certain instances: transection of tumour at a margin implies a large residue of disease contrasting to very focal involvement or if an apparently rounded lesion appears to have been 'scooped out'. Additionally superficial basal cell carcinoma at an edge may be treated more conservatively if a main, more clinically apparent tumour of another subtype is entirely resected. Cutaneous adnexal carcinomas can have ill-defined infiltrative lateral and deep margins compromising complete primary excision e.g. microcystic adnexal carcinoma.

Other Pathology

Squamous cell carcinoma: more prone to lymph node metastases particularly if >2 cm diameter or > 2 mm in thickness, poorly differentiated or with perineural spread. General *prognostic indicators* for squamous cell carcinoma are stage, level of dermal invasion and tumour thickness. *Recurrent tumours* tend to be ≥4 mm thick with involvement of the deep dermis, and *very high risk tumours* at least 1 cm thick with extension into subcutaneous fat. Tumours arising in non-sun exposed sites (e.g. trunk, perineum, penis) and areas of trauma (e.g. burns, Marjolin's ulcer) have a higher risk of metastasis.

Predisposing lesions to cutaneous carcinoma are:

- Actinic keratosis/solar elastosis: sun exposure.
- Psoralen plus ultraviolet A (PUVA) treatment for psoriasis.
- Varicose ulcers (Marjolin's), lichen planus, hidradenitis suppurativa.
- Immunosuppression post transplant or chemotherapy, HIV.
- Squamous cell carcinoma *in situ*: indolent progression to carcinoma.
- Condyloma accuminatum, Bowenoid papulosis, HPV infection: perineum/ perianal margin squamous carcinoma.
- Epidermodysplasia verruciformis, xeroderma pigmentosum.
- Naevus sebaceous of Jadassohn.
- Naevoid basal cell carcinoma (Gorlin) syndrome.

Double pathology: may be encountered e.g. basal or squamous cell carcinoma overlying Merkel cell carcinoma, basal cell carcinoma and syringocystadenoma papilliferum in naevus sebaceous of Jadassohn, basal cell carcinoma and dermatofibroma.

Pseudoepitheliomatous (pseudocarcinomatous) hyperplasia: may be seen in association with: chronic venous stasis, ulceration, chronic inflammation e.g. pyoderma gangrenosum, and overlying neoplasms e.g. granular cell tumour.

Actinic keratosis, carcinoma in situ and invasive squamous carcinoma: distinction can be difficult and some of these lesions may be designated "best regarded as squamous cell carcinoma". Treatment (primary surgical excision) is the same for both. Invasive squamous cell carcinoma may be recognized by jagged islands with eosinophilic keratinization of dermal invasive foci (multiple tissue levels may be required for demonstration).

Sebaceous carcinoma: both eyelid (also known as Meibomian gland carcinoma) and extraocular sites have a 30–40% risk of local recurrence, a 20–25% of distant metastasis and a 10–30% mortality risk. A minority of patients have Muir-Torre syndrome (a subset of the hereditary non-polyposis colorectal carcinoma (HNPCC) syndrome).

Immunophenotype

Most cutaneous carcinomas are reported without immunochemical stains. However, there are a number of scenarios where a particular immunophenotype may help secure the correct diagnosis.

Squamous cell carcinoma: AE1/3, 34BetaE12, CK5/6, EMA, p63, CEA positive; BerEP4 negative.

Basal cell carcinoma: BerEP4 positive; EMA, CEA negative.

A combination of EMA and BerEP4 is often helpful in distinguishing between squamous cell carcinoma and basal cell carcinoma.

Adnexal carcinomas: usually EMA and CEA positive, and differential molecular weight cytokeratin expression according to their differentiation. In general they are CK7, CAM 5.2 (low molecular weight), AE1/3, HMFG1 and GCDFP-15 positive.

Other Malignancy

Leukaemia

- Leukaemia cutis describes any cutaneous presentation of leukaemia. Most cases represent widespread systemic or recurrent disease but in around 5% skin involvement may be the first manifestation. Tumour cell immunophenotype (together with clinical information, bone marrow and peripheral blood findings) is vital for diagnosis. Specialist haematopathology input is essential.
- Children: acute lymphoblastic leukaemia (most common childhood leukaemia). CD79a, CD34, CD10 positive ± tdt, Ki-67 >90%.
- Adults:
  - Chronic lymphocytic leukaemia (CLL)—CD5, CD20, CD23, CD43 positive and CD10 negative
  - Chronic myeloid leukaemia (granulocytic sarcoma, chloroma)—CD34, CD43, CD117, myeloperoxidase

Primary Cutaneous Lymphoma

- Heterogenous group of T and B cell lymphomas of the skin in the absence of extracutaneous disease at diagnosis. Staging is required to exclude secondary cutaneous involvement by systemic lymphoma
- In western countries: 75–80% are T cell; 20–25% are B cell.

Immunohistochemistry (for cell lineage and light chain restriction) and *molecular studies (T cell receptor gene and immunoglobulin heavy chain gene rearrangements)* are also of use in cutaneous malignant lymphoma. *T cell malignant lymphomas* show *epidermotropism* while *B cell malignant lymphomas* often have a *dermal*

grenz zone and a *"bottom-heavy" infiltrate extending into the subcutaneous fat*. Note that the latter can also show reactive germinal centres and a polymorphous reactive cellular infiltrate. Low-grade T cell malignant lymphomas have a horizontal band like dermal growth pattern while high-grade lesions and B cell malignant lymphomas are sharply demarcated with a nodular, vertical and three-dimensional growth. Molecular studies may be helpful in inflammatory conditions simulating cutaneous malignant lymphoma (e.g. lymphocytoma cutis, lupus erythematosus profundus, and lymphomatoid reactions to drugs and insect bites) but may provide inconclusive results. Designation of malignant lymphoma can sometimes be difficult and should be clinicopathological in the context of a multidisciplinary meeting. In some cases the subsequent clinical progression or lack thereof is the final arbiter.

Some malignant lymphomas present in the skin and never as a primary lesion in lymph node or extracutaneous site, e.g. mycosis fungoides. Others can resemble their lymph node counterparts but show a different clinical behaviour.

T Cell, Indolent Behaviour

Mycosis fungoides (MF): the most common cutaneous T cell lymphoma and comprises nearly 50% of cutaneous T cell malignant lymphomas. MF has overlapping patch, plaque, tumour, erythrodermic and poikilodermic stages with late lymph node, blood and extracutaneous involvement. Cells are small to medium sized with cerebriform nuclei. There is epidermotropism (CD3+cells with increased CD4/CD8 ratio of positivity). This immunochemical profile may help in differentiating potential mimics such as spongiotic dermatitis and lichenoid keratosis. Multiple biopsies may be required before a histologic diagnosis is made.

Folliculotropic MF, pagetoid reticulosis and granulomatous slack skin are distinct variants of MF:

- *Pagetoid reticulosis:* intraepidermal (pagetoid) T cell infiltrate.
- *Granulomatous slack skin disease:* T cell infiltrate with giant cell elastophagocytosis in the major skin folds. Malignant lymphoma may occur years later.
- *Folliculotropic MF:* perifollicular infiltrate with variable infiltration of follicular epithelium. Cases may or may not show mucinous degeneration of hair follicles.

Primary cutaneous CD30+ T cell lymphoproliferative disorders (second most common group of cutaneous T cell lymphomas—30%) and comprises lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma (C-ALCL).

Lymphomatoid papulosis: recurring self-healing papulonodular eruption of uncertain malignant potential with variable polymorphous/monomorphous pictures including CD30 positive large cells. A wedge shaped infiltrate at low power. Several subtypes exist (without treatment or prognostic implications), their importance in recognition relating to avoiding misdiagnosis. Most cases follow an indolent course but some may be at risk of developing another form of cutaneous or nodal lymphoma and therefore long term follow-up is recommended.

C-ALCL: usually cohesive sheets of anaplastic cells and >75% of these are CD30 positive. Usually T cell, sometimes null, 40% spontaneously regress and a 10 year survival of 90%. If clinical evidence of MF then diagnosis more likely to be MF with large cell transformation. Exclude systemic anaplastic large cell lymphoma with cutaneous involvement (this is EMA and ALK positive in contrast to C-ALCL).

T Cell, Aggressive Behaviour

Sézary syndrome: erythroderma, generalized lymphadenopathy and neoplastic T cells with cerebriform nuclei (Sézary cells). May appear histologically similar to MF. 5 year overall survival of 10–30%.

Adult T cell lymphoma: human T cell leukaemia virus type 1 linked. Various degrees of tumor cell infiltration in skin biopsy from epidermis to subcutis. May resemble MF. Some cases run a

protracted course, particularly if limited to skin but more extensive disease associated with greater disease aggression.

Cutaneous γδ T cell lymphoma: 1% of all cutaneous T cell lymphomas; 12 month median survival. May be epidermotropic, dermal and subcutaneous.

Subcutaneous panniculitis like T cell lymphoma: Rare. Multiple subcutaneous lumps in the extremities of young adults. Honeycomb panniculitic infiltrate of the subcutaneous fat with sparing of dermis/epidermis. CD8 positive, αβ T cell phenotype.

Extranodal NK/T cell lymphoma, nasal type: angiocentric/destructive, may involve dermis diffusely and extend into subcutis. CD56 positive, occasionally T cell positive. 25% 5 year survival especially if multiple lesions.

Primary Cutaneous B Cell, Indolent Behaviour (>95% 5 Year Survival)

Follicle centre lymphoma: 50% of all primary cutaneous B cell lymphomas. Trunk and scalp. Must rule out systemic disease. CD20/CD10 (negative in diffuse morphology)/bcl-6 positive but bcl-2 negative. Widely spaced follicles in the deep dermis and subcutaneous fat.

Marginal zone lymphoma: good prognosis—a minority have *Borrelia burgdorferi* organism as a chronic antigenic stimulus. Nodular perivascular/periadenexal, or diffuse dermal infiltrate of centrocytoid/monocytoid cells including reactive germinal centres. Neoplastic cells are bcl2 positive; CD10/bcl6 negative (reactive follicles are CD10/bcl6 positive; bcl2 negative). Preferentially located on trunk and arms.

B Cell, Intermediate Behaviour

Mantle cell lymphoma: rare but skin involved in 1–12% of cases; exclude spread from systemic disease.

Primary cutaneous diffuse large B cell lymphoma (DLBCL), leg type: typically elderly females. 10% occur at other sites. Grenz zone, with a dermal/subcutaneous, perivascular/periadnexal infiltrate. It is CD20/CD10/bcl2/MUM1/bcl-6 positive. Variable 50—95% 5 year survival. Multiplicity of lesions is adverse. Exclude secondary involvement by systemic DLBCL.

B Cell, Aggressive Behaviour

Intravascular large B cell lymphoma.

Primary cutaneous—DLBCL.

Lymphoblastic lymphoma in children and adults: tdt positive. Aggressive but can be cured particularly in children.

Lymphomatoid granulomatosis (EBV positive large B cells, with reactive small T cells). Skin is most common extrapulmonary site involved (EBV positive B cells rare to absent in skin lesions). Poor prognosis in most patients with mortality related to lung involvement.

Maligant Lymphoma: Secondary

- Secondary to nodal/systemic disease.

For details on the classification, immunophenotyping and staging of malignant lymphoma refer to Chap. 35.

Other

Langerhans cell histiocytosis: S100/CD1a positive, epidermotropic dendritic cell proliferation. Considered an inflammatory myeloid neoplasm. Can be single system but also potentially in bone, lung and lymph nodes. Single system disease has a good prognosis in contrast to multisystem disease.

Cutaneous mastocytosis: abnormal accumulation of clonal mast cells. Either solitary mastocytoma, maculopapular cutaneous mastocytosis (urticaria pigmentosa), or diffuse cutaneous mastocytosis (whole body). Skin involvement may be part of a systemic presentation (often bone mar-

row). A clonal mast cell infiltrate with a "fried egg" appearance (can also be spindle shaped), tryptase/toluidine blue/CD117 positive. Aberrant expression of CD25 and/or CD30 helps confirm a clonal mast cell origin.

Sarcoma

Soft tissue sarcomas are outnumbered 100 to 1 by benign soft tissue tumours. There are multiple different histological types often with more than one subtype. They vary in their behaviour from indolent to aggressive but *cutaneous sarcomas are more favourable* than their deep sited fascial counterparts. In general *5 year survival is 65–75%* with *complete local excision being the most important determinant.* A majority are locally infiltrative and a minority potentially metastatic. The latter depends on tumour type, grade, size and depth from the skin surface. They usually arise in older patients in the extremities (particularly thigh), trunk, head and neck and retroperitoneum. Cutaneous sarcomas form an elevated plaque or nodule that can ulcerate when malignant. Superficial lesions smaller than 2 to 5 cm can be *excised in their entirety.* Larger, deeper tumours may require initial diagnostic sampling by *needle core* or *deep punch biopsy* prior to *radical extirpative surgery. Molecular genetic analysis* has a *diagnostic* and *prognostic role* to play in select cases and to determine any indication for *neoadjuvant therapy.*

Dermal and subcutaneous soft tissue tumours may have classical clinical features, e.g. angiosarcoma of the scalp in the elderly and Kaposi's sarcoma in HIV. However, they are classified according to their cell of origin and malignancy is assessed by cellularity, cellular atypia, mitotic activity, necrosis and infiltrative margins. *Immunohistochemistry* is often very useful in determining histogenesis e.g. desmin, h-caldesmon, SMA, myogenin (muscular), S100 (neural, melanocytic (also HMB45, melanA, SOX10), chondroid, adipose), CD31, CD34, FLI1, ERG, factor VIII (vascular) and CD68 ((fibro-)histiocytic). Examples are: cutaneous leiomyosarcoma (SMA, desmin), dermatofibrosarcoma protuberans (DFSP) (CD34), angiosarcoma (CD31, CD34, FLI1, ERG—epithelioid variant may expression cytokeratins), epithelioid haemangioendothelioma, malignant nerve sheath tumour and pleomorphic liposarcoma (S100) and Ewing sarcoma/PNET (CD99). See Chap. 36 for further details.

Immunohistochemistry is also important in the differential diagnosis of *cutaneous spindle cell lesions, e.g. spindle cell squamous carcinoma versus malignant melanoma, leiomyosarcoma and atypical fibroxanthoma (AFX).* A working panel is CAM5.2, MNF116, AE1/3, CK5/6, p63, S100, melanA, SOX10, desmin, h-caldesmon, smooth muscle actin and CD68. Other morphological clues are dysplasia of the surface squamous epithelium (carcinoma), junctional activity and melanin pigmentation (melanoma), Touton-like giant cells (AFX) and eosinophilic fusiform spindle cells (leiomyosarcoma). *Clinical history* is vital to exclude a metastatic spindle cell carcinoma or malignant melanoma. Hence AFX is a diagnosis of clinical, morphological and immunohistochemical exclusion. It arises on the sun exposed head and neck area of elderly patients, is a *low-grade malignant tumour* regarded by some as a spindle cell squamous carcinoma, but behaves in a benign fashion if completely excised. It can show false positive melanA staining in the pleomorphic cells as well as SMA. There is also a monomorphic spindle cell variant. Temper a diagnosis of AFX in small biopsies when the base of the lesion is not seen. AFX is excluded by the following: perineural, lymphovascular or extensive subcutaneous invasion, or, necrosis (reported metastatic examples should be considered with extreme skepticism). If any of these are present it is designated *pleomorphic dermal sarcoma* with 30% recurrence rate and 10% metastatic rate with resultant high mortality.

Kaposi's sarcoma is found in the elderly (solitary) or young (HIV, multiple). The earlier patch and plaque phases are subtle, characterised by linear vascular slit-like spaces in the dermal collagen orientated parallel to the epidermis: promontory sign may be present (small vessel

protruding into an abnormal vascular space). Later there is a sieve-like pattern with extravasation of red blood cells and a spindle cell proliferation in the nodular phase (differential diagnoses in this phase include angiosarcoma, DFSP, leiomyosarcoma and spindle cell amelanotic melanoma). The causative agent is human herpes virus 8 (HHV8) and lesions express HHV8 immunochemistry (as well as CD31, CD34 and D2–40).

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