

Moshim Kukar, Jacqueline Oxenberg,
Edward Eun Cho, Nathalie C. Zeitouni,
and Joseph Skitzki

Abbreviations

5-FU	5-fluorouracil	MCC	Merkel cell carcinoma
AJCC	American Joint Committee on Cancer	MCV	Merkel cell polyomavirus
AK	Actinic keratosis	MPD	Mammary Paget's disease
AS	Angiosarcoma	NCCN	National Comprehensive Cancer Network
BCC	Basal cell carcinoma	NMSC	Nonmelanoma skin cancer
CCI	Crude cumulative incidence	PDT	Photodynamic therapy
CK-20	Cytokeratin 20	PTCH1	Patched 1 gene
CLL	Chronic lymphocytic leukemia	RT	Radiation therapy
DFSP	Dermatofibrosarcoma protuberans	SCC	Squamous cell carcinoma
ED&C	Electrodesiccation and curettage	SEER	Surveillance epidemiology and end results
EMPD	Extramammary Paget's disease	SLNB	Sentinel lymph node biopsy
EPC	Eccrine porocarcinoma	TTF-1	Thyroid transcription factor 1
		UV	Ultraviolet light

M. Kukar, M.D. • J. Oxenberg, D.O.
J. Skitzki, M.D. (✉)
Surgical Oncology, Roswell Park Cancer Institute,
Elm and Carlton Street, Buffalo, NY 14263, USA
e-mail: moshim.kukar@roswellpark.org;
Jackieofrg@yahoo.com; joseph.skitzki@roswellpark.org

E.E. Cho, M.D., Sc.M.
Department of Surgery, Kaleida Health/Buffalo
General Med Center, State University of New York
at Buffalo, 100 High St. Buffalo, 14203 NY, USA
e-mail: eecho@buffalo.edu

N.C. Zeitouni, M.D.C.M.
Dermatology, University of Arizona,
1515 N Campbell Avenue #1907, PO Box 245024,
Tucson, AZ 85724, USA
e-mail: nathaliezeitouni@email.arizona.edu

Learning Objectives

After reading this chapter, you should be able to:

- Describe the most common nonmelanoma skin cancers (NMSC) in terms of epidemiology and etiology
- Identify how NMSC types are diagnosed and select the proper biopsy method
- Define the surgical management options and considerations for NMSC
- Identify the variety of other nonsurgical treatment options and their indications including radiation therapy and topical therapies
- Understand the pattern of metastases for the range of NMSC
- Describe the surveillance for treated NMSC

Basal Cell Carcinoma

Basal cell carcinomas (BCC) are the most common type of skin cancer and arise from the basal layer of the epidermis and its appendages. These tumors were referred to as “epitheliomas” because of their low metastatic potential. It is extremely rare for BCC to metastasize to lymph nodes or distant organs. However, the term carcinoma is appropriate, since they are locally invasive and aggressive. The incidence of BCC is rapidly rising [1].

Ultraviolet (UV) light is the greatest risk factor for developing BCC with sun exposure being the most common mechanism. Populations at risk include people with fair skin, light-colored eyes, red hair, northern European ancestry, older age, farming occupations, and family history of BCC [2]. There is also an association between chronic arsenic exposure, ionizing radiation, and chronic immunosuppression [3].

The sonic hedgehog signaling pathway has emerged as having a pivotal role in the pathogenesis of BCC. Mutations in the patched 1 gene (PTCH1) on chromosome 9q, which codes for the sonic hedgehog receptor, are the underlying cause of nevoid basal cell carcinoma syndrome and are frequently seen in sporadic BCC. Specific UV-induced mutations in the tumor suppressor gene p53 also appear to be a common event in developing a malignant phenotype [4].

Approximately 70 % of BCCs occur on the face, consistent with the etiologic role of solar radiation. Fifteen percent present on the trunk, and only rarely is BCC diagnosed on penial, vulvar, or perianal skin. BCC can be divided into several groups, and the three most common ones, based on histopathology, are nodular, superficial, and infiltrative/morpheaform. Nodular BCC is most frequently seen and presents as a pearly or translucent-appearing papule or nodule. Approximately 30 % of BCCs are superficial and most commonly occur on the trunk as a scaly plaque that is erythematous in color. Infiltrative/morpheaform BCCs account for about 5 % of BCCs and are characterized by their ill-defined borders, plaque-like appearance, and high risk of recurrence [5, 6].

A typical, superficial BCC is contrasted to a locally advanced infiltrative BCC as depicted in Fig. 2.1a, b. The current American Joint Committee on Cancer (AJCC) TNM staging classification for BCC overlaps with squamous cell carcinoma of the skin and is listed in Table 2.1 [7].

Surgical Considerations

A detailed clinical examination is paramount, and most BCC can be diagnosed by their appearance. A skin biopsy is usually performed to provide histologic confirmation of the diagnosis. Shave biopsies, punch biopsies, and excisional biopsies can be used for the diagnosis of BCC.

Surgical options for BCCs at low risk for recurrence include conventional surgical excision, Mohs surgery, and electrodesiccation and curettage (ED&C). Typically, surgical excision of the BCC is the preferred option and can often be performed under local anesthesia. Generally, surgical excision of the trunk, extremity, or small facial BCCs of the head or neck with anywhere from 1 to 10 mm margins has been associated with 5-year cure rates exceeding 95 %; therefore, 3–5 mm surgical margins are commonly used for the excision of these lesions [8]. Infiltrative/morpheaform lesions may require wider (5–10 mm) margins due to their indistinct borders. Mohs surgery is usually reserved for lesions that exhibit features associated with an increased risk for recurrence and for locations in which tissue sparing is of great value due to cosmetic or functional concerns. When standard surgical excision is performed, all extremity lesions should be removed in a longitudinal fashion. While a longitudinal incision of the extremity may not be the most cosmetic, it allows for an easier re-excision if the lesion recurs and also disrupts less lymphatic tissue so that lymphedema is minimized (See Chap. 1, Fig. 2.2). The concept of longitudinal excisions of the extremities is critical for all NMSCs and should be considered the standard. Cryosurgery may be used for small superficial lesions, but for larger nodules, its use is infrequent. With proper lesion selection and operator skill/experience, ED&C is capable of achieving a high cure rate.

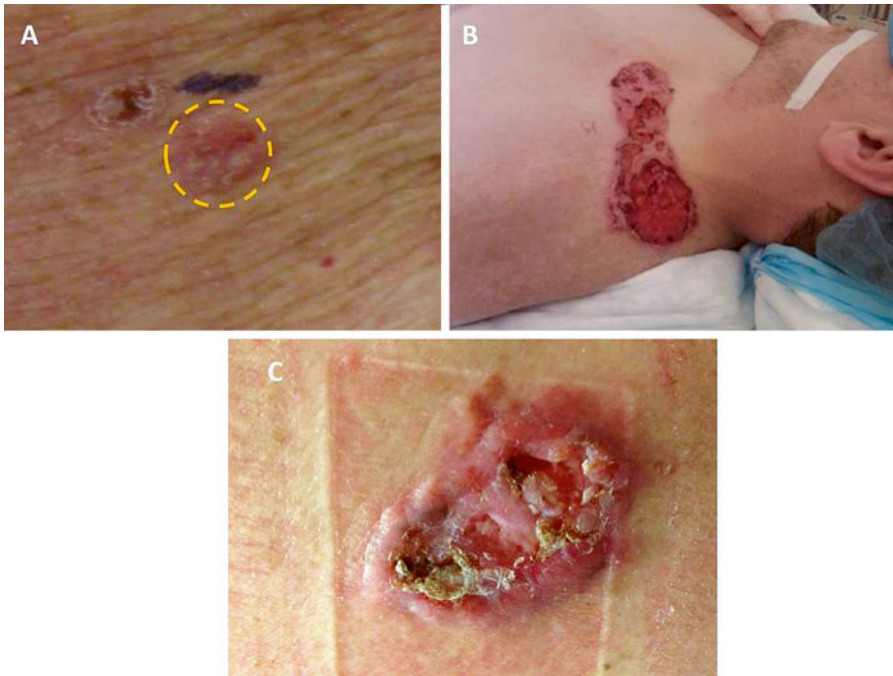


Fig. 2.1 A superficial basal cell carcinoma (BCC) with a characteristic raised, “pearly” appearance is depicted (**a**, yellow circle, **c**). A locally advanced infiltrative BCC is shown

on the left shoulder/neck area (**b**). While this advanced lesion has low metastatic potential, it was infiltrative into the underlying muscle and along the spinal accessory nerve

Other Treatments

Photodynamic therapy (PDT) is a nonsurgical treatment option for superficial BCCs. The three components of PDT are a light source; exogenous photosensitizer, such as aminolevulinic acid or methyl-aminolevulinic acid; and oxygen. Excellent response rates have been reported for this modality in selected BCC.

The superficial nature of early BCCs allows for effective topical treatments of these lesions. Options for topical therapy include 5-fluorouracil (5-FU) and imiquimod. 5-FU is a pyrimidine analogue that induces cell cycle arrest and apoptosis. Extensive experience with topical 5-FU indicates that this treatment should be restricted to superficial BCCs in non-critical locations. Imiquimod 5 % cream is an immune response modifier that is approved by the US Food and Drug Administration for the treatment of superficial BCCs in low-risk sites. Topical agents require active patient participation and close practitioner

surveillance to prevent BCC progression and/or recurrence. All nonresponding lesions should be biopsied for persistent or recurrent disease. Radiation therapy (RT) is utilized as a primary modality in patients who are poor surgical candidates. As an adjuvant therapy, radiation therapy can achieve good results with excellent cosmetic results if applied appropriately especially in patients with high risk of recurrence. A randomized study in 347 patients receiving either surgery or RT as primary treatment of BCC found RT to result in higher recurrence rates than surgery alone (7.5 % vs 0.7 %) [9]. For multiple recurrent BCC that have failed to be cleared by surgical excisions, RT is often a useful option, particularly for microscopically involved margins.

Advances in the understanding of the molecular mechanisms that lead to BCC formation has led to the FDA recently approving a novel agent Vismodegib, a first-in-class Hedgehog pathway inhibitor. This agent can be used for refractory

Table 2.1 American Joint Committee on Cancer (AJCC) TNM staging for cutaneous squamous cell carcinoma and other cutaneous carcinomas (7th edition)

Primary tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension with less than two high-risk features**
T2	Tumor > 2 cm in greatest dimension or tumor any size with two or more high-risk features**
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base
*Excludes cSCC of the eyelid	
**High-risk features for the primary tumor (T) staging	
Depth/invasion	>2 mm thickness Clark level ≥ IV Perineural invasion
Anatomic location	Primary site ear Primary site hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastases
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm ≤ 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest diameter
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

(continued)

Table 2.1 (continued)

Anatomic stage/prognostic groups			
Group	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-T3	N1	M0
Stage IV	T1-T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

Reprinted Ref. [46]. With permission from Springer Verlag

locally advanced BCCs that have failed all other options or for the rare metastatic BCC patient. While this treatment is currently quite expensive, the results can be significant in clearing the tumors. Multiple side effects have been reported with this agent which may limit its use in certain patients.

Close follow-up is required following treatment to diagnose both local recurrences and new skin cancers and to assess posttreatment outcomes. Most dermatologists recommend reevaluation every 3–6 months for the first year following treatment and then every 6–12 months thereafter. About 30–50 % of patients may develop another NMSC within 5 years. Therefore, close skin surveillance is mandatory.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common type of NMSC, accounting for approximately 20 % of all NMSC cases. SCCs can arise de novo, but unlike BCCs, SCCs often arise from precursor lesions that show partial-thickness epidermal dysplasia, such as actinic keratosis (AK). AK presents as slightly scaly papules with ill-defined borders, on sun-exposed skin. Seborrheic keratosis is tan to dark brown stuck-on appearing benign, warty growths located anywhere on the body. The rate of malignant transformation from AK to SCC is estimated to range from 0.025 % to 16 % per year for an individual lesion [10]. Intraepithelial SCC or



Fig. 2.2 A superficial squamous cell carcinoma (SCC) is noted with a typical raised, scaly/crusty appearance (**a**, yellow circle) in the background of multiple actinic keratosis (scaly, red patches) or possibly SCC in situ. An advanced SCC of the left hand/forearm demonstrated rapid growth and nodal and visceral metastases (**b**). This

local disease was not responsive to systemic treatment, and despite the presence of metastatic disease, surgery was required in the form of an amputation for palliation of pain, bleeding, and infection. (**c**) A neglected SCC of the right scalp was completely excised with clear margins (**c**: Courtesy of Quyen D. Chu, MD, MBA, FACS)

carcinoma in situ is believed to be the next step in the progression to invasive SCC. Risk factors for developing SCC include sun exposure, radiation, chronic inflammation, immunosuppression, and virally induced.

SCC typically develops on areas that are commonly exposed to the sun, including the head and neck, scalp, face, dorsum of hand, shoulder, and chest. The majority of these lesions occur on the head and neck areas. SCCs appear as ill-defined keratotic papules and nodules which may be ulcerated. They can be reddish brown, erythematous, or flesh colored. Occasionally, cutaneous horns from hyperkeratosis may be seen, and bleeding can occur with SCC. A typical SCC in the background of extensive AK is compared to a locally advanced SCC as depicted in Fig. 2.2a, b. Histologically, they show nests of atypical keratinocytes with dermal invasion.

In situ lesions, also known as Bowen's disease, are characterized by full-thickness atypical epidermal involvement. Histologic grading is divided into well, moderately, or poorly differentiated. Poorly differentiated lesions have a higher recurrence (28.6 % versus 13.6 %) and metastatic rate (32.8 % versus 9.2 %) compared to well-differentiated lesions [11].

Clinical workup includes a complete history and physical examination, with emphasis on full skin and regional lymph node examinations. Patients may have concurrent cancer located in various sites, and individuals with SCC may be at increased risk of developing BCC and/or melanoma.

A skin biopsy is performed, making sure to obtain full-thickness sample down to the deep reticular dermis. Punch biopsies are simple to perform in the clinic under local anesthesia and yield

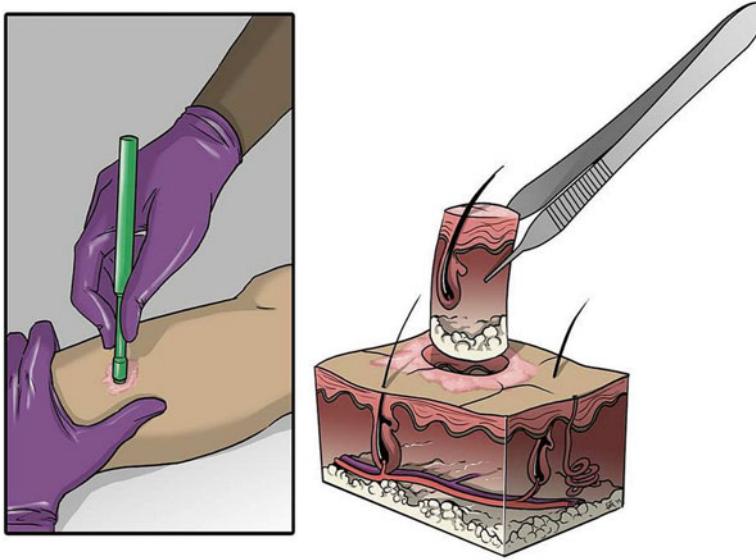


Fig. 2.3 A standard punch biopsy is depicted. The skin lesion is prepped with alcohol, anesthetized with 1 % lidocaine, and a punch biopsy is performed to obtain a full-thickness specimen for further pathologic analysis.

An absorbable suture or steri-strip can be placed for re-approximation of the skin (Illustrator-Karen Howard; Courtesy of Quyen D. Chu, MD, MBA, FACS)

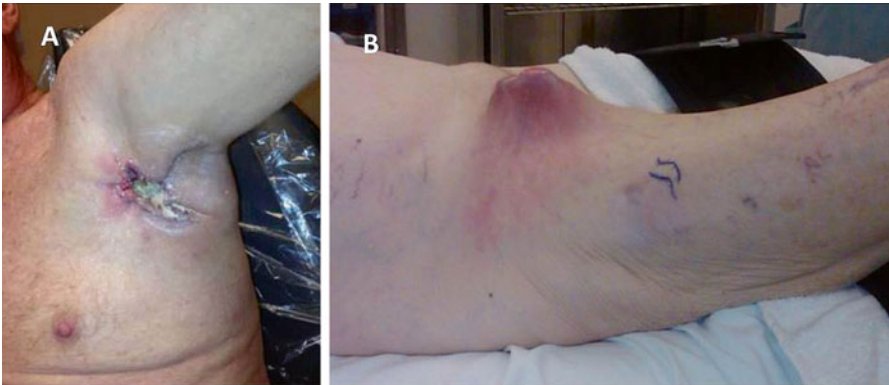


Fig. 2.4 Advanced metastatic lymph nodes to the axillary (a) and groin (b) lymph node basins. As depicted, these lesions are locally destructive and are prone to necrosis, infection, and significant disability. Extensive surgical

resection is required often with the need for soft tissue coverage for closure and adjuvant radiation therapy to improve regional control (a: Courtesy of Quyen D. Chu, MD, MBA, FACS)

good full-thickness samples for pathologic evaluation (Fig. 2.3). Imaging studies are rarely necessary and typically reserved only for locally advanced or clinically detected metastatic lesions.

The presence of palpable lymph nodes identified by clinical examination or imaging studies should prompt a fine-needle aspiration for diagnosis. Regional nodal involvement significantly

increases the risk of recurrence and mortality and is often associated with other histologic findings including lymphovascular invasion, poor differentiation, and perineural invasion (Fig. 2.4a, b). A fine-needle aspiration or core biopsy is generally sufficient for pathologic diagnosis, and excisional biopsies are discouraged as they may confound future definitive surgical interventions.

Fortunately, the rate of lymph node metastasis from cutaneous SCC is estimated to only be 0.1 % for early lesions, but increases with more advanced lesions.

The American Joint Committee on Cancer (AJCC) TNM staging classification for cutaneous squamous cell carcinoma is listed in Table 2.1 [7].

Surgical Considerations

Surgical excision with at least 4–6 mm margins is the standard of care for small, low-risk squamous cell cancers and is the current recommendation in the NCCN guidelines. Zitelli and colleagues reported that for SCC less than 2 cm in diameter, a 4 mm clinical margin of surgical specimen yielded a complete removal with negative margins with a 95 % confidence interval [12]. Postoperative margin assessment should be performed, and re-excision is indicated for positive margins.

Mohs surgery is an excellent surgical technique for high-risk SCC and those in cosmetically sensitive areas. A meta-analysis reported a 5-year disease-free survival rate after Mohs surgery of 97 % for SCC [11]. Another surgical option is excision with complete circumferential peripheral and deep margin assessment using intraoperative frozen sections or delayed closure/skin grafting with a detailed postoperative margin assessment.

Curettage and electrodesiccation is a process of scraping away tumor tissue then denaturing the area. Up to three cycles can be performed in one session. Overall 5-year cure rate reported for low-risk SCC is 96 % [13]. Three caveats are underscored in the NCCN guidelines: (1) this technique should not be used to treat areas with hair growth due to tumor extending down the follicular structures; (2) if the subcutaneous layer is reached during the course of curettage, surgical excision should be used instead; and (3) biopsy samples should be taken at the time of curettage to analyze for high-risk pathologic features.

The current NCCN recommendations for low-risk SCC are surgical excision with 4–6 mm margins with primary closure, skin graft, or healing by secondary intention, curettage with

electrodesiccation, or radiotherapy for nonsurgical candidates. For high-risk SCC, or those in cosmetically sensitive areas, Mohs surgery or resection with intraoperative frozen sections or radiotherapy is indicated. Sentinel lymph node biopsy (SLNB) for the evaluation of occult nodal metastatic disease can be performed and may allow for more accurate staging in high-risk feature patients. Criteria to perform an SLNB for SCC are not standardized but often include high-risk features of the primary tumor (size >2 cm, poorly differentiated, evidence of perineural or lymphatic invasion) [14]. Positive sentinel lymph node biopsies should be followed by imaging for complete staging and then completion lymphadenectomy in the absence of distant metastatic disease.

If suspicious lymph nodes are seen clinically or by imaging, FNA or core biopsy is indicated. If the lymph nodes return positive for SCC, regional lymph node dissection is recommended. Those with multiple nodes involved should be considered for adjuvant radiotherapy as multiple studies have shown decreased locoregional recurrence and improved 5-year disease-free survival with this modality [15]. Surgical interventions for widely metastatic SCC are limited to palliative procedures to control bleeding, infection, and/or pain when systemic therapy and/or radiation therapy fails. Although exceedingly uncommon, amputation for uncontrolled tumor is a potential option in advanced SCC arising in the extremities.

Other Treatments

Photodynamic therapy (PDT) is a nonsurgical treatment option for actinic keratosis and superficial SCC. Although superficial BCC is most responsive to PDT, there has been some success with SCC. In a retrospective study of 35 superficial SCC defined as carcinoma confined to the papillary dermis, complete response rate was reported to be 54 %. However, projected disease-free rate at 36 months after treatment was only 8 % [16]. A few case reports and series report a high recurrence rate, up to 52 %, for SCC in situ

and even higher, 82 %, for invasive SCC lesions [17]. Therefore, PDT is not a recommended treatment modality for invasive SCC tumors.

Topical 5-FU applied twice daily or once daily under occlusion for 1.5–2 months has been reported to have a 54–85 % cure rate for intraepithelial SCC. Less intense regimen reduces the clearance rate to only 27–56 % [18]. Imiquimod stimulates the innate immune response by activating cytokines that ultimately induces interferon-gamma release by T cells. Use of imiquimod for SCC is limited. A randomized, double-blind placebo-controlled trial showed 73 % of SCC in situ lesions that achieved clearance after 16 weeks of imiquimod therapy [19]. Current evidence supports the use of topical imiquimod in poor surgical low-risk candidates with SCC in situ lesions.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase 2 (COX 2) and thereby reduces the production of prostaglandins. COX 2 enzymes are believed to be upregulated in NMSC lesions. Thus far, topical diclofenac 3 % gel has been approved only for the treatment of actinic keratosis.

Epidermal growth factor receptor (EGFR) is an extracellular signaling receptor in the tyrosine kinase receptor family. Activation of this receptor by various ligands stimulates keratinocyte proliferation. It has been shown that advanced SCC lesions contain EGFR mutation causing overexpression in 43–73 % of cases [20]. Cetuximab is a chimeric monoclonal antibody directed against EGFR. It is currently approved for treatment of recurrent or metastatic SCC of the head and neck. A study comparing radiotherapy alone versus cetuximab combined with radiotherapy showed improved locoregional control and overall survival rate in those that received cetuximab [21]. Erlotinib and gefitinib, which disrupt the intracellular signaling cascade after EGFR is activated, are being investigated for use in cutaneous SCC.

External beam radiation therapy can function both as a primary treatment, especially for advanced head and neck SCC in poor surgical candidates or as adjuvant therapy after surgical excision. A meta-analysis reported a 5-year recurrence rate of 10 % after radiotherapy on patients with high-risk primary SCC [11].

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine malignancy that arises in the dermoepidermal junction. It commonly affects elderly Caucasians and was originally described by Toker in 1972 as trabecular carcinoma of the skin. Other names include Toker tumor, primary small cell carcinoma of the skin, primary cutaneous neuroendocrine tumor, and malignant trichodiscoma. Although rare, MCC incidence rates are increasing rapidly. The tumor often appears as an asymptomatic erythematous nodule and may resemble a basal cell carcinoma, a common misdiagnosis both clinically and histologically (Fig. 2.5). The pathogenesis of MCC is controversial. One thought is it arises from Merkel cells, which are part of the amine precursor uptake and decarboxylation system located in the basal layer of the epidermis and hair follicles. Another hypothesis is that MCCs originate from immature stem cells that acquire neuroendocrine features during malignant transformation.

MCCs can be characterized by **AEIOU** features: **A**symptomatic/lack of tenderness, **E**xpanding rapidly, **I**mmune suppression, **O**lder than 50 years, and **U**ltraviolet-exposed site on a person with fair skin [22]. In a SEER data review of 1,034 patients, MCC was more common in males and patients geographically located in sun-exposed climates; 94 % were Caucasian, 76 % were older than 65 years (median 75), and 48 % occurred on the head [23]. MCC has been shown to be more common in immunosuppressed populations such as solid organ transplant recipients and HIV patients. Accordingly, MCC can be aggressive and should be considered to have a high lethal potential with an estimated 1 in 3 patients succumbing to the disease. Of the patients for which MCC is the cause of mortality, half of the patients will die within 4 years of the initial diagnosis.

In 2008, Merkel cell polyomavirus (MCV) was discovered and found to be integrated into the host genome of over 80 % of patients with MCC, and this association has been validated by multiple other studies [24]. An increased incidence of MCCs was found in patients with chronic lymphocytic leukemia (CLL) who are

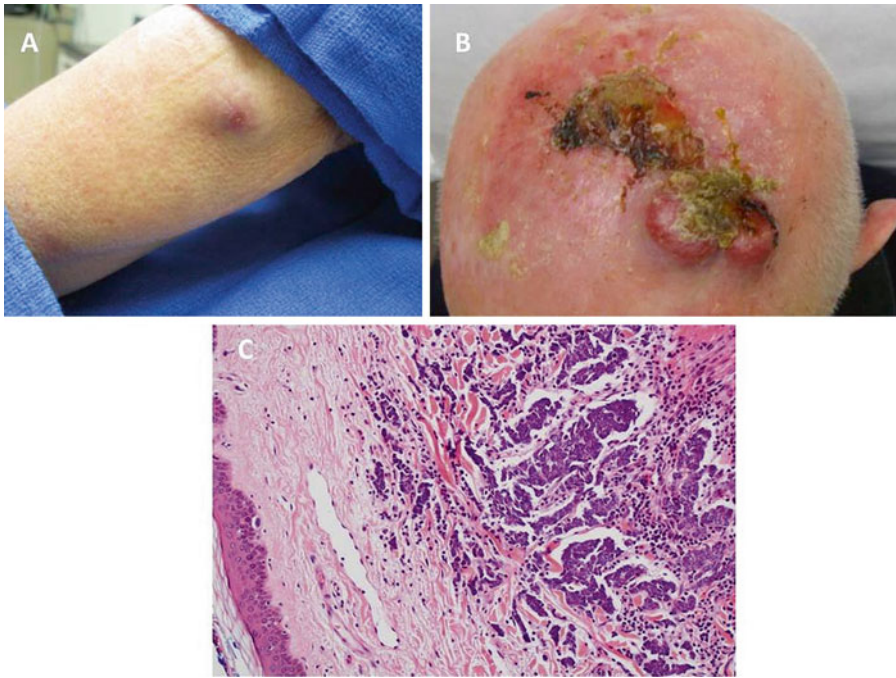


Fig. 2.5 A typical Merkel cell carcinoma (MCC) is shown on the extremity as an erythematous nodule that exhibited a rapid growth phase (a). MCC can be locally aggressive and has a high potential for recurrence and metastasis (b). Adjuvant radiation therapy following the wide excision of MCC has proven benefit in reducing the

local recurrence rate for advanced lesions. (c) Photomicrograph depicting clusters of neoplastic cells within the dermis having the finely granular chromatin pattern characteristic of Merkel cell carcinoma (hematoxylin and eosin X 200) (c: Courtesy of Barry DeYoung, MD, Wake Forest School of Medicine)

relatively immunosuppressed and have a high rate of MCV detected in their MCC tumors [22].

When MCC is suspected, a punch biopsy or full-thickness biopsy should be performed. There are three main histologic patterns: (1) solid type-most common type, composed of irregular groups of tumor cells interconnected by strands of connective tissue; (2) trabecular type- well-defined cords of cells that form invading columns or cords; and (3) diffuse type- exhibits poor cohesion and a lymphoma-like diffuse type of growth. The pathologic diagnosis is difficult due to its similarity to small round blue cell tumors (small cell carcinoma of the lung, cutaneous large cell lymphoma, neuroblastoma, metastatic carcinoid, amelanotic melanoma, sweat gland carcinoma, Langerhans cell histiocytosis, and Ewing sarcoma). Hematoxylin and eosin (H&E) staining should be confirmed by immunohistochemistry (IHC). CK-20 is both sensitive and specific for

MCC with a positivity in 89–100 % cases, and thyroid transcription factor 1 (TTF-1) is consistently negative in MCC [25].

Histologic features that may have prognostic significance include: tumor thickness, presence of lymphovascular invasion, and tumor growth pattern. The AJCC lists site-specific prognostic factors: measured thickness (depth), tumor base transection status, profound immune suppression, tumor infiltrating lymphocytes in the primary tumor, growth pattern of primary tumor, size of tumor nests in regional lymph nodes, clinical status of regional lymph nodes, regional lymph nodes pathologic extracapsular extension, isolated tumor cells in regional lymph node(s) [7]. The majority of patients die from distant metastases involving liver, bone, lung, brain, or distant lymph nodes. Tumors greater than 2 cm in diameter at the time of diagnosis have been shown to have a negative influence on survival.

Surgical Considerations

MCC has a propensity for local recurrence and regional lymph node metastases. Diagnosis is typically made with a skin biopsy after a complete skin and lymph node examination. In 2010, the AJCC published the new staging system for MCC, which is based on primary tumor size and nodal status. The primary lesion should be examined for satellite lesions or dermal seeding and the extent of disease assessed. If lymph nodes are clinically involved, fine-needle aspiration or core biopsy should be performed with consideration of open biopsy if negative. Diagnostic imaging such as CT, MRI, and/or PET/CT should be performed to evaluate disease extent and rule out distant visceral metastases particularly when signs or symptoms of metastatic disease warrant further investigation.

Surgical management continues to be the primary treatment for clinically localized MCCs. Wide local excision with 1–2 cm margins to investing fascia and SLNB are the current recommendations for early stage cancers. In one study, an average margin width of 1.1 cm had a low (8 %) recurrence rate if negative, and a decreased local recurrence rate was not associated with a margin of more than 1 cm [26]. In areas of difficult margins, Mohs micrographic surgery may be an additional option. Primary radiation therapy has also been used successfully in selected patients.

SLNB, although not clearly proven to impact survival, is recommended. The techniques performed are similar to melanoma. Sentinel lymph nodes should be assessed using IHC for more effective metastatic identification, including CK-20 staining. A low rate of lymph node metastases from primary tumors <1 cm has been observed, but the low risk has not been clearly reproducible, and omitting the SLNB procedure for smaller tumors does not appear to be widely accepted. If lymph nodes are clinically positive, FNA or core biopsy should be performed for confirmation followed by either complete lymphadenectomy and/or radiation therapy (RT) for regional control.

Other Treatments

MCC is radiosensitive, and therefore RT is often used adjunctly for locoregional disease control. In an extensive review of the literature, a decreased local recurrence of 10.5 % with RT versus 52.6 % without was found [27]. SEER data review of patients stage I–III had an increased overall survival when treated with surgery plus radiation compared with patients treated with surgery alone. Adjuvant radiation was a component of therapy in 40 % of the surgical cases, and the median survival for those patients receiving adjuvant RT was 63 months compared with 45 months for those treated without. The use of RT was associated with an improved survival for patients with all sizes of tumors, but the improvement was particularly prominent for primary lesions larger than 2 cm [28]. However, not all studies have found an increased survival benefit. NCCN guidelines recommend a total radiation dose of 50–56 Gy in patients with clinically negative margins who are considered to be at significant risk for residual subclinical disease at the resection site.

Data on chemotherapy for MCC is scarce. It is used more often for stage IV and node-positive disease. The Trans-Tasman Radiation Oncology Group (TROG 96:07) performed a phase II trial using carboplatin and etoposide that did not demonstrate an improvement in survival, although the study was thought to be underpowered. When evaluating chemoradiation, TROG 96:07 had 87 % patients complete all 4 cycles of chemotherapy, with a locoregional control rate of 77 % in patients treated in an adjuvant manner and 71 % for those treated therapeutically [29]. The small numbers of patients diagnosed annually with MCC have limited the ability to conduct meaningful clinical trials regarding optimal chemotherapy regimens.

Follow-Up

Close follow-up is recommended for nearly all stages and includes a physical examination of the skin and regional lymph nodes. Current

recommendations include exams performed every 3–6 months for the first 2 years and then every 6–12 months.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a relatively unusual, locally aggressive cutaneous tumor, characterized by high rates of local recurrence, but low risk of metastasis. DFSP is a rare tumor that constitutes 0.1 % of all malignancies and 1 % of all soft tissue sarcomas. Nevertheless, DFSP is the most common sarcoma of cutaneous origin [30]. The age spectrum varies from congenital cases to patients >90 years old and is equally represented in both sexes. DFSP is an asymptomatic tumor with a slow growth. DFSP is preferentially located on the trunk with 40–50 % of cases found to occur in this area. In 30–40 % of cases, the tumor is located in the proximal portion of the limbs (more often on the arms than the legs), and in 10–15 % of cases, DFSP affects the head and neck areas [30].

Over 90 % of DFSPs are characterized by a unique chromosomal translocation t(17;22) (q22;q13). This translocation results in the gene for platelet-derived growth factor beta polypeptide (PDGFB) being fused with the highly expressed collagen type 1A1 (COL1A1) gene. The resulting PDGFB/COL1A1 fusion protein is processed to produce fully functional PDGFB, which results in continuous autocrine activation of the PDGF receptor b, a tyrosine kinase. This molecular alteration, which has been demonstrated in over 90% of DFSPs, is thought to be fundamental to the development of the tumor [31].

Histologically, DFSP appears as a poorly circumscribed tumor that infiltrates the whole dermis down to fat and muscle and spreads in a tentacle-like fashion into the cellular subcutaneous tissue. The tumor is composed predominantly of a dense, uniform array of cells with spindle-shaped nuclei embedded in varying amounts of collagen. DFSP should be suspected in any patient with a history of a firm, slow-growing

cutaneous nodule, and definitive diagnosis requires an incisional or deep punch biopsy representative of the lesion (Fig. 2.6).

Surgical Considerations

The primary treatment of DFSP is surgical removal to obtain clear margins. A wide excision of 2 cm margins including the investing fascia is often definitive; however, larger margins (3–4 cm) can be taken for recurrent or extensive tumors. Deep undermining or raising large flaps should be avoided. Alternatively, Mohs micrographic surgery has been shown to be associated with high cure rates and very low recurrences. Recent reviews have suggested that either wide local excision with appropriate margins or Mohs surgery may have similar outcomes, but that Mohs surgery may be preferable for head and neck tumors or tumors located in areas where tissue sparing is of importance. Irrespective of the approach, the status of the surgical margins is the most important prognostic factor in patients with DFSP. The prognostic importance of resection margins was shown in a series of 159 patients (134 DFSP, 25 DFSP with sarcomatous transformation). At a median follow-up of 57 months, there were 34 recurrences, 29 of which developed in patients with positive or close margins [32].

Other Treatments

Given DFSPs' characteristic chromosomal translocation, t(17;22), orally active small molecule tyrosine kinase inhibitors (TKIs) have been utilized for the rare unresectable or metastatic tumor. The most commonly used agent is imatinib followed by sunitinib and sorafenib often with mixed and transient responses [33].

Although DFSP is a radiosensitive tumor, radiation is rarely used a primary treatment. Despite the absence of randomized clinical trials proving benefit, adjuvant RT may be recommended in conjunction with wide local resection of large tumors or when the surgical margins are

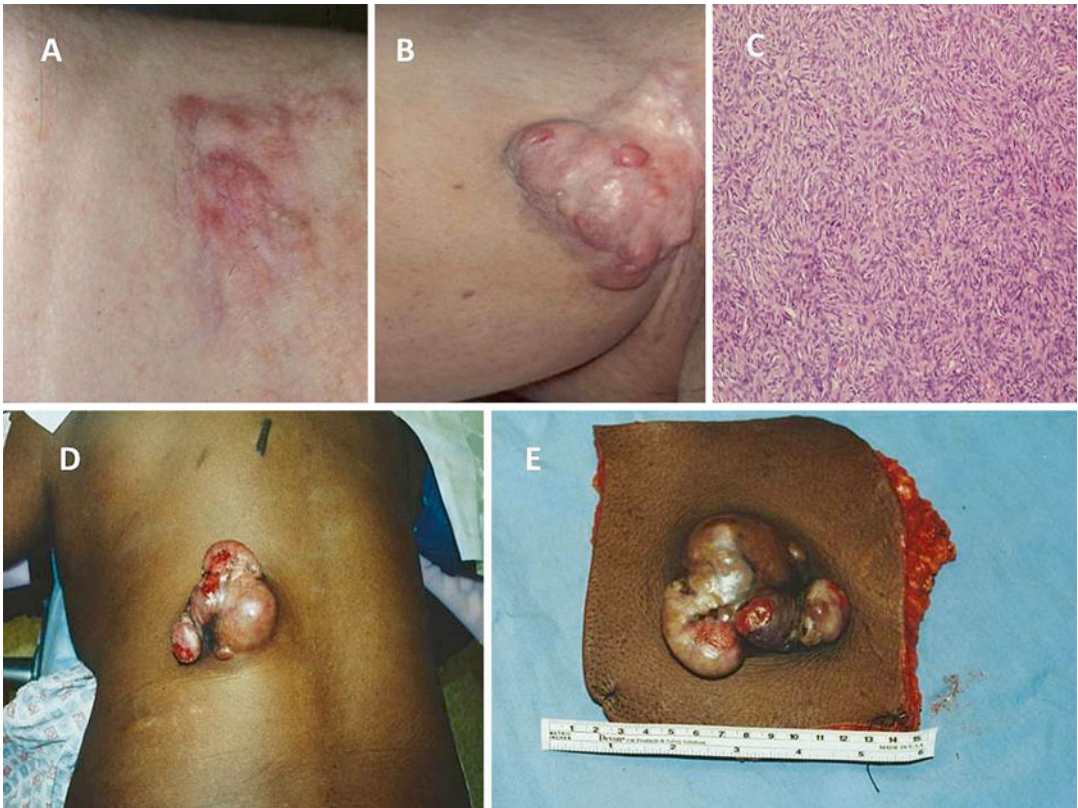


Fig. 2.6 Dermatofibrosarcoma protuberans (DFSPs) present as slow-growing firm nodules in the skin (**a, b, d, e**) and are the most common sarcoma of cutaneous origin. Moh's surgery can be the preferred method in select DFSP; however, larger lesions may require a surgical wide excision.

(**c**) Photomicrograph showing mildly atypical spindle cells arranged in a cartwheel or storiform pattern indicative of DFSP (hematoxylin and eosin X 200) (**c**: Courtesy of Barry DeYoung, MD, Wake Forest School of Medicine; **d, e**: Courtesy of Quyen D. Chu, MD, MBA, FACS)

close or positive and further surgery is not feasible. If a negative margin is achieved, no adjuvant treatment is necessary.

Current recommendations include follow-up of the primary site every 6–12 months including complete history and physical to rule out metastatic disease. Imaging is rarely required except for high-risk lesions.

Angiosarcoma

Angiosarcomas (AS) are rare endothelial-derived tumors that account for 1–2 % of all soft tissue sarcomas. They can occur anywhere, but are frequently in the skin and soft tissues, most

commonly in the head and neck or areas of prior RT. AS may present as blue or erythematous patches, nodules, or tumors on the skin and can occur at a median time of 7 years (3–25 years) from time of radiotherapy. When associated with radiation, AS are usually cutaneous and maybe with edema similar to inflammatory breast cancer or cutaneous infection. Their involvement is often extensive, diffuse, high grade, and can be associated with bleeding.

With an increasing number of cases reported, there is concern about radiation-induced AS in the setting of breast conserving therapy for breast cancer (Fig. 2.7). A cumulative incidence after 15 years was found to be 0.9 per 1,000 for cases receiving radiation and 0.1 per 1,000 for

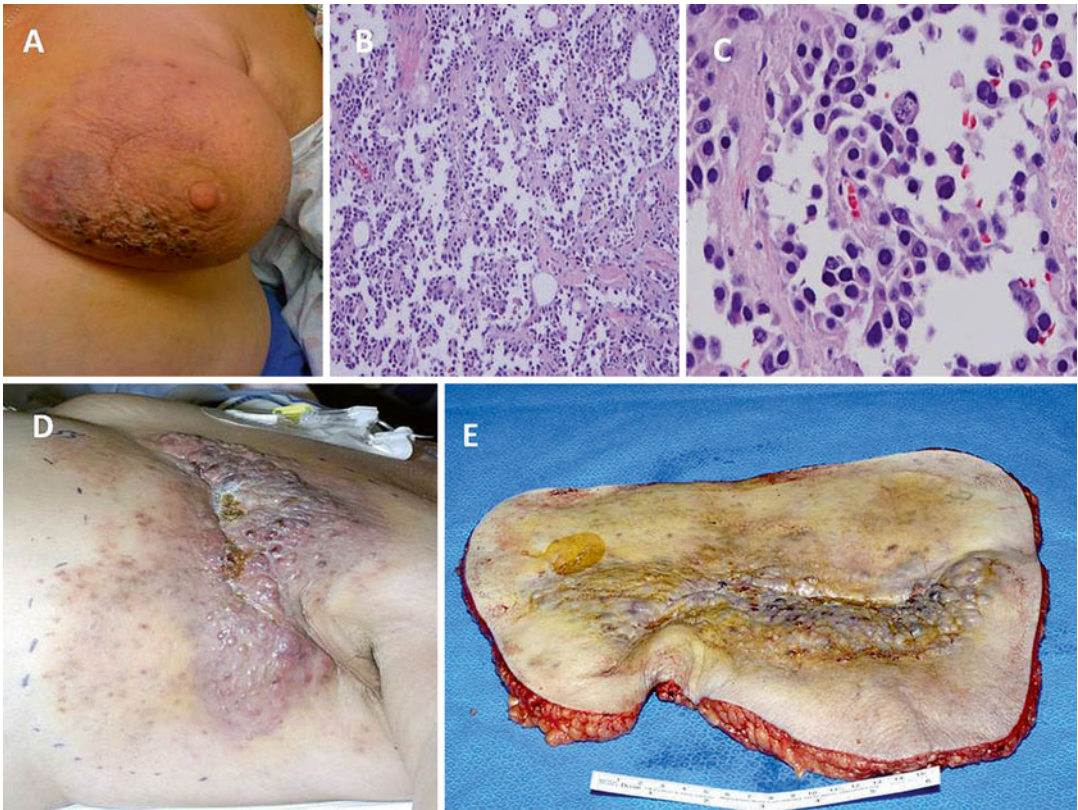


Fig. 2.7 Angiosarcomas may arise in previously irradiated skin and are increasing in frequency with the widespread use of adjuvant radiation for breast cancer (**a, d, e**). The diffuse nature and characteristic appearance of cutaneous angiosarcoma are noted on the left chest wall in the background of cutaneous radiation changes (**d**). These lesions typically necessitate an excision with wide margins due to their infiltrative nature and tendency for recur-

rence (**e**). Hematoxylin and eosin (H&E) sections (**b, c**) show a high-grade angiosarcoma with dilated vascular spaces that are dissecting and splitting tissue planes. The vascular spaces are lined and filled with highly pleomorphic malignant cells with easily identified mitosis (**a, d, e**): Courtesy of Quyen D. Chu, MD, MBA, FACS; **b, c**: Courtesy of Xin Gu, MD, Louisiana State University Health Sciences Center-Shreveport)

cases not receiving radiation [34]. While the occurrence of sarcoma was low, RT was associated with an increased risk of AS in or adjacent to the radiation field. The relative risk was found to be significant within 5 years of RT, but maximum risk was between 5 and 10 years.

Another variant is Stewart-Treves syndrome, also known as lymphangiosarcoma, which was first reported in a series of six patients in 1948 [35]. It is associated with chronic, long-standing lymphedema. Exogenous toxins or chemicals are also associated with AS including Thorotrast and vinyl chloride which are associated with liver

angiosarcoma formation. Similarly, cutaneous angiosarcomas have been related to arsenic, radium, anabolic steroids, and gouty tophus.

Suspicious areas require a punch biopsy or a full-thickness incisional biopsy in areas of suspected AS. FNA can be performed, but are not usually definitive for the diagnosis of AS, particularly in breast cancer survivors where it can be misinterpreted as recurrent carcinoma. A correct diagnosis of this tumor requires immunohistochemical evidence of endothelial differentiation. Typical markers for AS include vimentin, factor VIII, CD31, and CD34 [36].

Surgical Considerations

Lesion size and presence of metastases often determine treatment options. Tumor imaging modalities such as CT or MRI are recommended as well as abdominal/pelvic CT and central nervous system imaging to rule out metastatic disease, which is common to the lungs and liver.

AS are biologically aggressive tumors with a propensity for metastases and being multifocal. Surgical resection with negative (R0) margins continues to be the standard for curative treatment. Wide margins are recommended which often necessitate complex reconstructions, especially when AS is RT induced. Clinically undetectable intradermal spread in addition to a high incidence of multicentricity and unclear borders results in high local recurrence rates even after R0 resections.

Other Treatments

Despite its biologic aggressiveness, a fair number of AS will respond to systemic chemotherapy. Previous literature shows a 3.8–44 % complete response rate and a 88–93 % clinical response rate with regimens using combinations of paclitaxel, doxorubicin, and gemcitabine [37]. Response rates of approximately 10 % are found with antiangiogenic agents that are mainly used for locally advanced or metastatic disease. There is limited data, but neoadjuvant chemotherapy may be useful prior to surgical excision to reduce local recurrence rates and improve recurrence-free survival.

Although seemingly counterintuitive as many AS are radiation induced, additional RT (mostly wide-field electron-beam therapy) has been found to result in regression of local skin disease and potentially prolonged survival.

Follow-Up

Patients should have a history and physical every 3–6 months for 2–3 years and then annually. Disease progression or recurrence should be

managed accordingly depending on local or distant progression. Chest imaging can be considered every 6–12 months as well as primary site imaging (US, MRI, or CT).

Paget's Disease

Paget's disease is a rare cutaneous adenocarcinoma that occurs in elderly women more often than in men. It typically presents as an erythematous, scaly, eczematous plaque frequently misdiagnosed as inflammatory or infectious dermatitis. Most commonly affected sites include unilateral nipple/areola complex in mammary Paget's disease (MPD) and the vulva, perianal skin, scrotum, and penis in extramammary Paget's disease (EMPD).

EMPD occurs in apocrine-rich skin most commonly in the elderly. The most frequently affected site is the labia majora. Two thirds of cases occur on the vulva, and one third on the perianal skin and 14 % occur on the male genitalia (scrotum). Only 2 % of cases are found in the axilla, eyelids, external ear canals, trunk, and mucosal surfaces.

While most cases of MPD are associated with underlying breast carcinoma (82–92 %), EMPD is less often associated with an underlying neoplasm (9–32 %) [38]. It was therefore proposed that cases of extramammary Paget's disease can arise as epidermotropic spread from an *in situ* or invasive neoplasm arising in an adnexal gland within the dermis, analogous to mammary Paget's disease without a primary breast neoplasm. Of all patients with EMPD, 36 % have a strong anatomic association of internal malignancy with the EMPD site, and EMPD in the perianal area has a higher association rate (50–86 %) with an internal malignancy than those with EMPD on the labia majora (5–25 %) [39].

Several punch biopsies should be performed for diagnosis and assessment of depth of invasion. The use of immunohistochemistry may be necessary to confirm the diagnosis. For EMPD, underlying gastrointestinal or genitourinary neoplasms must be ruled out. Imaging of the abdomen and pelvis, colonoscopy, barium enema, cystoscopy, intravenous pyelogram, chest X-ray

and mammogram (for the rare association of EMPD and MPD), and blood work (CEA) are all appropriate tests. FDG-PET may have utility in ruling out lymph node metastases and identifying a primary, but it is not a standard recommendation at this time.

Surgical Considerations

While there is no consensus on treatment of EMPD, surgical wide excision or Mohs micrographic surgery continues to be preferred treatments. No clear recommendations for margin width exist. Typically, wide margins up to 3 cm are recommended, but wide local excision with a 1 cm margin from the clinical border may produce negative margins and low local recurrence rates in select patients [40]. Unfortunately, multifocal and unclear borders may lead to high margin positivity. Intraoperative frozen margin assessment in addition to wide local excision and intraoperative re-excision for margin positivity is recommended. Mohs surgery can be effective and may be associated with lower rates of recurrence compared to wide local excision. Preoperative mapping biopsies to evaluate the extent of disease are often very helpful. When invasive to the subcutaneous tissues, EMPDs have a high rate of lymph node metastasis, and SLNB should be considered for staging.

Other Treatments

Trials for EMPD are few since the tumor is rare, and therefore most data for nonsurgical management consists of small series and case reports. Use of nonsurgical modalities to treat EMPD including topical imiquimod, topical 5-FU, topical bleomycin, photodynamic therapy, CO₂ laser ablation, and topical retinoids has been reported with mixed results. Photodynamic therapy is not recommended for scrotal lesions or lesions <4 cm due to high recurrence rates. Radiation therapy was found effective and well tolerated for EMPD and can provide good local control. Radiation can be used to treat the primary lesion in inoper-

able patients or as an adjuvant for positive margins or high-risk tumors.

No optimal chemotherapy regimen for EMPD exists. Case reports for combination chemotherapy including mitomycin C and epirubicin, vincristine, cisplatin, docetaxel, and 5-FU have shown pathologic and complete responses [41]. Additionally, the overexpression of HER-2/neu in primary EMPD suggests a role for directed therapy with trastuzumab in patients with recurrent disease [42].

Follow-Up

While no clear guidelines exist, patients should have long-term follow-up with routine skin as well as regional lymph node examinations similar to other NMSC protocols. If a primary source is suspected, but not yet found, other imaging modalities as well as laboratory tests may be useful and may be repeated on a regular basis.

Eccrine Porocarcinoma

Eccrine porocarcinoma (EPC) is a rare malignancy arising from intraepidermal eccrine sweat ducts (Fig. 2.8). EPC lesions occur most commonly in the lower extremities but are also found on the head and neck. EPC may arise de novo into a malignant form but most often develops from a long-standing benign eccrine poroma that has undergone degenerative changes [43]. EPC has been reported to arise in association with extra mammary Paget's disease, sarcoidosis, chronic lymphocytic leukemia, pernicious anemia, Hodgkin's disease, HIV, and in rare cases, xeroderma pigmentosum and chronic radiation exposure.

EPC lesions present as firm, erythematous to violaceous nodules usually less than 2 cm in size. Signs and symptoms of malignant transformation include bleeding, ulceration, pain or itching, or sudden increase in size. Immunostaining is essential in establishing a diagnosis, especially to rule out the possibility of metastatic adenocarcinoma or an amelanotic melanoma. The presence of ductal structures and a PAS-positive cuticle

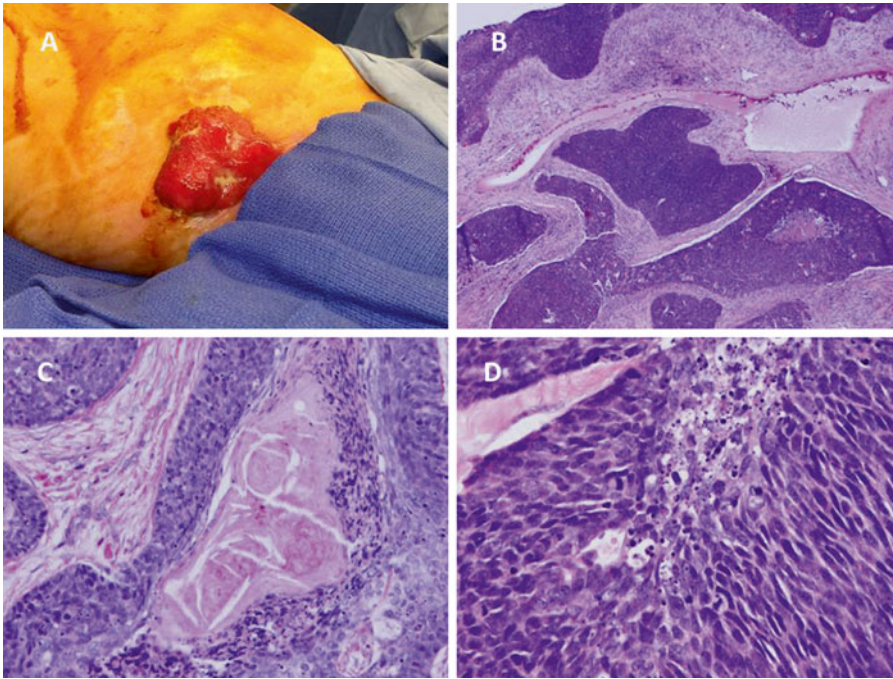


Fig. 2.8 Eccrine carcinoma occurring in a thigh (a). This tumor is presented in the epidermis and extends into the dermis with large cords, lobules, and islands. There is frequent central necrosis, and the tumor cells are large, hyperchromatic with marked nuclear atypia. Brisk mitosis and apoptosis are also present. The tumor shows ductal

differentiation with forming PAS-positive curtile materials (b–d) (a: Courtesy of Roger Kim, MD, Louisiana State University Health Sciences Center-Shreveport; b–d: Courtesy of Xin Gu, MD, Louisiana State University Health Sciences Center-Shreveport)

makes metastatic adenocarcinoma less likely. Poor prognostic features include thickness >7 mm, lymphovascular invasion, and more than 14 mitoses per high power field [44].

Surgical Considerations

Primary surgical excision is the treatment of choice for EPC including either wide excision or Mohs surgery. One study reviewing 9 cases of EPC reported a curative rate of 70–80 % after excision with 2 cm margins [45]. For recurrent or metastatic EPC tumors, limited data exist. Response to radiation therapy is often partial and is reserved for palliative care. Systemic chemotherapy has also shown limited response. Therefore, early detection and definitive excision provides the highest chance of survival. Due to EPC rarity, the role of sentinel lymph node biopsy

for staging EPC has not been defined, but should be considered for accurate staging.

Special Consideration: Neglected NMSC

Not uncommonly, patients will present to the surgeon with locally advanced BCC and SCC. The causes of late presentations include neglect due to patient anxiety, denial, and/or economic considerations. However, some lesions such as MCC may grow rapidly and present in a locally advanced state despite patient diligence. The standard evaluation should be performed including a thorough history and physical examination looking for signs or symptoms of distant metastatic disease. When appropriate, imaging should be obtained to rule out distant metastases. If distant metastases are found, then the treatment options should favor

a systemic approach such as chemotherapy or targeted therapy. In the background of metastatic disease, surgery should be employed for the locally advanced primary lesion only for palliation of uncontrolled bleeding, pain, or infection. If no evidence of metastatic disease is identified, then an extensive surgery to obtain clear margins should be planned with the likelihood of delayed closure if all margins are free of tumor. Primary suture closure is usually not possible, so consideration for healing by secondary intention, delayed skin grafting, and/or rotational or free flaps may be necessary. Given the often extensive nature of these lesions, either neoadjuvant or adjuvant radiation therapy should also be considered.

Salient Points

- *Basal cell carcinoma (BCC)*
 - The most common type of skin cancer.
 - Treatment is wide local excision (WLE).
 - 3–5 mm margin is adequate.
 - 5–10 mm margin for infiltrative/morpheaform lesions.
 - Moh's surgery is also appropriate.
 - Nonsurgical options include PDT, topical 5-FU, imiquimod, and XRT.
 - Vismodegib: Hedgehog pathway inhibitor FDA approved for refractory locally advanced BCC or metastatic BCC.
- *Squamous cell carcinoma (SCC)*
 - The second most common type of nonmelanoma skin cancer.
 - Can arise from actinic keratosis.
 - Bowen's disease: in situ lesion.
 - Treatment is WLE with 4–6 mm margin.
 - Moh's surgery is also appropriate.
 - Sentinel lymph node biopsy (SLNBx) is an option for high-risk lesions (size >2 cm, poorly differentiated, perineural or lymphatic invasion).
 - Palpable lymph nodes require FNA for diagnosis.
 - Positive LNs require node dissection.
 - Nonsurgical options include PDT for superficial SCC but not invasive SCC, topical 5-FU, imiquimod, and XRT.
 - Topical diclofenac is indicated for actinic keratosis.
- Cetuximab: anti-EFR approved for recurrent or metastatic SCC of the head and neck.
- *Merkel cell carcinoma*
 - Aggressive neuroendocrine tumor arises in the dermoepidermal junction.
 - Affects elderly Caucasians.
 - Associated with Merkel cell polyomavirus.
 - AEIOU features: asymptomatic, expanding rapidly, immune suppression, older than 50 years, ultraviolet-exposed site on a person with fair skin.
 - Common in immunosuppressed populations (organ transplant recipient and HIV patients).
 - Positive staining for CK-20, but negative for thyroid transcription factor 1 (TTF-1).
 - Size >2 cm in diameter portends a poor prognosis.
 - Treatment is WLE (1–2 cm margins) and SLNBx.
 - Lymphadenectomy for involved lymph nodes
 - XRT is used adjunctly for locoregional control.
 - Other treatment options: Moh's surgery.
- *Dermatofibrosarcoma protuberans (DFSP)*
 - Locally aggressive with high rates of local recurrence but low risk of metastasis.
 - The most common sarcoma of cutaneous origin.
 - Ninety percent due to chromosomal translocation resulting in PDGFB/COLIA1 fusion protein.
 - Treatment: WLE with at least 2 cm margins including the investing fascia.
 - Larger margins (3–4 cm) may be required for recurrent or extensive tumors.
 - Moh's is also an option.
 - Imatinib, sunitinib, and sorafenib have been used with mixed results.
 - XRT may be used for large tumors or when margins are close or positive, and further surgery is not feasible.
- *Angiosarcoma*
 - Highly aggressive tumor with poor outcome

- Associated with radiation, especially in the setting of breast conserving therapy for breast cancer
 - Stewart-Treves syndrome (lymphangiosarcoma): variant of angiosarcoma, associated with long-standing lymphedema
 - Need to rule out metastatic disease as part of the workup
 - Requires wide margin of resection
 - May require paclitaxel, doxorubicin, and gemcitabine
 - *Paget's Disease*
 - Rare cutaneous adenocarcinoma, scaly eczematous plaque.
 - Affects nipple/areolar complex.
 - Recommended margins: 3 cm.
 - Moh's surgery may be an option.
 - *Eccrine porocarcinoma*
 - Arises from intraepidermal eccrine sweat ducts.
 - Treatment is WLE with 2 cm margins.
4. Features that are associated with a worse prognosis in SCC include all of the following *EXCEPT*:
 - A. Poorly differentiated histology
 - B. Evidence of perineural invasion
 - C. Lymph node metastasis
 - D. Noninvasive or in situ disease at time of presentation
 5. Which of the following is a true statement regarding MCC:
 - A. Associated with Merkel cell polyomavirus
 - B. Less common in immunosuppressed populations
 - C. Radiation resistant
 - D. Can be distinguished as cutaneous in origin by TTF-1 staining
 6. DFSPs are accurately characterized by each of the following statements *EXCEPT*:
 - A. Associated with a distinct chromosomal translocation.
 - B. Commonly spreads to lymph nodes.
 - C. Maybe treated with tyrosine kinase inhibitors.
 - D. Clear surgical margins are generally curative.
 7. True or False: Angiosarcomas rarely arise from previously irradiated fields.
 - A. True
 - B. False
 8. True or False: Surgery remains the most important, curative treatment modality for NMSCs.
 - A. True
 - B. False

Questions

1. All of the following characteristics regarding BCC are true *EXCEPT*:
 - A. Induced by UV radiation.
 - B. Frequently metastasize to distant sites.
 - C. Associated with a known mutation in hedgehog signaling.
 - D. Surgical therapy is often curative.
2. Regarding NMSCs, incisional biopsies or definitive wide excisions should be performed:
 - A. Transversely on extremities
 - B. Longitudinally on extremities
 - C. With no consideration for the next step
 - D. In the easiest manner to close
3. A 38-year-old, red-headed woman who has an extensive history of tanning presents with a raised, pearly white lesion on her shoulder. The immediate next step in management is:
 - A. Close follow-up
 - B. Wide excision with 3 mm margins
 - C. Radiation therapy
 - D. Full-thickness biopsy

Answers

1. B
2. B
3. D
4. D
5. A
6. B
7. B
8. A

References

1. Kasper M, Jaks V, Hohl D, Toftgard R. Basal cell carcinoma – molecular biology and potential new therapies. *J Clin Invest.* 2012;122(2):455–63. Epub 2012/02/02.
2. Hogan DJ, To T, Gran L, Wong D, Lane PR. Risk factors for basal cell carcinoma. *Int J Dermatol.* 1989;28(9):591–4. Epub 1989/11/01.
3. Roewert-Huber J, Lange-Asschenfeldt B, Stockfleth E, Kerl H. Epidemiology and aetiology of basal cell carcinoma. *Br J Dermatol.* 2007;157 Suppl 2:47–51. Epub 2007/12/11.
4. de Zwaan SE, Haass NK. Genetics of basal cell carcinoma. *Australas J Dermatol.* 2010;51(2):81–92; quiz 3–4; Epub 2010/06/16.
5. Dourmishev LA, Rusinova D, Botev I. Clinical variants, stages, and management of basal cell carcinoma. *Indian Dermatol Online J.* 2013;4(1):12–7. Epub 2013/02/27.
6. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. *Br J Dermatol.* 2003;148(2):195–202. Epub 2003/02/18.
7. Edge SB, Byrd DR, Compton CC, et al. Cutaneous squamous cell carcinoma and other cutaneous carcinomas. In: *AJCC cancer staging manual.* 7th ed. New York: Springer; 2010. p. 523–6.
8. Gulleth Y, Goldberg N, Silverman RP, Gastman BR. What is the best surgical margin for a Basal cell carcinoma: a meta-analysis of the literature. *Plast Reconstr Surg.* 2010;126(4):1222–31. Epub 2010/10/05.
9. Avril MF, Auperin A, Margulis A, Gerbaulet A, Duvillard P, Benhamou E, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer.* 1997;76(1):100–6. Epub 1997/01/01.
10. Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. *J Drugs Dermatol: JDD.* 2012;11(12):1462–7. Epub 2013/02/05.
11. Rowe DE, Carroll RJ, Day Jr CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol.* 1992;26(6):976–90. Epub 1992/06/11.
12. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 1992;27(2 Pt 1):241–8. Epub 1992/08/01.
13. Samarasinghe V, Madan V. Nonmelanoma skin cancer. *J Cutan Aesthet Surg.* 2012;5(1):3–10. Epub 2012/05/05.
14. Kwon S, Dong ZM, Wu PC. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: clinical experience and review of literature. *World J Surg Oncol.* 2011;9:80. Epub 2011/07/21.
15. Veness MJ. High-risk cutaneous squamous cell carcinoma of the head and neck. *J Biomed Biotechnol.* 2007;2007(3):80572. Epub 2007/06/02.
16. Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. *Arch Dermatol.* 1998;134(7):821–6. Epub 1998/07/29.
17. Marmur ES, Schmults CD, Goldberg DJ. A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. *Dermatol Surg.* 2004;30(2 Pt 2):264–71. Epub 2004/02/12.
18. Morton C, Horn M, Leman J, Tack B, Bedane C, Tjioe M, et al. Comparison of topical methyl aminolevulinic acid photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. *Arch Dermatol.* 2006;142(6):729–35. Epub 2006/06/21.
19. Patel GK, Goodwin R, Chawla M, Laidler P, Price PE, Finlay AY, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol.* 2006;54(6):1025–32. Epub 2006/05/23.
20. Uribe P, Gonzalez S. Epidermal growth factor receptor (EGFR) and squamous cell carcinoma of the skin: molecular bases for EGFR-targeted therapy. *Pathol Res Pract.* 2011;207(6):337–42. Epub 2011/05/03.
21. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567–78. Epub 2006/02/10.
22. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol.* 2008;58(3):375–81. Epub 2008/02/19.
23. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol.* 2003;49(5):832–41. Epub 2003/10/25.
24. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science.* 2008;319(5866):1096–100. Epub 2008/01/19.
25. Scott MP, Helm KF. Cytokeratin 20: a marker for diagnosing Merkel cell carcinoma. *Am J Dermatopathol.* 1999;21(1):16–20. Epub 1999/02/23.
26. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23(10):2300–9. Epub 2005/04/01.
27. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol.* 2001;8(3):204–8. Epub 2001/04/21.
28. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *Journal Clin Oncol.* 2007;25(9):1043–7. Epub 2007/03/21.

29. Poulsen M, Rischin D, Walpole E, Harvey J, Mackintosh J, Ainslie J, et al. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study–TROG 96:07. *J Clin Oncol.* 2003;21(23):4371–6. Epub 2003/12/04.
30. Sanmartin O, Llombart B, Lopez-Guerrero JA, Serra C, Requena C, Guillen C. Dermatofibrosarcoma protuberans. *Actas dermo-sifiliograficas.* 2007;98(2):77–87. Epub 2007/04/03.
31. Llombart B, Serra-Guillen C, Monteagudo C, Lopez Guerrero JA, Sanmartin O. Dermatofibrosarcoma protuberans: a comprehensive review and update on diagnosis and management. *Semin Diagn Pathol.* 2013;30(1):13–28. Epub 2013/01/19.
32. Gloster Jr HM. Dermatofibrosarcoma protuberans. *J Am Acad Dermatol.* 1996;35(3 Pt 1):355–74; quiz 75–6; Epub 1996/09/01.
33. Malhotra B, Schuetze SM. Dermatofibrosarcoma protuberans treatment with platelet-derived growth factor receptor inhibitor: a review of clinical trial results. *Curr Opin Oncol.* 2012;24(4):419–24. Epub 2012/04/19.
34. Monroe AT, Feigenberg SJ, Mendenhall NP. Angiosarcoma after breast-conserving therapy. *Cancer.* 2003;97(8):1832–40. Epub 2003/04/04.
35. Stewart FW, Treves N. Lymphangiosarcoma in post-mastectomy lymphedema; a report of six cases in elephantiasis chirurgica. *Cancer.* 1948;1(1):64–81. Epub 1948/05/01.
36. Breiteneder-Geleff S, Soleiman A, Kowalski H, Horvat R, Amann G, Kriehuber E, et al. Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium. *Am J Pathol.* 1999;154(2):385–94. Epub 1999/02/23.
37. DeMartelaere SL, Roberts D, Burgess MA, Morrison WH, Pisters PW, Sturgis EM, et al. Neoadjuvant chemotherapy-specific and overall treatment outcomes in patients with cutaneous angiosarcoma of the face with periorbital involvement. *Head Neck.* 2008;30(5):639–46. Epub 2008/01/24.
38. Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. *J Clin Pathol.* 2000;53(10):742–9. Epub 2000/11/07.
39. Goldblum JR, Hart WR. Perianal Paget's disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. *Am J Surg Pathol.* 1998;22(2):170–9. Epub 1998/03/21.
40. Murata Y, Kumano K. Extramammary Paget's disease of the genitalia with clinically clear margins can be adequately resected with 1 cm margin. *Eur J Dermatol: EJD.* 2005;15(3):168–70. Epub 2005/05/24.
41. Moretto P, Nair VJ, Hallani SE, Malone S, Belanger E, Morash C, et al. Management of penoscrotal extramammary Paget disease: case series and review of the literature. *J Cutan Oncol.* 2013;20(4):e311–20. Epub 2013/08/02.
42. Plaza JA, Torres-Cabala C, Ivan D, Prieto VG. HER-2/neu expression in extramammary Paget disease: a clinicopathologic and immunohistochemistry study of 47 cases with and without underlying malignancy. *J Cutan Pathol.* 2009;36(7):729–33. Epub 2009/06/13.
43. Penneys NS, Ackerman AB, Indgin SN, Mandy SH. Eccrine poroma: two unusual variants. *Br J Dermatol.* 1970;82(6):613–5. Epub 1970/06/01.
44. Robson A, Greene J, Ansari N, Kim B, Seed PT, McKee PH, et al. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. *Am J Surg Pathol.* 2001;25(6):710–20. Epub 2001/06/08.
45. Lozano Orella JA, Valcayo Penalba A, San Juan CC, Vives Nadal R, Castro Morrondo J, Tunon AT. Eccrine porocarcinoma. Report of nine cases. *Dermatol Surg.* 1997;23(10):925–8.
46. Compton C, Byrd D, Garcia-Aguilar J, et al. Cutaneous squamous cell carcinoma and other cutaneous carcinomas. In: Compton C, Byrd D, Garcia-Aguilar J, Kurtzman S, Olawaiye A, Washington M, editors. *AJCC cancer staging atlas.* 2nd ed. New York: Springer; 2012. p. 357–70.