INTRODUCTION

EPIDEMIOLOGY OF NONMELANOMA SKIN CANCER

Skin cancers are divided into two main groups: malignant melanoma (MM) and nonmelanoma skin cancer (NMSC). The term "NMSC" encompasses a wide variety of skin cancers including basal cell carcinomas (BCC), cutaneous squamous cell carcinomas (cSCC), dermatofibrosarcoma protuberans (DFSP), cutaneous lymphomas, adnexal tumors, and Merkel cell carcinoma (MCC), and only excludes malignancies involving melanocytes. BCC and cSCC comprise the vast majority of NMSC tumors (estimated between 75% and 80% and 20% and 25%, respectively)9,10 and their incidence is approximately 18 to 20 times higher than that of MM.1 This chapter will focus on the management of advanced BCC, cSCC, DFSP, and MCC.

The incidence of NMSC is highest in Australia and the lowest in parts of Africa.4 In the United States, the total number of NMSC cases is reported to be higher than lung, breast, prostate, and colon cancers combined.5 Over one million new cases of NMSC are diagnosed each year in the United States alone, and this has continued to increase at a rate of approximately 3% to 8% since the 1960s.3,6 NMSCs are also widely believed to be the most commonly diagnosed malignancy worldwide.2,7

BASAL CELL CARCINOMAS

BCC INCIDENCE AND RISK FACTORS. BCC is the most common type of cancer worldwide.9 In the United States, the estimated annual incidence is estimated to be 0.1% to 0.5%9. It is especially common in light-skinned populations, with the estimated lifetime risk of developing BCC up to 30% in the United States white population.10 The incidence is about 30% higher in men than in women,11–13 and increases with age.14 Interestingly, the incidence of BCC among Americans younger than 40 years of age, especially among women, seems to be increasing.15

Both environmental and genetic factors play a role in the development of BCC: these include ultraviolet (UV) radiation,16–19 arsenic exposure,20–22 history of radiation therapy (RT),23–25 immunosuppression (from various causes including solid organ transplantation, HIV infection, or chronic steroid use secondary to autoimmune disorders),26,27 fair skin,28 light-colored eyes, red hair, northern European ancestry, older age, childhood freckling, history of blistering sunburns, history of tanning bed use,29 smoking,19,30 and genetic conditions, such as basal cell nevus syndrome (BCNS) and epidermolysis bullosa.17,18,29,31–33 Of these, UV radiation is one of the most important causes of BCC. In addition to the total radiation dose, the timing and mode of exposure also seem to contribute to BCC development. Recent studies showed that acute, intense incremental UV exposure increases BCC risk more than similar doses of UV radiation delivered in a more chronic fashion over the same total period of time.26,34 There have also been studies suggesting that childhood and adolescence are critical periods for establishing adult BCC risk, thus highlighting the importance of early photoprotective measures to prevent the development of BCCs.35–37 Lifestyle factors such as smoking have also been suggested to contribute to the development of BCCs.19,30

Pathways involved in the growth, apoptosis, or differentiation of keratinocytes,38–40 as well as genes that influence immune response such as CTLA140 also contribute to BCC development. Better understanding of these genetic abnormalities has led to a better understanding of BCC pathogenesis.

MOLECULAR PATHOGENESIS OF BCCS. Major advances in the understanding of the pathogenesis of BCCs have come from extensive studies of patients with BCNS and the subsequent discovery of mutations in the tumor suppressor gene, PTCH1. BCNS, also known as Gorlin’s syndrome, is a rare, autosomal dominant syndrome, in which patients develop numerous BCCs starting in childhood, and are at risk of developing medulloblastomas and rhabdomyosarcomas.31,41 BCNS is caused by loss-of-function mutations in the tumor suppressor gene, human PTCH1, on chromosome 9q22, which is the primary inhibitor of Hedgehog (Hh) signaling.42,43 The Hh signaling pathway plays a critical role in embryonic growth and patterning, as well as in the maintenance of homeostasis postembryonically through effects on stem cells or progenitor cells in invertebrate and vertebrate organisms.44 This signaling pathway is constitutively repressed under normal circumstances, and only activated by binding of Hh ligand, such as Sonic hedgehog (SHH), Indian hedgehog (IHH), and desert hedgehog (DHH), to the transmembrane receptor PTCH1.45 When not bound by Hh ligand, PTCH1 receptor suppresses the activity of transmembrane protein Smoothened (SMO). When the PTCH receptor is bound by Hh ligand, the repression is released, thus permitting SMO to transmit downstream signals, leading to production of Gli family transcription factors (Fig. 29-1).47–49 This receptor ligand association is reversible and has feedback
Figure 29-1 Molecular pathogenesis of basal cell carcinoma.

The important role of epithelial–stromal interaction in creating a favorable environment for tumor cell proliferation has also been demonstrated. Stromal cells isolated from human BCCs express increased levels of gremlin 1, which antagonizes the pro-differentiation factors, BMP2 and BMP4.66,77

TREATMENT OF BASAL CELL CARCINOMA.

Appropriate treatment of BCC is necessary due to the locally invasive and destructive nature of this tumor. The majority of BCCs represent only local disease and carry an excellent prognosis. The goal of treatment is complete tumor extirpation with maximal preservation of function and cosmesis. Currently, the widely accepted treatment modalities include: cryotherapy, electrodesiccation and curettage (ED&C), surgical excision, Mohs micrographic surgery (MMS), topical and intralesional agents (5-FU, imiquimod, resiquimod, ingenol mebulate, cyclooxygenase-2 inhibitors, cyclosporine), radiation therapy (RT), photodynamic therapy, and systemic chemotherapeutic agents (capecitabine, interferon, EGFR inhibitors, GDC-0449, LDE-225, vismodegib).73,74 Several factors determine the recurrence potential of BCC, including size, location (Fig. 29-2), histopathologic subtype, perineural involvement, clinically indistinct borders, patient immune status, primary versus recurrent lesions, and history of radiation exposure to the affected area. These risk factors, as well as a thorough understanding of the different treatment modalities, including their associated risks, complications, cosmetic outcome, and recurrence rates, should be considered in order to make appropriate treatment choices.

Several studies have looked into various characteristics of BCC to determine the risk of tumor recurrence.79–81 The National Comprehensive Cancer Network (NCCN) guidelines assess the risk factors for BCC recurrence, as well as proposed primary treatments for low-risk and high-risk BCCs (Table 29-1, Fig. 29-3).82

The majority of NMSC are low risk and can be successfully treated by ED&C, surgical excision, cryotherapy, photodynamic therapy, and topical agents. Patients with BCC who are not considered surgical candidates may be referred for radiotherapy, which has a 4 year locoregional control rate of 86% with a median time to recurrence of 40.5 months.83 The use of radiotherapy may be limited in patients with tumors located near the eyes or on the eyelids,84 which may be difficult to treat, and patients nearing their
TABLE 29-1
Risk Factors for BCC Recurrence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary vs. recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Location: Eyelids, ears, nose, lips, genitals, hands, feet Cheeks, forehead, scalp, neck Trunk, extremities</td>
<td>Size &lt;20 mm</td>
<td>Size ≥20 mm</td>
</tr>
<tr>
<td>Location: Cheeks, forehead, scalp, neck Trunk, extremities</td>
<td>Size &lt;10 mm</td>
<td>Size ≥10 mm</td>
</tr>
<tr>
<td>Location: Trunk, extremities</td>
<td>Size &lt;6 mm</td>
<td>Size ≥6 mm</td>
</tr>
<tr>
<td>Pathology</td>
<td>Nodular, superficial</td>
<td>Aggressive growth pattern</td>
</tr>
<tr>
<td>Perineural involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Site of previous radiation treatment</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 29-3  Treatment algorithm for basal cell carcinoma.

Primary treatment of low-risk BCC

Surgical candidate

Radiation therapy

In hair-bearing region?

Excision with postoperative margin assessment

Fat reached?

Curettage and electrodesiccation*

Negatives margins?

Re-excision, Mohs surgery or resection with complete circumferential and deep margin assessment with frozen or permanent sections

Regular follow-up
maximum safe lifetime dose of radiation. Use of radiotherapy is contraindicated in Gorlin's syndrome as well as in BCC that has recurred after prior radiotherapy.

Certain BCCs are at higher risk for recurrence based on their size and location, as well as clinical and microscopic factors. Evidence-based treatment options for BCC are few because of the rarity of randomized, prospective studies comparing different treatment modalities and their recurrence rates. According to a large systematic review that included studies with at least 50 patients and 5 years' follow-up, totaling 9930 primary BCC cases, MMS had the lowest rate of recurrence, followed by surgical excision, cryosurgery, and ED&C. The authors suggested that MMS be used for larger, morpheaform or recurrent BCCs located in danger zones (Fig. 29-4), and that surgical excision with 4 mm margins around the clinical borders of the tumor be used for well-circumscribed nodular or superficial BCCs <2 cm in diameter, as well as for re-excision of low-risk primary BCCs located on the trunk and extremities. They recommended that other treatment modalities be used in patients for whom surgery is contraindicated.

A Cochrane review analyzing randomized controlled trials examining BCC recurrence rates found that MMS and conventional surgical excision were the most effective treatments, followed by radiotherapy, cryotherapy, and photodynamic therapy. ED&C can be a cost-effective and appropriate treatment choice for low-risk tumors if three important factors are kept in mind:

1. This technique should not be used to treat lesions in hair-bearing sites because of the risk of tumor extending down hair follicles;
2. If the subcutaneous layer is reached during the ED&C procedure, surgical excision should be performed;
3. If curettage is performed based on the clinical appearance of tumor, a biopsy should be taken to confirm that there are no high-risk pathologic features. Further guidelines and treatment algorithms can be found on the NCCN website: [http://www.nccn.org/](http://www.nccn.org/).

Although surgical and other destructive treatments are considered the gold standard of therapy for localized BCC, advancements in understanding BCC pathogenesis have led to the development of targeted therapies for more advanced disease. These treatments are valuable for patients with unresectable tumors as well as metastases. As discussed earlier, the Hh signaling pathway is now well established as playing a critical role in BCC pathogenesis.

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**Figure 29-4** Treatment algorithm for high-risk basal cell carcinoma.

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
In 1998, it was observed that lambs developed cyclopia after maternal ingestion of corn lilies, which contain cyclopamine, a potent inhibitor of the Hh signaling pathway by direct binding to SMO.\textsuperscript{49,50} Subsequent in vitro and in vivo studies demonstrated that the oral and topical administration of cyclopamine reduced BCC growth and development in mice and humans.\textsuperscript{51,52} These observations led to the synthesis of a novel class of Hh antagonists derived from cyclopamine with improved pharmaceutical properties and in vitro potency.\textsuperscript{53} Vismodegib (GDC-0449), a SMO inhibitor, showed promising results in a phase I trial of patients with locally advanced or metastatic BCC.\textsuperscript{54,55}

In a phase II clinical trial of vismodegib, investigators observed such promising results among patients with locally advanced or metastatic BCC\textsuperscript{56} and BCNS patients with multiple BCCs that the Data Safety Monitoring Board recommended ending the placebo arm of the study.\textsuperscript{68} Vismodegib demonstrated a 30% response rate in patients with metastatic BCC ($n = 33$), and a 43% response rate in those with locally advanced BCC ($n = 63$); 21% showed complete responses (CRs).\textsuperscript{57} More than 30% of patients reported adverse events including muscle spasms, alopecia, dysgeusia (taste disturbance), weight loss, and fatigue; seven deaths were noted. Acquired resistance during continuous vismodegib therapy has been reported in a case series in 21% of patients ($n = 28$) with advanced BCCs.\textsuperscript{58} The novel use of vismodegib as a neoadjuvant to shrink a locally advanced BCC prior to resection has been reported recently in a patient with Gorlin’s syndrome.\textsuperscript{59}

Potential challenges in the use of Hh signaling pathway antagonists exist. Studies show that after dramatic reduction in tumor mass, a small population of residual tumor cells insensitive to Hh inhibition persist in both the mouse model\textsuperscript{100} and in clinical trials of LDE224.\textsuperscript{68,101} Another challenge is the development of resistance caused by mutations in SMO and amplification of downstream genes including Gli2 and cyclin D1.\textsuperscript{102,103} Recently, an alternative SMO inhibitor, itraconazole, an FDA-approved antifungal agent, was found to inhibit Hh signaling pathway by binding SMO at a site different from that of cyclopamine, delaying BCC development in a mouse model.\textsuperscript{104} Itraconazole is currently undergoing a phase II study to evaluate its potential as a BCC treatment option. Given the common adverse effects of systemic SMO inhibitors, including loss of taste, muscle spasms, hair loss, fatigue, and hyponatremia,\textsuperscript{105–107} a topical formulation of SMO inhibitor LDE224 was developed, which produced a decrease in Hh gene expression in the majority of treated tumors without treatment-related side effects.\textsuperscript{108} A number of inhibitors of the Hh signaling pathway with targets downstream of SMO, such as Gli transcription factors, or independent of SMO, are currently under investigation.\textsuperscript{109–111}

**SQUAMOUS CELL CARCINOMAS**

**INCIDENCE AND RISK FACTORS OF cSCC.**

Cutaneous SCC (cSCC) is the second most common type of skin cancer in Caucasians after BCC, accounting for one-fifth of all cutaneous malignancies and 90% of all head and neck cancers.\textsuperscript{112,113} In the United States, the incidence of SCC in men is 81 to 136 per 100,000 and 26 to 59 per 100,000 in women.\textsuperscript{114} The risk factors for developing cSCCs include fair skin, male gender, older age (>65 years old), increased sun exposure, and immunosuppression such as solid organ transplantation.\textsuperscript{115} For the last several decades, the incidence of cSCCs has been rising. This is likely attributable to several factors including an expanding older population; the incidence of cSCC is three times higher for those over the age of 75 compared to those between 50 to 55 years of age.\textsuperscript{116} Additionally, there is a growing population of solid organ transplant recipients whose immunosuppression and longevity of transplant predispose these patients to numerous and high-risk cSCCs.\textsuperscript{117–119}

While the majority of cSCCs are minimally invasive in their early stages, the potential for metastasis exists\textsuperscript{120} with an approximately 2% to 3% overall rate of regional metastasis to lymph nodes of the head and neck, primarily to parotid lymph nodes.\textsuperscript{121} When cSCCs do metastasize, they account for 20% of all skin cancer-related deaths.\textsuperscript{122} Thus, with an increase in the geriatric population and longer life expectancy of immunosuppressed patients, the incidence of cSCC will likely continue to rise.

cSCC most frequently develops on sun-exposed areas of the skin.\textsuperscript{2,119} Up to 75% of NMSCs occur in the head and neck region\textsuperscript{123} with 68% of all cSCCs occurring on the head and neck.\textsuperscript{122} Epidemiologic studies support the role of UV light in NMSC pathogenesis since increased rates are correlated with proximity to the equator\textsuperscript{2,117,124} and are also seen in areas of ozone depletion, such as Australia, where the incidence of NMSC is approximately 1000 to 2000 per 100,000 per year.\textsuperscript{1,12} Northern European countries have much lower rates of NMSC.\textsuperscript{122}

The increased incidence of NMSCs following transplantation has been well documented.\textsuperscript{124–128} One report documented a three- to five-fold increase in cancer risk in the posttransplant population compared to the general population\textsuperscript{129} with the incidence of de novo malignancy in this population ranging between 6% and 18% in some studies.\textsuperscript{130} Interestingly, the types and distributions of cancers that affect this population are quite different from those of the general population.\textsuperscript{131} While the most common tumors in the general population are breast, prostate, colon, and lung cancers, the most common types of malignancies in transplant recipients are cSCC, BCC, and non-Hodgkin’s lymphoma, with the most common sites of involvement being on the head and neck.\textsuperscript{129–131} The cSCCs in immunocompromised patients are clinically aggressive; these patients tend to develop multiple lesions with a higher rate of recurrence and a higher rate of metastasis.\textsuperscript{124} In particular, transplant patients have a 65 times greater risk of developing cSCCs compared to age-matched controls.\textsuperscript{132}

**CLINICAL AND HISTOLOGIC FEATURES OF HIGH-RISK SCC**

**Staging.** The staging system most often used for NMSCs is the American Joint Commission on Cancer (AJCC) TNM system. The seventh edition of AJCC (Tables 29-2 and 29-3) includes the clinical and histologic features that should be taken into account to better ascertain the prognosis and natural history of cSCCs.
**Pathogenesis.** cSCC is thought to manifest as a spectrum of progressive changes, from actinic keratoses (AKs) to SCC in situ (SCCIS), invasive cSCC, and metastatic SCC.

According to the classic multistep model of carcinogenesis, mutations in tumor suppressor genes may cause development of precursor lesions with increased genetic instability, and additional mutations in oncogenes permit the emergence of invasive carcinoma. In the case of cSCC, the mechanism leading to genomic instability is likely due to UVB-induced inactivation of p53, as demonstrated in a study where p53 knockout mice developed increased numbers of AKs and cSCCs after UV-B exposure, as well as a number of studies confirming the presence of p53 mutations in majority of cSCCs. In addition to UV radiation induced signature mutations (CC→TT and C→T), aberrant activation of EGFR and Fyn, an Src-family tyrosine kinase, were shown to down-regulate p53 in a c-Jun-dependent manner.

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**TABLE 29-2**

**Staging of Basal and Squamous Cell Skin Cancer by Size/Presence of Lymph Node Involvement or Metastases**

<table>
<thead>
<tr>
<th>Primary Tumor (excludes eSCC of eyelid)</th>
<th>Stage</th>
<th>Definition</th>
<th>High-Risk Features</th>
</tr>
</thead>
</table>
| **Tx** | Cannot be assessed | Depth >2 mm 
Clark level ≥4 
On ear or non–hair-bearing lip 
Poorly or not differentiated |
| **T0** | No evidence of primary tumor |
| **Tis** | Carcinoma in situ |
| **T1** | ≤2 cm and <2 high risk features |
| **T2** | >2 cm OR has ≥2 high risk features |
| **T3** | Invades maxilla, mandible, orbit, or temporal bones |
| **T4** | Invades axial or appendicular skeleton or perineural skull base |

<table>
<thead>
<tr>
<th>Regional Lymph Node Involvement</th>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NX</strong></td>
<td>Lymph nodes can not be assessed</td>
<td></td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td>No lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>Involves single lymph node ≤3 cm</td>
<td></td>
</tr>
<tr>
<td><strong>N2a</strong></td>
<td>≥3 cm to ≤6 cm in single lymph node OR</td>
<td></td>
</tr>
<tr>
<td><strong>N2b</strong></td>
<td>≤6 cm in multiple ipsilateral lymph nodes OR</td>
<td></td>
</tr>
<tr>
<td><strong>N2c</strong></td>
<td>≤6 cm in bilateral or contralateral lymph nodes</td>
<td></td>
</tr>
<tr>
<td><strong>N3</strong></td>
<td>Metastasis &gt;6 cm in lymph node</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis</th>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M0</strong></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>M1</strong></td>
<td>Present</td>
<td></td>
</tr>
</tbody>
</table>
Recently, amplification and activating mutations of Ras oncogene, a family of GTP-binding proteins that activates the Raf/Mek/Erk1/Erk2 kinase pathway, have been found in SCCs and AKs.\textsuperscript{142–147} The Ras family of proto-oncogenes promotes cellular growth and proliferation, and aberrant Ras activation can result in tumorigenic phenotypes.\textsuperscript{145} Interestingly, one study showed that activation of oncogenic Ras alone was not sufficient to induce SCC, but that it was necessary to couple Ras overexpression with activation of the cell cycle progression mediator CDK4, or to modulate NF-\kappaB activity to bypass Ras-mediated G1 arrest and induce epidermal tumorigenesis (Figs. 29-5 and 29-6).\textsuperscript{134,146,147}

**TREATMENT.** The approach to treating cSCC depends on its risk classification according to the NCCN. The NCCN characterizes high-risk cSCC as having any of the following risk factors: large diameter (>2 cm or >1 cm on cheeks, forehead, scalp, or neck, or >6 mm on other areas of face, genitalia, hands, feet), depth >4 mm or beyond the papillary dermis, ill-defined margins, recurrence after definitive treatment, immunosuppression, prior radiation, chronic inflammation, rapid growth, neurological symptoms, perineural or vascular invasion, moderately or poorly differentiated histology, infiltrative or acantholytic pattern, or mucin production.\textsuperscript{85} For non high-risk cSCC, the NCCN considers standard surgical excision adequate, in which the margin assessment is made from representative tissue sections. For high-risk cSCC, complete margin analysis is advised by the NCCN either by MMS or excision with complete circumferential peripheral and deep margin assessment (CCPDMA). Standard excision is permissible for tumors greater than 2 cm on the trunk and extremities with no other high-risk factors, which can be excised with a 1 cm clinical margin with a primary closure.\textsuperscript{86} In MMS, the surgeon performs the complete margin assessment whereas the pathologist performs this assessment in CCPDMA. Lower recurrence rates have been reported with MMS in a systematic review comparing MMS to standard excision.\textsuperscript{148} The cure rate of primary cSCC with MMS (97%) is reported to be higher than that of standard excision (92%); similarly, the cure rate of recurrent disease is reportedly higher following MMS (90%–94%) than after standard excision (77%).\textsuperscript{144,149}

RT is another treatment option for cSCC but is reserved for tumors that are difficult to treat surgically, particularly on the eyelids, lips, and ears.\textsuperscript{150} While radiation can be used as a primary treatment option for cSCCs, it is important to note that reported cure rates are higher with surgical therapy, and that there are long-term cutaneous risks of radiation and as well as short-term scheduling challenges.\textsuperscript{151} As monotherapy, radiation is generally reserved for patients in whom surgery would lead to unacceptable cosmetic or functional impairment, patients with inoperable tumors, or in whom the risks of surgery outweigh the benefits. With high-risk cSCC, local control rates with RT range from 80% to 85%.\textsuperscript{152} When implemented in the right context, RT may match surgery in restoring oral function and cure rates for lower lip cSCC.\textsuperscript{153} In cSCC with aggressive features, RT has been reportedly used as adjuvant therapy to surgery and chemotherapy with some degree of efficacy.\textsuperscript{152,154,155}
Chemotherapy as a treatment modality for metastatic cSCC thus far remains inconsistently effective. Combinations of cisplatin with 5-flourouracil (5-FU), doxorubicin, or bleomycin have been reported to yield some degree of efficacy, with a subset achieving CRs in some cases.\(^{155-160}\) For distant metastatic disease or regional recurrence, the NCCN recommends consideration of cisplatin-based chemotherapeutic regimens and participation in clinical trials.\(^{156}\) Combination therapy with 13-cis-retinoic acid and interferon-alpha therapy, with and without cisplatin, are in clinical trials for unresectable cSCC.\(^{159,161}\) With the recognition that some cSCCs overexpress EGFR, EGFR inhibitors have been used off label in inoperable cases.\(^{162}\) There are currently four EGFR inhibitors on the market: two are small molecules (erlotinib and gefitinib) and two are antibodies (cetuximab and panitumumab).\(^{163}\) In a phase II clinical trial, cetuximab has shown some success as a monotherapeutic agent in controlling inoperable or metastatic cSCC: after 6 weeks of treatment, 69% of enrolled patients were observed to have some degree of disease control.\(^{164}\)

Combined radiotherapy and EGFR inhibition have also shown promising results compared to monotherapy alone. In an NEJM 2006 article, the authors demonstrated that, in patients with locally advanced head and neck SCC, radiotherapy with cetuximab achieved 49.0 months median survival compared to 29.3 months after radiotherapy alone.\(^{165}\) A paper reviewing case reports and a phase II trial concluded that cetuximab combined with radiotherapy is superior to cetuximab alone; combination therapy showed a total response in 50% of advanced SCC cases.\(^{166}\) As radiotherapy combined with EGFR inhibition has gained traction for advanced cSCC treatment, clinical trials are underway to elaborate the cutaneous side effects due to radiation versus cetuximab in a large national prospective study in Germany as of 2013.\(^{167}\) In very high-risk SCC, characterized by lymphovascular or extracutaneous invasion, cetuximab appears to confer an advantage in controlling disease in combination with surgery and/or radiation in a recent retrospective study at an academic institution.\(^{168}\)

Comparison studies of radiotherapy with adjunctive cisplatin-based chemotherapy versus adjunctive EGFR inhibition are sparse. One recent retrospective study of patients receiving these combination interventions shows the superiority of adjunctive cisplatin \((n = 18)\) over adjunctive cetuximab \((n = 29)\): 83% of patients achieved a 3 year disease-specific survival period in the cisplatin group compared with 18% in the cetuximab group.\(^{169}\)

The advent of EGFR inhibitors marks an exciting period of discovery of new molecular targets for treatment of advanced cSCC. With novel molecules targeting alternative pathways, including PI3 K-ARK, ALK-1, NOTCH1, and Hh, new monotherapeutic or adjuvant agents promise new ways to control disease or at least overcome tumor resistance to EGFR inhibition.\(^{168}\)

**MERKEL CELL CARCINOMA**

**EPIDEMIOLOGY AND RISK FACTORS.** MCC is a rare, aggressive neuroendocrine carcinoma of the skin, with a high risk of recurrence and metastasis. Overall, MCC has a 1 year survival rate of approximately 80% and a 2 year survival rate of approximately 50%. It most commonly affects the older Caucasian population with adjusted incidence rates of 0.18 to 0.41 per 100,000 person-years.\(^{169}\) In the United States, approximately 1500 new cases are diagnosed each year and the incidence continues to be on the rise.\(^{162,170}\) MCC is more common in sun-exposed areas, such as the head, neck, and extremities.\(^{171}\) The risk of MCC is significantly higher in patients who are immunosuppressed\(^{172,173}\) and in those with other malignancies, including multiple myeloma, chronic lymphocytic leukemia, and MM.\(^{174,175}\)

**PRESENTATION.** Clinically, MCC lesions often lack distinctive features and can present as a rapidly growing, asymptomatic, flesh-colored to bluish-red dermal papule or nodule, clinically mimicking epidermal inclusion cyst, BCC, or amelanotic melanoma. In 2008, Heath et al.\(^{176}\) proposed clinical characteristics of MCC called “AEIOU features” observed in a series of 195 MCC cases over a period of 27 years: asymptomatic; expanding rapidly; immune suppression, older than 50 years; and UV-exposed site on person of fair skin. Maintaining vigilance and a high index of suspicion for biopsy followed by histopathologic confirmation facilitates a timely diagnosis.

**STAGING.** Once the diagnosis is established, the tumor is staged according to AJCC TNM criteria (Tables 29-4 and 29-5).\(^{177}\) The staging system was first released in 2010; the criteria and stage groupings are based on the analysis of National Cancer Database data from more than 4000 MCC patients with at least 5 years’ follow-up. Figure 29-7 shows the significant difference in survival rates found between patients presenting with local, regional, and distant metastatic disease.\(^{178}\)

**PATHOGENESIS.** Although the molecular pathogenesis of MCC has not yet been completely elucidated, multiple factors appear to contribute to the development of MCC, including immunosuppression, UV exposure and Merkel cell polyomavirus. The relative risk of MCC development increases significantly with immunosuppression, with a 13 fold increase in the HIV population\(^{172}\) and a 10 fold increase in solid organ transplant patients.\(^{173}\) There are multiple reports to support the possible important role of UV radiation exposure in the etiology of MCC. In one study of 195 cases of MCC, the lesions were observed to arise in sun-exposed areas 81% of the time.\(^{176}\) In one population-based study of 425 cases of MCC from nine areas of the United States, the Surveillance, Epidemiology, and End Results (SEER) Program database demonstrated that regional incidence rates of both cancers increased with increasing sun exposure as measured by the UV-B solar index.\(^{179}\) One prospective study of 1380 patients with psoriasis who were treated with oral psoralen and UV-A phototherapy (PUVA) showed an increased risk of MCC development in the PUVA treated group compared to controls.\(^{180}\) In addition, a C-to-T mutation, a typical UV-B induced mutation, is found in MCC cell lines, further supporting
TABLE 29-4  
Staging of Merkel Cell Carcinoma

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>Tx</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>≤2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2 cm and ≤5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Invades musculoskeletal structures</td>
</tr>
</tbody>
</table>

**Regional Lymph Node Involvement**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SX</td>
<td>Lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>pNX</td>
<td>Lymph nodes cannot be assessed on pathology</td>
</tr>
<tr>
<td>cN0</td>
<td>Lymph nodes cannot be detected clinically</td>
</tr>
<tr>
<td>pN0</td>
<td>No lymph node metastasis detected on pathology</td>
</tr>
<tr>
<td>N1a</td>
<td>Micrometastasis (diagnosed after sentinel or elective lymphadenopathy)</td>
</tr>
<tr>
<td>N1b</td>
<td>Macrometastasis (clinically detectable and confirmed by biopsy or therapeutic lymphadenopathy)</td>
</tr>
<tr>
<td>N2</td>
<td>In-transit metastasis (distinct from and distal to primary lesion or between primary lesion and draining regional lymph node)</td>
</tr>
</tbody>
</table>

**Distant Metastasis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>None</td>
</tr>
<tr>
<td>M1a</td>
<td>In skin, subcutaneous tissue or distant lymph nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>In lungs</td>
</tr>
<tr>
<td>M1c</td>
<td>In other visceral site</td>
</tr>
</tbody>
</table>

TABLE 29-5  
Prognostic Staging of Merkel Cell Carcinoma

<table>
<thead>
<tr>
<th>Prognostic Groups</th>
<th>Stage 0</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIC</th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tis, N0, M0</td>
<td>T1, pN0, M0</td>
<td>T1, cN0, M0</td>
<td>T2-T3, pN0, M0</td>
<td>T2-T3, cN0, M0</td>
<td>T4, N0, M0</td>
<td>Tis-T4, N1a, M0</td>
<td>Tis-T4, N1b/N2, M0</td>
<td>M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic Grade</th>
<th>GX</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cannot be assessed</td>
<td>Well differentiated</td>
<td>Moderately differentiated</td>
<td>Poorly differentiated</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

The role of sun exposure as a factor contributing to MCC development.\(^{181}\)

The observation of clonal integration of polyomavirus (MCPyV) in human MCC by Feng et al. in 2008 initiated great interest in the study of viral tumorigenesis.\(^{182–184}\) MCPyV is a nonenveloped, double-stranded DNA virus with a reported prevalence in MCC lesions ranging from 77% to 86%.\(^{182,185–187}\) Notably, it is not exclusively observed in MCC, but has also been detected in normal skin and cSCC.\(^{188–192}\) Some studies also attempted to demonstrate the association of improved survival with the presence of MCPyV\(^{187,193}\); other studies were not able to show the prognostic relevance of MCPyV.\(^{186,194}\) Although the emerging role of MCPyV provides promising insights into the etiology of MCC, the exact molecular pathogenesis has yet to be elucidated fully.

**TREATMENT.** Currently, the main treatment modalities for MCC are surgical resection and radiotherapy, although much controversy exists regarding the specific role of each modality. The following are the updated NCCN consensus recommendations for the treatment of MCC.

Wide local excision (WLE) of the primary tumor with negative margins is the standard treatment for newly diagnosed MCC patients without evidence of metastasis. The current recommendation for surgical margins depends on the clinical size of the tumor: a 1 cm margin for ≤2 cm
tumors and 2 cm margins for >2 cm tumors. Almost one-third of clinically node-negative patients have microscopic nodal disease; therefore, for untreated primary tumors, sentinel lymph node (SLN) biopsy is recommended at the time of WLE, examined by both hematoxylin and eosin (H&E) and immunoperoxidase staining, including CK20. If the SLNs are positive, completion lymph node dissection with subsequent radiotherapy of the basin is recommended.

MCC has been shown to be a radiosensitive tumor, and radiotherapy is currently used as an adjuvant therapy to surgery in the majority of cases. In one study of 1254 MCC patients, surgery combined with local radiotherapy was shown to significantly decrease the incidence of local and regional recurrence compared with a control group treated with surgery alone. Another study demonstrated improved survival in patients who underwent adjuvant RT. In inoperable cases radiation monotherapy can provide an alternative therapeutic option.

The role of chemotherapy in MCC treatment remains controversial. In general, MCC chemotherapy regimens are adapted from those used for small cell carcinoma of the lung. The most common agents include a combination of platinum-containing agents with etoposide, which are associated with significant morbidity and, rarely, mortality. There have been no randomized trials evaluating the efficacy of chemotherapy. Even in patients with locally advanced or distant disease showing initial response to chemotherapy, chemotherapy thus far has not shown any survival benefit. Chemotherapy is, therefore, used mostly as palliative treatment in disseminated disease rather than as primary or adjuvant therapy.

**DERMATOFIBROSARCOMA PROTUBERANS**

**EPIDEMIOLOGY AND PRESENTATION.** DFSP is a rare, locally aggressive mesenchymal neoplasm with a generally low malignant potential. Its incidence ranges from 0.8 to 4.5 cases per million people per year, accounting for 2% to 6% of all soft-tissue sarcomas diagnosed in the United States. It typically affects middle-aged individuals with males more commonly affected than females (3:2 ratio), and presents as an erythematous to violaceous dermal plaque or exophytic tumor with surrounding telangiectases. The most commonly involved anatomic sites include the trunk (47%), followed by the lower extremity (20%), upper extremity (18%), and head and neck (14%). The lesions show an initial indolent radial growth pattern with satellite peripheral nodules; if untreated, the lesion grows vertically, invading underlying structures including subcutaneous tissue, fascia, muscle, or bone with satellite nodules coalescing into a larger tumor to give it its "protuberant" appearance. The diagnosis is made by histologic evaluation, often confirmed by immunohistochemistry, most notably by the presence of CD34, hyaluronate, and vimentin, and the absence of factor XIIIa and S100.

**PATHOGENESIS.** DFSP is characterized by a specific cytogenetic abnormality. In 1997 Simon et al. identified the fusion gene COL1A1/PDGFβ resulting from the rearrangement of upstream regions of the COL1A1 gene in 17q21 to 17q22 and exon 2 of PDGF in 22q13.1. This translocation results in the deregulation of platelet-derived growth factor-beta (PDGFβ) expression, thus producing continuous autocrine activation of tyrosine kinase PDGF Receptor B (PDGFRB). This mechanism is thought to be fundamental to the development of DFSP, as this fusion gene was observed to be present in nearly all cases of DFSP. The fusion gene product COL1A1/PDGFβ provides a useful molecular diagnostic test as well as a target for new molecular therapeutic options.

**TREATMENT.** The standard of care in the treatment of patients with localized DFSP is complete resection with negative margins. The NCCN guidelines recommend some form of complete histologic surgical margin evaluation whenever possible, implementing different approaches including: MMS; modified MMS (MMS technique with an additional final margin taken for permanent section assessment); CCPDMA; and 2 to 4 cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible. Recent studies conducted in different parts of the world consistently show a significant decrease in the rate of recurrence (under 10%), compared to the recurrence rate of 20% to 60% reported in older studies. Especially in anatomically challenging areas such as head and neck, MM5S was shown to achieve a high cure rate, with the local recurrence rate averaging approximately 1.5%. The efficacy of RT as primary therapy for DFSP is still controversial given the scant data available. Currently, RT is not indicated routinely and is mostly utilized in the adjuvant setting when negative margins cannot be achieved surgically.

DFSP metastasis to the lymph nodes is extremely rare. Although the management strategy is controversial, lymphadenectomy is generally recommended for patients with lymph node spread. In extremely rare cases of hematogenous metastases, the lungs are the most common site of involvement, followed by brain, bone, and other soft tissues. For isolated, resectable metastatic disease, resection is recommended.

Systemic treatment is indicated for metastatic disease and surgically unresectable cases. As discussed previously, the majority of DFSP tumors have the characteristic fusion gene product, COL1A1/PDGFβ, which is the molecular target of the small molecule tyrosine kinase inhibitors (TKI), such as imatinib, sunitinib, and sorafenib. Imatinib, a chemotherapeutic agent commonly used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, inhibits the PDGFR and other receptor tyrosine kinases, such as c-kit. There have been multiple studies, including large retrospective series and multicenter prospective phase II trials, demonstrating that most patients with advanced DFSP with this specific translocation benefit from imatinib therapy. Interestingly, one case report in a patient with locally advanced DFSP with a negative 17q,22 translocation by RT-PCR showed a partial response to imatinib. These promising results promoted interest in the use of imatinib in the neoadjuvant setting for large unresectable or recurrent tumors. Early studies have demonstrated potential benefits, including...
a decreased extent of excision and reconstruction and an improved rate of complete resection with negative margins.212,249,253–257 The current NCCN guidelines recommend molecular analysis prior to initiation of imatinib. In the United States and Europe, imatinib treatment is indicated for adult patients with unresectable, recurrent and/or metastatic DFSP (Fig. 29-8).

The management of advanced NMSC appears to be entering a new phase of creative growth as new molecular targets are being discovered and translational research materializes into clinical applications.258 The age of rationally designed molecular medicine not only instills hope but also raises concern for untoward effects that have yet to be elucidated. As new generations of drugs reach the clinic, we have reasons to be cautiously optimistic regarding the prognosis of those patients with advanced NMSC who were considered beyond hope just a generation ago.

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