Comprehensive care for Cutaneous Squamous Cell Carcinoma
No Financial or Disclosures to report
Learning Objectives

- Etiopathogenesis of Actinic Keratosis
- Risk Factors for developing Actinic Keratosis
- Treatment options for Actinic Keratosis
- Actinic Keratosis prevention
- Prognosis Squamous cell skin cancer developing from Actinic Keratosis
- Prognosis for Squamous cell skin cancer developing from Bowen’s Disease
- Squamous cell skin cancer workup and risk status
- Squamous cell skin cancer primary and adjuvant treatments
- Treatment of palpable or abnormal regional lymph nodes
- Squamous cell skin cancer follow-up and Recurrence/Disease progression
- Squamous cell skin cancer Risk factors for local recurrence or metastasis
- Principles of treatment for squamous cell skin cancer
- Identification and management of High risk patients
Ever been curious about your skin?
Out of 193 species of monkeys and apes only humans (*Homo sapiens sapiens*) are not covered in hair.
“Somebody should tell us right at the start of our lives that we’re dying. Then we might live life to the limit. Every minute of every day. Whatever you want to do, do it now. There are only so many tomorrows.”

-Pope Paul VI
The patient reported that he had driven a delivery truck for 28 years.

- Ultraviolet A (UVA) rays transmit through window glass, penetrating the epidermis and upper layers of dermis.
  - Chronic UVA exposure can result in thickening of the epidermis and stratum corneum, as well as destruction of elastic fibers.
  - This photoaging effect of UVA is contrasted with photocarcinogenesis.
    - Although exposure to ultraviolet B (UVB) rays is linked to a higher rate of photocarcinogenesis, UVA has also been shown to induce substantial DNA mutations and direct toxicity, leading to the formation of skin cancer.

- The use of sun protection, topical retinoids and periodic monitoring for skin cancer were recommended for the patient.
ACTINIC KERATOSIS

- Epidemiology
  - Actinic keratoses (AKs) are very common, premalignant lesions, with the potential of becoming invasive squamous cell carcinomas (SCC).

- Risk factors:
  - Individual susceptibility (older age, male gender, fair skin phenotype, and light eye color), immunosuppression, lifetime sun exposure, and some genetic syndromes such as albinism and xeroderma pigmentosum.
Etiology

- Ultraviolet radiation B (UVB) from sunlight is responsible for AK development.
  - It triggers the formation of thymidine dimers both in DNA and RNA, resulting in mutated keratinocytes.
  - The mutations occur on the tumor suppressor gene p53 within the keratinocytes resulting in impairment of the mechanism of apoptosis. Therefore, clonal expansion of mutated keratinocytes may occur leading to the formation of AKs.
Clinical Presentation

- Patients are usually elderly with fair complexion and evident solar elastosis due to a history of chronic sun exposure.
  - Therefore, lesions are commonly found on sun-exposed areas (head, neck, forearms, dorsal hands) with 60% found on upper extremities. Typical AKs appear as erythematous, flat, rough macules or papules.
    - Better felt than seen
Several forms of therapy are available for the treatment of AKs, including:
- lesion targeted therapy
- field-directed therapy
- oral therapy
Lesion targeted therapy

- Cryotherapy: The most common treatment for AKs with a cure rate of 98.8%
- Topical treatment with 5-FU or Imiquimod
- Curettage, with or without electrosurgery: it is quite effective, at the expense of potential scarring
- Shave Excision: indicated when AK is suspicious for SCC or BCC and histopathologic examination is needed
- Photodynamic Therapy (PDT) with Aminolevulinic Acid (ALA): Found to have similar effectiveness, but better cosmetic outcome, when compared to cryotherapy for single lesions
- Other treatment options that may be considered include
  - topical diclofenac (category 2B)
  - Chemical peels
  - Ablative skin resurfacing
Prognosis

- Reports in the literature on the risk of AK progression into invasive SCC ranges from 0.025% to 16% per year and the average rate of risk is approximately 8% among the studies reviewed.

- A more recent systematic review showed that progression rates of AK to SCC ranged from 0% to 0.075% per lesion-year.
Prevention

- Sun avoidance
- Sunscreen
- Oral Niacinamide 500mg PO TID
- Topical 5% Efudex (5-Fluorouracil, 5-FU) cream
- Oral Retinoids (acitretin, isotretinoin) in certain high risk patients
- Monthly self skin examinations taught to patient
Bowen’s disease (BD) is a form of squamous cell carcinoma (SCC) in situ that may occur both in skin and mucous membranes.

- The exact incidence of BD is unknown.
- It affects elderly adults of both sexes, with a slight predominance in the female gender.

Multiple etiologic factors have been associated with the development of BD including:

- Chronic sun exposure
- Arsenic exposure
- Ionizing radiation
- Immunosuppression
- Human papilloma virus (HPV)
Erythroplasia of Queyrat is a term used to designate mucosal BD confined to the genitals.

- It is primarily seen in uncircumcised men and typically involves the inner surface of the foreskin, the glans penis, as well as the coronal sulcus.
- In women, it is most commonly found on the labia minora.
Prognosis

- It is estimated that approximately 5% of patients with BD develop invasive SCC.
  - 13% of these carcinomas will metastasize
    - of these cases, 10% will result in death.
Risk factors:

- chronic sun exposure
- skin types I and II
- chemical carcinogens (arsenic, tobacco, coal, tar)
- immunosuppression (due to immunosuppressive treatment in transplant patients, or immunodeficiency syndromes such as HIV)
- chronic ulcers
- burn scars
- genetic syndromes (e.g., xeroderma pigmentosa)
SCC is the second most common skin cancer accounting for approximately 20% of all NMSC

- UVB radiation is the major causative agent for the development of SCC.
  - It produces specific mutations (C to T transitional mutations) in the tumor suppressor gene p 53
  - Recently loss of function of NOTCH1 and NOTCH2 identified in 75% of cutaneous SCCs

- It is more common in the male gender (a lifetime risk 9-14% in men vs. 4-9% in women)

- The incidence also increases with age (35 times higher in individuals older than 75 years of age when compared to ages 50-55)
  - The incidence of SCC doubles for each 8 to 10 degree decline in latitude; therefore populations living closer to the equator have a greater risk
Etiology

- Actinic keratosis (AK) is the precursor lesion of SCC.
  - There is a sequence or continuum between actinic keratoses, SCC in situ (Bowen’s disease) and invasive SCC.
  - However, some SCCs develop de novo and do not form from a previous AK.
  - Keratinocytes with one mutation in p53 after UV radiation may undergo apoptosis.
  - However, if these keratinocytes with mutated p53 suffer a second hit or mutation, then they become resistant to further apoptosis and instead experience clonal expansion.
    - This is clinically evident as actinic keratoses.
      - Uncontrolled proliferation of these abnormal keratinocytes leads to the development of SCC in situ and ultimately invasive SCC.
Human papilloma virus (HPV) infection has been linked with cutaneous SCC.
- Lesions on the genitals have been associated with HPV 6 & 11
- HPV 16 has been found in periungual lesions
Clinical Manifestations

- **SCCs**
  - Usually present as firm, skin-colored to pink, papules or plaques, commonly found on the head and neck region of elderly individuals
    - Other locations include the trunk, arms, dorsal hands and legs.
  - Hyperkeratosis, ulceration or crusting may be found on its surface.
  - Symptoms such as itching, pain and bleeding may be associated with the lesion.

- **Histopathology**
  - Histopathologic evaluation of SCC reveals a proliferation of atypical keratinocytes that extends beyond the basement membrane into the dermis.
Treatment

- Curettage and Electrodeessication (C & E)

- Cryotherapy for small, superficial, low-risk Lesions +/- Topical Immunotherapy creams (Efudex BID x 2-3 weeks)

- Conventional excision for low risk SCCs
  - Low-risk
    - less than 2cm in diameter
    - well differentiated pattern
    - located on the trunk or extremities
  - Recommended margins are 4 mm

- Overall cure rates with non-Mohs modalities for tumors greater than 2 cm is 58.3%
  - well-differentiated SCCs 81%
  - poorly differentiated lesions 46.4%
Mohs micrographic surgery
- Overall cure rates are estimated to be as high as 98.1% for lesions less than 2 cm
- Drop to 74.8% for those larger than 2 cm
- Well differentiated SCCs have a 97% cure rate with Mohs
- Rate drops to 67.4% for poorly differentiated lesions
  - Mohs is nonetheless indicated for primary aggressive SCC’s of any size, in either immunocompetent or immunocompromised hosts, as well as in any location of the body.

Mohs
- Is not indicated for any primary AK with focal SCC in situ of any size or anatomical location, regardless of host immune status
• Radiation therapy
  ○ used in combination with other modalities to treat aggressive, recurrent, large, inoperable tumors or elderly patients that may not tolerate surgical procedures
Prognosis

- The 10-year survival rate for individuals with regional and distant metastases is 20% and less than 10%, respectively.
  - When metastases occur, regional lymph nodes are more commonly affected
  - Hematogenous spread usually involve lungs, liver, brain, skin, and bone
- Management of the patients with high-risk cutaneous SCC and no clinical nor radiological evidence of regional metastasis remains controversial.
  - “watchful waiting” approach vs. elective lymph node dissection
On clinical presentation of patient with suspicious lesion, workup for both BCC and SCC:

- Begins with hx and physical exam
  - For BCC, emphasis on complete skin exam
  - For SCC, “” + regional lymph node examination.

- A full skin exam recommended b/c individuals with a skin cancer often have additional, concurrent pre-cancers or cancers located at other sites usually in sun exposed areas.
  - These individuals also increased risk of cutaneous melanoma.
Clinical Presentation and Work-up

- Skin biopsy performed on any suspicious lesion
  - Should include deep reticular dermis if more than superficial process suspected.
    - This is preferred as histology may sometimes be present only deeper, advancing margins of a tumor and superficial biopsies will frequently miss this component.

- High risk populations may be difficult to clinically assess and a low threshold for performing skin biopsies in these patients is necessary.

- Imaging may be done in all pts clinically indicated when extensive disease such as bone involvement, perineural invasion, deep soft tissue involvement, or lymphovascular invasion (for SCC) is suspected.
  - MRI more preferred over CT if perineural invasion suspected because more sensitive.
Clinical Presentation and Work-up

- Pt with palpable lymph node or abnormal nodal involvement noted on imaging
  - should prompt a fine needle aspiration (FNA) for diagnosis.

- On rare occasions may have extensive bone or cause significant local tissue destruction/distortion
  - would be appropriate to order imaging studies prior to excision for evaluation of margins.
After workup, a risk assessment of NMSC should be performed to determine the treatment plan.

- Again, for SCC, patients should also be evaluated for lymph node involvement.
Location

- Location has been known to be a risk factor for NMSC recurrence and metastasis for many years.

- The location and size criteria are mainly based on a 27-year retrospective review of 5755 BCCs by the Skin and Cancer Unit of the New York University School of Medicine.
  - The high-risk sites correspond roughly to the mask areas of the face.
  - Recurrences in the NYU study were significantly more common when tumors in high-risk locations were 6 mm or more in diameter and when tumors in moderate-risk locations were 10 mm or more in diameter.

- In general, both BCC and SCC that develop in the head and neck area are more likely to recur than those developing on the trunk and extremities. SCCs that develop on the genitalia, mucosal surfaces, and ears are also at greater risk of metastasizing. The concept of a so-called high-risk “mask area of the face” dates back at least to 1983.
Size

- Size also has been shown to be a risk factor for NMSC recurrence.
  - Various different divisions have been used; the most common has been greater than or less than 2 cm in diameter.
Appropriate Use Criteria (AUC)

- Based on 270 clinical scenarios including 69 BCCs and 143 SCCs.
  - Document for treatment of cutaneous neoplasms developed by The American Academy of Dermatology (AAD), American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery
  - These criteria also in agreement with similar work performed at the national level for the Centers for Medicare & Medicaid Services (CMS) that defines high-risk tumors appropriate for Mohs micrographic surgery.
Immunosuppression

- Immunosuppression is one key prognostic factor for metastasis in a prospective study by Brantsch and colleagues.
  - Organ transplantation
  - Long-term use of psoralen + UVA light (PUVA) significantly increase the incidence of SCC development.
    - BCC incidence also increases slightly in these settings
- The organ transplant literature provides evidence of aggressive tumor behavior.
  - The incidence of metastatic SCC is significantly greater in this population than in individuals who have not received a transplant (reviewed by Euvrard et al).
• BCC risk of recurrence & metastasis
  - A retrospective review of 307 patients with SCC confirmed that those who received organ transplants had more aggressive disease than those who did not, although the difference was not noted among 246 patients with BCC.
    - Uncertainty remains whether this is simply because of a greater number of tumors per patient or if this reflects more aggressive tumor behavior at the biological level.
  - Limited data suggest BCCs are more likely to recur or metastasize when they develop in immunosuppressed individuals.
    - Nevertheless, because of this evidence and the NCCN Panel Members’ own anecdotal experiences, the panel decided to classify both BCC and SCC that develop in settings of immunosuppression as potentially high-risk tumors.
  - Because organ transplant recipients have collectively worse outcomes, these patients and their neoplasms are designated as high risk.
Prior RT

- Tumors developing in sites of prior radiotherapy refer to primary NMSCs arising in areas within radiation fields given previously for unrelated conditions.
  - All recurrent tumors, irrespective of prior therapy, have already been defined as high risk
  - More historic studies provide data, although old, support prior radiotherapy for unrelated (frequently benign) conditions as a risk factor for NMSC recurrence or metastasis
Perineural Involvement

- Poses a greatly increased risk of recurrence, whether the tumor is a BCC or SCC, and an increased risk of metastasis for SCC.
- In a prospective cohort study of 315 patients with cutaneous SCC of the head and neck, Kyrgidis and colleagues identified perineural involvement as a factor associated with:
  - Lower overall survival
  - Decreased recurrence-free survival
Perineural Involvement

- Although perineural involvement is uncommon in any NMSC (2%–6%), it develops much more frequently in SCC than in BCC.
  - Associated with other risk factors including:
    - recurrent tumors
    - high grade
    - larger lesion size
  - SCC involving unnamed small nerves (<0.1 mm in caliber)
    - may have a low risk of poor outcomes in the absence of other risk factors
  - If large nerve involvement is suspected
    - MRI should be considered to evaluate extent and rule out skull involvement
In 1920 Broder’s grading system of Histologically dividing cancers into grades I-IV

- Broder initiated this quantitative grading of cancer in 1920 and his classification system has been used for many years.
  - A lack of correlation between Broder's’ grading system and prognosis.
- One of the main reasons is that, SCCs usually exhibit a heterogenous cell population with differences in the degree of differentiation.
The modern trend has been to reduce the divisions to two groups: 1) well or moderately differentiated; and 2) poorly differentiated.

- The NCCN Panel has adopted this modern approach in their guideline.

In their extensive meta-analysis of risk factors for local recurrence and metastasis of SCC, Rowe and colleagues found that patients with well-differentiated tumors fared significantly better than those patients with poorly differentiated lesions.

- Another cohort study of 315 patients also associated differentiation grade with overall survival.
- Eroglu and colleagues reported differentiation to be a significant risk factor of recurrence in an analysis of 1039 patients.

- Leffell and colleagues documented an increased percentage of BCC with aggressive histologic growth patterns in young persons.
  - Young Age is not a risk factor
    - Whether young age (typically, younger than 40 years) is an independent risk factor for aggressive NMSC behavior is debatable....
      - histologic feature is already a separate risk factor in the algorithm.
The NCCN Panel identified a few additional clinical parameters that increase the risk for SCC as follows:

- SITE OF A CHRONIC INFLAMMATORY PROCESS
- RAPID GROWTH TUMOR
- NEUROLOGIC SYMPTOMS IN REGION OF TUMOR
- HISTOLOGIC SUBTYPE
- DEPTH
A substantial body of literature has documented increased rates of metastasis for cutaneous SCC arising in the setting of chronic scarring.
Rapid Growth Tumor

- Only one article in the literature documents rapid growth of a cutaneous SCC as a risk factor for increased metastasis and even death.
  - Nevertheless, the NCCN Panel Members unanimously agreed this is a rare, albeit definite, clinical setting indicative of high-risk behavior.
For Tumors with Perineural Involvement clinical symptoms suggesting possible involvement of sensory or motor nerves may occur in up to 40% of cases.

- Symptoms may include pain, burning, stinging, anesthesia, paresthesia, facial paralysis, diplopia, and blurred vision.
- Any suggestion of neurologic involvement in the region of a SCC should place that tumor in a high-risk category.
Histologic Subtype

- Adenoid (or acantholytic) and adenosquamous (or mucin-producing) SCC are markers for an increased risk of recurrence or metastasis.
  - Only a few older studies document the prognostic significance of these subtypes.
  - However, because these tumors likely would not be included in the high-risk category on the basis of their degree of differentiation, the panel decided to list them as separate risk factors.

- Another high-risk histologic feature reported in the literature is the presence of desmoplasia.
  - In studies from Germany, desmoplastic cutaneous SCC was shown to pose a greatly increased risk of both recurrence and metastasis.
  - A recent review of 72 patients with desmoplastic SCC reported a high rate of recurrence of 80%.

- Risk of metastasis in SCC in situ is negligible (full thickness atypia)
  - *However risk of recurrence depends on presence or absence of any risk factors
Brantsch and colleagues prospectively examined potential risk factors for metastasis and local recurrence of SCC in 615 patients over a 20-year span with a median follow-up of 43 months.

- Metastasis occurred in:
  - 0% of tumors 2.0 mm in thickness
  - 4% of tumors 2.1 mm to 6.0 mm in thickness
  - 16% of tumors thicker than 6.0 mm

- Thicker lesions were also associated with a heightened risk of local recurrence.
A small, somewhat older body of literature found an association between invasion of SCC into the deep reticular dermis or subcutaneous adipose (corresponding to a Clark level IV or V melanoma) and aggressive behavior.

- Several more studies have suggested that squamous cell tumor depth, as measured in millimeters (similar to Breslow’s original work with melanoma), may also have prognostic value.
- A meta-analysis of SCC risk factors for recurrence and metastasis found that both types of depth measurements have prognostic value.
<table>
<thead>
<tr>
<th>Level</th>
<th>Clark</th>
<th>Breslow</th>
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<tbody>
<tr>
<td>I</td>
<td>No cells have penetrated the dermoepidermal junction</td>
<td>$\leq 0.75$ mm</td>
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<tr>
<td>II</td>
<td>Some cells are found in the papillary dermis</td>
<td>$0.75 - 1.5$ mm</td>
</tr>
<tr>
<td>III</td>
<td>Cells fill the papillary dermis</td>
<td>$1.51 - 2.25$ mm</td>
</tr>
<tr>
<td>IV</td>
<td>Cells invade the reticular dermis</td>
<td>$2.25 - 3.0$ mm</td>
</tr>
<tr>
<td>V</td>
<td>Cells invade into fat</td>
<td>$&gt; 3.0$ mm</td>
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Excluded Parameters

- The presence or absence of an infiltrative component at the advancing border of an SCC was one parameter discussed by the NCCN Panel.
  - Some authors have advocated this parameter as a risk factor
    - The pathologists on the NCCN panel believe this feature usually correlates well with the degree of differentiation, and it is a descriptive term not routinely applied to SCC.

- Similarly, the histologic subtype termed “spindle cell squamous cell cancer” has been associated with perineural invasion which, in and of itself, is a risk factor for aggressive SCC behavior
  - However, the panel decided this indirect association did not warrant the listing of spindle cell SCC as a separate risk factor.
High Risk Patients for Developing Multiple SCCs

- Individuals with immunocompromised status or rare genetic disorders such as Xeroderma pigmentosum are at increased risk of multiple SCCs
  - Clinicians are advised to follow the Identification and Management of High-Risk Patients for detailed guidance on the treatment of pre-cancers and skin cancers for these patients.
Treatment for Low-Risk NMSC

- **Primary treatment options for low-risk local SCC include:**
  - 1) **C&E**
    - In areas without hair growth provided that the treatment be changed to excision if the adipose is reached
  - 2) **Excision with Postoperative Margin Assessment (POMA) with 4 to 6 mm margins for SCC**
    - With reconstruction techniques such as:
      - linear closure
      - secondary intention healing
      - skin graft
  - 3) **RT**
    - For non-surgical candidates
      - generally limited to those over 60 years of age because of long-term toxicity and risk of secondary malignancy
If margins are positive after excision:

- Patients should receive adjuvant therapy:
  - Surgery (Preferred Choice)
    - Mohs surgery
    - Resection with complete circumferential peripheral and deep margin assessment (CCPDMC)
    - Re-excision with POMA for low risk anatomical regions
  - Radiation may be administered to non-surgical candidates
Options for high-risk lesions include:

- Mohs surgery or resection with CCPDMA
- Excision with POMA with wider surgical margins and primary or delayed repair
- RT for non-surgical candidates

- Patients treated with Mohs surgery or resection with CCPDMA should receive adjuvant radiation if clear margins cannot be achieved
  - In this case, clinicians should consider multidisciplinary board consultation for patients with SCC
  - Chemoradiation or clinical trial should be included in the discussion.
Treatment for High-Risk NMSC cont.

- Adjuvant RT is also recommended for patients with negative margins after Mohs surgery but with large nerve or extensive perineural involvement.
  - Due to the potential for skull involvement and intracranial extension, an MRI should be considered if large-nerve invasion is suspected.

- If negative margins are not achieved after excision with POMA
  - Patients should undergo one of the following
    - Mohs surgery
    - Resection with CCPDMA
    - Adjuvant RT

- For certain high-risk SCC lesions, sentinel lymph node mapping may be considered.
  - A systematic review of 692 patients with SCC reported positive sentinel nodes in 24% and 21% of anogenital and non-anogenital patients, respectively.
    - The survival benefits of sentinel lymph node biopsy remain unclear.
Regional LN Involvement

- For patients with SCC, regional nodal involvement significantly increases the risk of recurrence and mortality.
  - Nodal metastasis also commonly coincides with other adverse histopathologic findings such as lymphovascular invasion, poor differentiation, and perineural invasion
  - About 60% to 82% of patients presenting with nodal disease show involvement in the parotid gland
  - Cervical neck node disease without parotid invasion is observed in 18% to 41% of cases
Parotid Involvement

- Parotid involvement, as direct extension from an overlying cutaneous SCC, is a poor prognostic factor for SCC.
  - If the cancer extends down into the parotid fascia (ie, into the parenchyma), a superficial parotidectomy needs to be performed, as disease-specific survival is inferior with radiation alone.
  - The 5-year overall survival rate of patients treated by parotidectomy and adjuvant RT is 72%.
Nodal Metastasis

- Lymph node dissection plus adjuvant RT with or without concurrent chemotherapy is currently the standard of care
  - Data on SCC with nodal metastasis are limited to single-center case reviews

- A retrospective study of 167 patients with metastatic disease to nodes in the head and neck found with the addition of adjuvant RT to surgery compared to surgery alone
  - Decreased locoregional recurrence (20% vs. 43%)
  - Improved 5-year disease-free survival (73% vs. 54%)

- Similarly, in a single-institution analysis involving 52 patients with node-positive SCC of the head and neck, RT
  - Reduced the risk of death (HR, 0.18; 95% CI, 0.06–0.54)

- By the addition of adjuvant radiation in another study of 54 patients with SCC metastasized to cervical lymph nodes
  - Overall survival improved
  - Disease-free survival improved
Systemic Therapy

- A 10-year cohort study involving 985 patients with SCC found:
  - 3.7% risk of metastasis
  - 2.1% risk of disease-specific death

- In a review of 28 observational studies, systemic therapy in patients with SCC not amenable to local therapy
  - Reported response in 72% of patients
Systemic Therapy

- Cutaneous SCC with distant metastasis, while rare, is more common than metastatic BCC
  - No prospective phase III studies currently available
    - Cisplatin either as a single agent or combined with 5-FU has occasionally produced useful responses
      - Data is limited on cisplatin efficacy; actually scant evidence available regarding systemic therapy for the condition entirely

- In the only phase II study of biochemotherapy with interferon alfa, cis-retinoic acid, and cisplatin
  - 35 patients were assessed for response
    - 11 of whom had distant metastases
      - 1 of the 11 patients experienced a complete response
    - 12 patients with only regional lymph node metastases were treated
      - 2 partial response
      - 1 complete response
      - This lends some credence to a cisplatin-based regimen
Some have advocated using therapies useful in metastatic squamous cell head and neck cancer for patients with metastatic cutaneous SCC

- A small but growing number of case reports and one phase II study demonstrate sometimes dramatic tumor regression with the use of cetuximab in unresectable or metastatic SCC
  - The low toxicity profile of cetuximab holds an advantage over the toxic cisplatin regimen
  - Response to gefitinib has been documented in patients with recurrent or metastatic SCC in a phase II trial
What should be managed by a multidisciplinary tumor board?

- Complicated high-risk tumors
- Regional recurrence
- The development of distant metastasis
Recommendations

- Patients with metastatic SCC should receive appropriate therapy
  - NCCN encourages participation in a clinical trial
    - Trials for SCC Scarce due to high costs involved
  - Possible agents include:
    - cisplatin monotherapy
    - cisplatin plus 5-FU
    - epidermal growth factor receptor (EGFR) inhibitors such as cetuximab
  - If the patient is a solid organ transplant recipient taking immunosuppressive therapy
    - Should consider reducing the doses of immunosuppressive agents where appropriate
    - May try minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors
Follow-Up

- For follow-up schedules two well-established points to be aware of:
  - **1st point**
    - **30%-50%** of patients will develop another NMSC within **5 years**!
      - This represents a **10-fold** increase in risk compared to the general population
        - Recall, also at increased risk of developing cutaneous melanoma
  
  - **Second point**
    - **70% to 80%** of all cutaneous SCC recurrences develop within **2 years** of initial therapy!
      - **More frequent follow-ups** with these pts during this time period is critical.
- **Patient education** on values of continued long-term surveillance
- **Patient education** on values of sun protection
- **Patient education** on values of regular self-examination of the skin
This Web page provides evidence-based cancer information for health professionals about the genetics, prevention, screening, and treatment of skin cancer, as well as resources for supportive and palliative care. Information on skin cancer research, such as active clinical trials, clinical trial results, and other research findings, is also provided.

The PDQ® cancer information summaries provide comprehensive, peer-reviewed, evidence-based information intended to inform and assist clinicians who care for cancer patients. The summaries include level-of-evidence designations to help readers understand the strength of the evidence supporting the use of specific interventions or approaches.

Skin Cancer Treatment (PDQ®)

- This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of skin cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

- This summary is reviewed regularly and updated as necessary by the PDQ Adult Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).


You can register with NCBI and may request to receive e-mail alert when this is update

• Prevention Guidelines. Skin Cancer Foundation. Available at: http://www.skincancer.org/skin-cancer-in

  o The Skin Cancer Foundation is the only international organization devoted solely to education, prevention, early detection, and prompt treatment of the world’s most common cancer. Take your stand against skin cancer

  o The NCI has booklets and other materials for patients, health professionals, and the public. These publications discuss types of cancer, methods of cancer treatment, coping with cancer, and clinical trials. Some publications provide information on tests for cancer, cancer causes and prevention, cancer statistics, and NCI research activities. NCI materials on these and other topics may be ordered online or printed directly from the NCI Publications Locator. These materials can also be ordered by telephone from the Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237).
Your clothes are the single most effective form of protection against the sun’s harmful ultraviolet (UV) rays. They can absorb or block much of this radiation.
Help Us Stop Tanning on College Campuses
How You Can Take Action

Sun Safety at School
Learn How to Make Your School Sun Safe

TAKE A STAND
Host a Fundraising Event in Your Community

Learn How
Skin cancer prevention and early detection.
American Cancer Society.
Available at:
• SPOT skin cancer. American Academy of Dermatology.
Available at:  https://www.aad.org/spot-skin-cancer
NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.
## Risk Factors for Local Recurrence or Metastases

<table>
<thead>
<tr>
<th>H&amp;P</th>
<th>Low Risk</th>
<th>High Risk</th>
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<td></td>
<td>Area M $&lt;$ 10 mm&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Area M $\geq$ 10 mm</td>
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<td></td>
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<tr>
<td><strong>Borders</strong></td>
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<td><strong>Primary vs. recurrent</strong></td>
<td>Primary</td>
<td>Recurrent</td>
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<tr>
<td><strong>Immunosuppression</strong></td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Site of prior RT or chronic inflammatory process</strong></td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Rapidly growing tumor</strong></td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Neurologic symptoms</strong></td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

### Pathology

- **Degree of differentiation**: Well or moderately differentiated, Poorly differentiated
- **Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic or basosquamous (metatypical) subtypes**
- **Depth<sup>2,3</sup>: Thickness or Clark level**: <2 mm or I, II, III, 2 mm or IV, V
- **Perineural, lymphatic, or vascular involvement**

<sup>1</sup>Must include peripheral rim of erythema.
<sup>2</sup>If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
<sup>3</sup>A modified Breslow measurement should exclude parakeratosis or scale crust, and should be made from base of ulcer if present.
<sup>4</sup>Location independent of size may constitute high risk.
DEFINITION

- Certain patient groups are at high risk for developing multiple squamous cell skin cancers and tumors that can behave aggressively. These include:
  - Organ transplant recipients
  - Other settings of immunosuppression (e.g., lymphoma, chronic lymphocytic leukemia, drug-induced, HIV)
  - Xeroderma pigmentosum
- Within these high-risk groups, individual high-risk patients should be identified for closer follow-up.
- Important individual risk factors include:
  - Total number of tumors
  - Frequency of development
  - Occurrence of aggressive tumors (e.g., extension beyond cutaneous structures, perineural involvement, large and poorly differentiated, having $\geq 3$ risk factors for recurrence)
- In these patients, urgent diagnosis and treatment of lesions are important, and nodal staging (radiologic or pathologic) may be considered in those with significant risk of nodal metastases.

DIAGNOSIS

- Skin lesions in these high-risk populations may be difficult to assess clinically. Therefore, a low threshold for performing skin biopsies of suspect lesions is necessary.
IDENTIFICATION AND MANAGEMENT OF HIGH-RISK PATIENTS

TREATMENT OF PRECANCERS
- Actinic keratoses should be treated aggressively at first development.
  - Accepted treatment modalities include cryotherapy, topical 5-fluorouracil, topical imiquimod, photodynamic therapy (eg, amino levulinic acid [ALA], porfimer sodium), and curettage and electrodesicication.
  - Other modalities that may be considered include diclofenac (category 2B), chemical peel (trichloroacetic acid), and ablative skin resurfacing (eg, laser, dermabrasion).
  - Actinic keratoses that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.
  - Ablative laser vermilionectomy may be of value in the treatment of extensive actinic cheilitis.

TREATMENT OF SKIN CANCERS
- Because patients in high-risk groups may develop multiple lesions in short periods of time, destructive therapy (eg, curettage and electrodesiccation, cryotherapy) may be a preferred treatment for clinically low-risk tumors, because of the ability to treat multiple lesions at a single patient visit. If curettage has been performed based solely on the clinical appearance of a low-risk tumor, the pathology from the biopsy taken at the time of curettage should be reviewed to make sure there are no high-risk pathologic features that would suggest the need for further therapy beyond curettage.
- In patients who develop multiple adjacent tumors in close proximity, surgical excision of invasive disease sometimes does not include surrounding in situ disease, and tissue re-arrangement is minimized. In situ disease may then be treated with secondary approaches.
- In patients with multiple adjacent tumors of the dorsal hands and forearms, en bloc excision and grafting have been used with efficacy. However, healing is prolonged and morbidity is significant.
- Compared to the low-risk population, radiation therapy is used more frequently as an adjuvant therapy and for perineural disease.
- Satellite lesions and in-transit cutaneous metastases may occur more frequently in this population. They must be treated aggressively with multidisciplinary tumor board consultation.
- In organ transplant recipients, decreasing the level of immunosuppressive therapy and/or incorporating mTOR inhibitors may be considered in cases of life-threatening skin cancer or the rapid development of multiple tumors.

FOLLOW-UP
- Follow-up schedules should be titrated to the frequency of tumor development, and in rare cases may be as frequently as weekly.
IDENTIFICATION AND MANAGEMENT OF HIGH-RISK PATIENTS

PATIENT EDUCATION

- Individual risk assessment is necessary and should be discussed.
- Both extensive and repetitive patient education regarding sun avoidance and protection is required.
- Sun avoidance and protection methods must be stringent.
- Monthly self examination of all skin surfaces is recommended. With a history of invasive skin cancer, self examination of the lymph nodes should be taught and performed.
- Rapid entrance into the health care delivery system at the onset of tumor development is critical.
- Patient education should begin, in the case of organ transplant recipients, at transplantation and in the case of xeroderma pigmentosum, at birth or diagnosis.

PREVENTION

- Use of oral retinoids (acitretin, isotretinoin) has been effective in reducing the development of actinic keratoses and skin cancers in some high-risk patients. Side effects may be significant. Therapeutic effects disappear shortly after cessation of the drug. Oral retinoids are teratogenic and must be used with extreme caution in women of child-bearing potential.
- Aggressive treatment of precancers can prevent the development of subsequent invasive tumors.
PRINCIPLES OF TREATMENT FOR SQUAMOUS CELL SKIN CANCER

- The goals of primary treatment of squamous cell skin cancer are the cure of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference.

- Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing radiation therapy as primary treatment in order to achieve optimal overall results.

- In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated.

- In patients with squamous cell carcinoma in situ (Bowen's disease) that is low-risk, alternative therapies such as 5-fluorouracil, imiquimod, photodynamic therapy (eg, amino levulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered even though cure rate may be lower.
# PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Dose Time Fractionation Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Diameter</strong></td>
<td><strong>Examples of Dose Fractionation and Treatment Duration</strong></td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>64 Gy in 32 fractions over 6–6.4 weeks</td>
</tr>
<tr>
<td></td>
<td>55 Gy in 20 fractions over 4 weeks</td>
</tr>
<tr>
<td></td>
<td>50 Gy in 15 fractions over 3 weeks</td>
</tr>
<tr>
<td></td>
<td>35 Gy in 5 fractions over 5 days</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>66 Gy in 33 fractions over 6–6.6 weeks</td>
</tr>
<tr>
<td></td>
<td>55 Gy in 20 fractions over 4 weeks</td>
</tr>
<tr>
<td>Postoperative adjuvant</td>
<td>50 Gy in 20 fractions over 4 weeks</td>
</tr>
<tr>
<td></td>
<td>60 Gy in 30 fractions over 6 weeks</td>
</tr>
</tbody>
</table>

### Regional Disease: All doses at 2 Gy per fraction using shrinking field technique

- After lymph node dissection
  - Head and neck; with ECE: 60–66 Gy over 6–6.6 weeks
  - Head and neck; without ECE: 56 Gy over 5.6 weeks
  - Axilla, groin; with ECE: 60 Gy over 6 weeks
  - Axilla, groin; without ECE: 54 Gy over 5.4 weeks
- No lymph node dissection
  - Clinically (-) but at risk for subclinical disease: 50 Gy over 5 weeks
  - Clinically evident adenopathy: head and neck: 66–70 Gy over 6.6–7 weeks
  - Clinically evident adenopathy: axilla, groin: 66 Gy over 6.6 weeks

---

1Field margins for <2 cm primary tumors should be 1-1.5 cm; for tumors >2 cm, field margins should be 1.5-2 cm. Tighter field margins can be used with electron beam adjacent to critical structures (eg, the orbit) if lead skin collimation is used. Bolus is necessary when using electron beam to achieve adequate surface dose. An electron beam energy should be chosen which achieves adequate surface dose and encompasses the deep margin of the tumor by at least the distal 80% line. Electron beam doses are specified at 90% of the maximal depth dose (Dmax). Orthovoltage x-ray doses are specified at Dmax (skin surface) to account for the relative biologic difference between the two modalities of radiation. If intensity modulated radiation therapy is used to treat primary tumors, appropriate focus must be directed at assuring that there is adequate surface dose. Appropriate medical physics support is essential.
### Table 1

**American Joint Committee on Cancer (AJCC)**

**TNM Staging Classification for Cutaneous Squamous Cell Carcinoma (cSCC)**

(7th ed., 2010)

**Primary Tumor (T)**

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
- **T1**: Tumor 2 cm or less in greatest dimension with less than two high-risk features**
- **T2**: Tumor greater than 2 cm in greatest dimension or Tumor any size with two or more high-risk feature
- **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

**Regional Lymph Nodes (N)**

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastases
- **N1**: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- **N2**: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- **N2a**: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- **N2b**: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- **N2c**: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- **N3**: Metastasis in a lymph node, more than 6 cm in greatest dimension

**Distant Metastasis (M)**

- **M0**: No distant metastases
- **M1**: Distant metastases
### Table 1 Continued

#### American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Cutaneous Squamous Cell Carcinoma (cSCC)  
(7th ed., 2010)

<table>
<thead>
<tr>
<th>Anatomic Stage/Prognostic Groups</th>
<th>Histologic Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
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<tr>
<td>Stage III</td>
<td>T3</td>
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<td></td>
<td>T1</td>
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<td>T2</td>
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<td>T3</td>
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<td></td>
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</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
</tr>
<tr>
<td></td>
<td>T Any</td>
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</tbody>
</table>
THANK YOU

Contact with any questions at dmullens@affderm.com
References


