Basal Cell and Squamous Cell Skin Cancers

Version 2.2005
NCCN Basal Cell and Squamous Cell Skin Cancer Panel Members

*Stanley J. Miller, MD/Chair
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

James Andersen, MD
City of Hope Cancer Center

Samuel W. Beenken, MD
University of Alabama at Birmingham Comprehensive Cancer Center

Daniel Berg, MD
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Glen Bowen, MD
Huntsman Cancer Institute at the University of Utah

Richard T. Cheney, MD
Roswell Park Cancer Institute

Frank Glass, MD
H. Lee Moffitt Cancer Center & Research Institute at University of South Florida

Roy C. Grekin, MD
UCSF Comprehensive Cancer Center

James M. Grichnik, MD, PhD
Duke Comprehensive Cancer Center

Timothy M. Johnson, MD
University of Michigan Comprehensive Cancer Center

Anne Kessinger, MD
UNMC Eppley Cancer Center at The Nebraska Medical Center

Nancy Y. Lee, MD
Memorial Sloan-Kettering Cancer Center

Stuart Lessin, MD
Fox Chase Cancer Center

Daniel D. Lydiatt, DDS, MD
UNMC Eppley Cancer Center at The Nebraska Medical Center

Lawrence W. Margolis, MD
UCSF Comprehensive Cancer Center

Kishwer S. Nehal, MD
Memorial Sloan-Kettering Cancer Center

Paul Nghiem, MD
Massachusetts General Hospital

Allan R. Oseroff, MD, PhD
Roswell Park Cancer Institute

E. William Rosenberg, MD
St. Jude Children’s Research Hospital/University of Tennessee Cancer Institute

Ashok R. Shaha, MD, FACS
Memorial Sloan-Kettering Cancer Center

Ronald J. Siegle, MD
Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

Arthur J. Sober, MD
Dana-Farber/Partners CancerCare

David Wrone, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

* Writing Committee member
Table of Contents

NCCN Basal Cell and Squamous Cell Skin Cancer Panel Members
Basal Cell Skin Cancer (BCC)
BCC Clinical Presentation, Workup, and Risk Status (BCC-1)
BCC Primary and Adjuvant Treatments
• Low Risk (BCC-2)
• High Risk (BCC-3)
BCC Follow-up and Recurrence (BCC-4)
BCC Risk Factors for Recurrence (BCC-A)
Principles of Treatment for Basal Cell Skin Cancer (BCC-B)
Radiotherapy for Basal Cell Skin Cancer (BCC-C)

Squamous Cell Skin Cancer (SCC)
SCC Workup, and Risk Status (SCC-1)
SCC Primary and Adjuvant Treatments
• Local, low risk (SCC-2)
• Local, high risk (SCC-3)
• Palpable regional lymph node (SCC-4)
• Palpable intraparotid mass (SCC-4)
SCC Follow-up and Recurrence/Disease Progression (SCC-5)
SCC Risk Factors for Recurrence (SCC-A)
Principles of Treatment for Squamous Cell Skin Cancer (SCC-B)
Radiotherapy for Squamous Cell Skin Cancer (SCC-C)
Identification and Management of High-Risk Patients (SCC-D)

For help using these documents, please click here

Staging
Manuscript
References

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus:
All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Guidelines Index Print the Basal Cell and Squamous Cell Skin Cancers Guideline

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2005.
CLINICAL PRESENTATION WORKUP RISK STATUS

Suspicious lesion → H&P
  • Complete skin exam → Biopsy
  • If more than superficial lesion, inclusion of deep reticular dermis preferred
  • Imaging studies as indicated for extensive disease

Low risk → See Primary Treatment of Low-Risk Basal Cell Skin Cancer (BCC-2)

High risk → See Primary Treatment of High-Risk Basal Cell Skin Cancer (BCC-3)

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

a See Risk Factors for Recurrence (BCC-A).
bAny high-risk factor places the patient in the high-risk category.
Primary Treatment of Low-Risk Basal Cell Skin Cancer

**PRIMARY TREATMENT**

- **C&E:**
  - In nonhair-bearing areas
  - If fat reached, surgical excision must be performed

- Or

- **Excision with POMA:**
  - If lesion can be excised with 4 mm clinical margins and secondary intention, side-to-side repair, or skin graft

- Or

- **RT** (category 2B):
  - Patients > 55 y: Area H, excluding genitalia, hands, and feet; or area M

**ADJUVANT TREATMENT**

- Mohs or resection with CCPDMA or RT or Re-excision with POMA for area L regions

Margins:

- Positive
- Negative

C&E = curettage and electrodesiccation
POMA = postoperative margin assessment
CCPDMIA = complete circumferential peripheral and deep margin assessment with frozen or permanent section

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.
Primary Treatment of High-Risk Basal Cell Skin Cancer

**PRIMARY TREATMENT**

- Excision with POMA
  - Lesion ≥ 20 mm in area L with no other high-risk factors, if can be excised with 10-mm clinical margins and primary repair
  - Mohs or resection with CCPDMA
    - RT (category 2B)
      - Patients > 55 y: < 15 mm in area H, excluding genitalia, hands, and feet; or < 20 mm in area M, if there are no other high-risk factors

**ADJUVANT TREATMENT**

- Mohs or resection with CCPDMA or RT
  - Positive → Margins
  - Negative

- Multidisciplinary consultation and therapy (consider clinical trials)
  - Positive
  - If extensive perineural or large-nerve involvement, consider adjuvant RT
  - Negative

**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.

POMA = postoperative margin assessment
CCPDMA = complete circumferential peripheral and deep margin assessment with frozen or permanent section

**Return to Basal Cell and Squamous Cell Skin Cancers Table of Contents**
FOLLOW-UP

H&P
- Including complete skin exam every 6-12 mo for life

Patient education:
- Sun protection
- Self-examination

RECURRENT

Local

Follow Primary Treatment Pathways (BCC-1)

Regional or distant

Multidisciplinary consultation and therapy

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**RISK FACTORS FOR RECURRENCE**

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&amp;P</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location/size</td>
<td>Area L ( \leq 20 \text{ mm} )</td>
<td>Area L ( \geq 20 \text{ mm} )</td>
</tr>
<tr>
<td></td>
<td>Area M ( \leq 10 \text{ mm} )</td>
<td>Area M ( \geq 10 \text{ mm} )</td>
</tr>
<tr>
<td></td>
<td>Area H ( \leq 6 \text{ mm} )(^1)</td>
<td>Area H ( \geq 6 \text{ mm} )(^1)</td>
</tr>
<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Primary vs. Recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Site of prior RT</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td>Nodular, superficial</td>
<td>Aggressive growth pattern(^2)</td>
</tr>
<tr>
<td>Perineural involvement</td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

\(^1\)Location independent of size may constitute high risk in certain clinical settings.

\(^2\)Having morpheaform, sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor.

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

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Area H = “mask areas” of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

Area M = cheeks, forehead, scalp, and neck.

Area L = trunk and extremities.
PRINCIPLES OF TREATMENT FOR BASAL CELL SKIN CANCER

- The goal of primary treatment of basal cell skin cancer is 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 patient’s preference. Customary age and size parameters may have to be modified.

- 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 low-risk superficial basal cell skin cancer, where surgery or radiation may be contraindicated, local therapy (5-fluorouracil, imiquimod, and photodynamic therapy) may be considered even though the cure rate may be lower.

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.
## RADIOTHERAPY FOR BASAL CELL SKIN CANCER

### Dose and Field Size

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Margins</th>
<th>Orthovoltage Dose and Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 mm</td>
<td>5-10 mm</td>
<td>Total of 4,500-5,000 cGy in 250-300 cGy fractions</td>
</tr>
<tr>
<td>≥ 20 mm</td>
<td>15-20 mm</td>
<td>Total of 6,000-6,600 cGy in 200 cGy fractions or Total 5,000-6,000 cGy in 250 cGy fractions.</td>
</tr>
</tbody>
</table>

- Varying energies of orthovoltage or electron-beam equipment should be available.
- Add 10%-15% to total and daily doses if using electron beam and add bolus for low-energy electrons.
- Maximize fractions to maximize cosmesis.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, nevoid basal cell carcinoma, xeroderma pigmentosum) and connective tissue diseases (eg, lupus, scleroderma).

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**CLINICAL PRESENTATION**

- **Suspicious lesion**

**WORKUP**

- **H&P:** Complete skin and regional lymph node exam

**RISK STATUS**

- Low risk
- Local
- High risk**c**

**Biopsy:**
- If more than superficial lesion, inclusion of deep reticular dermis preferred
- Imaging studies as indicated for extensive disease

- Palpable regional lymph node
  - Palpable intraparotid mass

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**a** Including basosquamous carcinoma and squamous cell skin cancer in situ (showing full-thickness epidermal atypi, excluding actinic keratoses).

**b** See Risk Factors for Recurrence (SCC-A).

**c** Any high-risk factor places the patient in the high-risk category.

*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.*
**Primary Treatment**

**C&E:**
- In non-hair-bearing areas
- If fat reached, surgical excision must be performed

or

**Excision with POMA:**
- If lesion can be excised with 4-6 mm clinical margins and secondary intention, side-to-side repair, or skin graft

or

**RT**
- Patients > 55 y:
  - Area H (excluding genitalia, hands, and feet) or area M

**Adjuvant Treatment**

**Margins**

Positive

- Mohs or resection with CCPDMA or RT or Re-excision with POMA for area L regions

Negative

C&E = curettage and electrodesiccation

POMA = postoperative margin assessment

CCP_DMA = complete circumferential peripheral and deep margin assessment with frozen or permanent section

---

**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.

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**See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).**

**See Radiotherapy for Squamous Cell Skin Cancer (SCC-C).**

**See Follow-up (SCC-5)**

**Return to Basal Cell and Squamous Cell Skin Cancers Table of Contents**
**Primary Treatment**

- **Excision with POMA**
  - **Lesion ≥ 20 mm in area L** with no other high-risk factors, if can be excised with 10 mm clinical margins + primary repair
  - or
  - **Mohs or resection with CCPDMA**
    - or
    - **RT (category 2B)**
      - **Patients > 55 y:**
        - < 15 mm in area H (excluding genitalia, hands, and feet), or
        - < 20 mm in area M, if there are no other high-risk factors.

**Adjuvant Treatment**

- **Margins**
  - **Positive**
    - Mohs or resection with CCPDMA or RT
  - **Negative**
    - Multidisciplinary consultation + therapy (consider clinical trials)

- **Margins**
  - **Positive**
    - If extensive perineural or large-nerve involvement, consider adjuvant RT
  - **Negative**

**Note:**
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- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**PRIMARY TREATMENT**

- Palpable regional lymph node(s)
  - FNA
    - Positive → Imaging as clinically indicated → Regional lymph node dissection
    - Negative → Open biopsy with frozen section
      - Positive → Regional lymph node dissection
      - Negative → Superficial parotidectomy

- Palpable intraparotid mass → Superficial parotidectomy

**ADJUVANT TREATMENT**

- Adjuvant RT, except if only one lymph node ≤ 3 cm with no evidence of extracapsular spread

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**See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).**

**Return to Basal Cell and Squamous Cell Skin Cancers Table of Contents**
FOLLOW-UP

Local disease:
- H&P<sup>h</sup>
  - Every 3-6 mo for 2 y, then every 6-12 mo for 3 y, then annually for life
- Patient education
  - Sun protection
  - Self examination of skin

Regional disease:
- H&P<sup>h</sup>
  - Every 3 mo for 2 y, then every 4 mo for 1 y, then every 6 mo for 2 y, then annually for life
- Patient education
  - Sun protection
  - Self examination of skin

RECURRENT/DISEASE PROGRESSION

Local → Regional recurrence or distant metastases → Multidisciplinary consultation + therapy<sup>i</sup>

Regional → See Primary Treatment for regional disease (SCC-4)

Local → See Primary Treatment for local disease (SCC-1)

<sup>h</sup>Including complete skin and regional lymph node exam.
<sup>i</sup>Consider clinical trials.

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## RISK FACTORS FOR RECURRENCE

<table>
<thead>
<tr>
<th>H&amp;P</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
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<tbody>
<tr>
<td>Location/size</td>
<td>Area L &lt; 20 mm</td>
<td>Area L ≥ 20 mm</td>
</tr>
<tr>
<td></td>
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<td>Area M ≥ 10 mm</td>
</tr>
<tr>
<td></td>
<td>Area H &lt; 6 mm</td>
<td>Area H ≥ 6 mm</td>
</tr>
<tr>
<td>Borders</td>
<td>Well-defined</td>
<td>Poorly-defined</td>
</tr>
<tr>
<td>Primary vs recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Site of prior RT or chronic inflammatory process</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Rapidly growing tumor</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of differentiation</td>
<td>Well differentiated</td>
<td>Moderately or poorly differentiated</td>
</tr>
<tr>
<td>Adenoid (acantholytic), adenosquamous (showing mucin production), or desmoplastic subtypes</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Depth: Clark level or thickness</td>
<td>I, II, III, or &lt; 4 mm</td>
<td>IV, V, or ≥ 4 mm</td>
</tr>
<tr>
<td>Perineural or vascular involvement</td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

1. Must include peripheral rim of erythema.
2. A modified Breslow measurement should exclude parakeratosis or scale/crust, and should be made from base of ulcer if present.
3. Location independent of size may constitute high risk in certain clinical settings.

Area H = “mask areas” of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

Area M = cheeks, forehead, scalp, and neck.

Area L = trunk and extremities.

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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. Customary age and size parameters may have to be modified.

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. (See Identification and Management of High-Risk Patients SCC-D)

In patients with low-risk squamous cell carcinoma in situ (Bowen's disease), where surgery or radiation is contraindicated, local therapy (5-fluorouracil, imiquimod, and photodynamic therapy) may be considered even though cure rate may be lower.

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## RADIOTHERAPY FOR SQUAMOUS CELL SKIN CANCER

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- Varying energies of orthovoltage or electron-beam equipment should be available.
- Add 10%-15% to total and daily doses if using electron beam and add bolus for low-energy electrons.
- Maximize fractions to maximize cosmesis.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, xeroderma pigmentosum), connective tissue diseases (eg, lupus, scleroderma), and verrucous carcinomas.

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

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IDENTIFICATION AND MANAGEMENT OF HIGH-RISK PATIENTS

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 (lymphoma, drug-induced, HIV, etc.)
  - 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 ≥ 3 risk factors for recurrence (See Risk Factors for Recurrence SCC-A)
- In these patients, urgent diagnosis and treatment of lesions are important

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 (continued)

TREATMENT OF PRECANCERS

- Actinic keratoses should be treated aggressively at first development.
  - Accepted treatment modalities include cryosurgery, topical 5-fluorouracil, topical imiquimod, photodynamic therapy, and curettage & electrodessication.
  - Other modalities that may be considered include chemical peel (trichloroacetic acid) and ablative skin resurfacing (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 therapies (curettage & electrodessication, cryosurgery) may be a preferred treatment for clinically low-risk tumors, because of the ability to treat multiple lesions at a single patient visit.
- 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 split thickness skin grafting have been used with efficacy. However, healing is prolonged and morbidity is significant.
- Compared to the normal population, radiation therapy is often used more frequently as an adjuvant therapy and for perineural disease, and less frequently for the treatment of primary tumors.
- Satellite lesions (in-transit cutaneous metastases) may occur more frequently in this population. They must be treated aggressively with strong consideration of radiation therapy as the primary therapy.
- In organ transplant recipients, decreasing the level of immunosuppressive therapy 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.
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, etretinate, isotretinoin) has been effective in reducing the development of precancers 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.
# Staging

### Table 1

<table>
<thead>
<tr>
<th>2002 American Joint Committee on Cancer (AJCC) TNM Staging System for Non-Melanoma Skin Cancer</th>
</tr>
</thead>
</table>

| **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 |
|T2| Tumor more than 2 cm but not more than 5 cm in greatest dimension |
|T3| Tumor more than 5 cm in greatest dimension |
|T4| Tumor invades deep extradermal structures (i.e., cartilage, skeletal muscle, or bone) |

*Note:* In the case of multiple simultaneous tumors, the tumor with the highest T category will be classified and the number of separate tumors will be indicated in parentheses, e.g., T2 (5).

| **Regional Lymph Nodes (N)** |  |
|NX| Regional lymph nodes cannot be assessed |
|N0| No regional lymph node metastasis |
|N1| Regional lymph node metastasis |

| **Distant Metastasis (M)** |  |
|MX| Distant metastasis cannot be assessed |
|M0| No distant metastasis |
|M1| Distant metastasis |

| **Stage Grouping** |  |
|Stage 0| Tis N0 M0 |
|Stage I| T1 N0 M0 |
|Stage II| T2 N0 M0 |
| | T3 N0 M0 |
|Stage III| T4 N0 M0 |
| | Any T N1 M0 |
|Stage IV| Any T Any N M1 |

| **Histologic Grade (G)** |  |
|GX| Grade cannot be assessed |
|G1| Well differentiated |
|G2| Moderately differentiated |
|G3| Poorly differentiated |
|G4| Undifferentiated |

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Basal cell and squamous cell skin cancers are the most common human cancers; collectively they are termed non-melanoma skin cancers. In 2005, they are estimated to have an incidence of more than one million cases in the United States; the incidence is rising rapidly. Basal cell carcinomas are about four to five times more common than squamous cell carcinomas. Although rarely metastatic, basal cell and squamous cell cancers can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. The estimated annual cost of treating these two diseases in the United States exceeds $500 million. However, non-melanoma skin cancers generally have a good prognosis.

Genetics

The genetics of both basal cell and squamous cell cancers are still being determined. Mutations in the tumor-suppressor PTCH (patched) gene system found on chromosome 9q are present in most of the basal cell cancers. Mutations in the tumor suppressor gene p53 appear to be an early common event in cutaneous squamous cell cancer development. Mutations in several oncogenes (eg, ras and fos) have also been identified. However, in non-melanoma skin cancer development, the role any specific oncogene plays is unclear.

Finally, certain genetic syndromes greatly predispose affected individuals to non-melanoma skin cancer formation, such as albinism (in which skin pigment is absent) xeroderma pigmentosum (in which defects exist in ultraviolet light-induced unscheduled DNA repair), and nevoid basal cell carcinoma syndrome; certain settings of immunosuppression (most notably, organ transplantation) also predispose affected individuals.

Steps in Developing the Guidelines

In developing the practice guidelines for the treatment of non-melanoma skin cancer, the NCCN Panel decided to limit the initial algorithms to basal cell and squamous cell cancers, which account for most of the non-melanoma skin cancers. The panel decided to expand the American Joint Committee on Cancer (AJCC) staging system (see Table 1), because more than 95% of basal cell and squamous cell...
cancers only involve local disease. Thus, the panel decided to
develop a more comprehensive stratification system. This
stratification system would reflect clinically relevant “levels” or “tiers of difficulty” involved in treating primary tumors.

The NCCN panel examined risk factors for basal cell and squamous cell cancers associated with inadequate treatment of primary tumors (ie, risk factors associated with recurrence and metastasis). For each parameter, the group agreed on specific criteria indicative of when a given tumor is at “high” risk for recurrence or metastasis. If a tumor has any one parameter indicating high-risk behavior, then that tumor enters the high-risk category. In this way, the panel produced specific risk factors for recurrence for basal cell cancer (see BCC-A) and for squamous cell cancer (see SCC-A).

Clinical Risk Factors

Several clinical risk factors apply to both basal cell and squamous cell cancers (see BCC-A and SCC-A, respectively). These risk factors include tumor location and size, the status of tumor borders, whether the tumor is primary or recurrent, certain settings of immune-suppression, and tumors developing in previously irradiated sites.

Location and Size

The NCCN panel elected to group together two separate risk factors: location and size. The science of dividing these factors into low-risk and high-risk categories is somewhat arbitrary because, to a certain extent, both factors, especially size, involve a continuous spectrum of risk.

Location has been known to be a risk factor for non-melanoma skin cancer recurrence and metastasis for many years. Stated in general terms, both basal cell and squamous cell cancers that develop in the head and neck area are more likely to recur than are those carcinomas developing on the trunk and extremities. Squamous cell carcinomas that develop on the genitalia, mucosal surfaces, and ear 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 (see Figure 1). Size also has been shown to be a risk factor for non-melanoma skin cancer recurrence. Various different divisions have been used; probably the most common has been “greater than (or less than) 2 cm in diameter.”

The NCCN Panel ultimately elected to base the location and size criteria, for the most part, on a 27-year retrospective review of the experience of the Skin Cancer Unit of the New York University (NYU) School of Medicine. This review, published in 1991, evaluated a database containing information on 5755 basal cell cancers. Of the 5755 basal cell cancers evaluated, 2314 primary tumors were treated by curettage and electrodesiccation. Based on modified life-table 5-year recurrence rates generated in this study, anatomic sites were divided into high-risk, middle-risk, and low-risk sites for recurrence. The high-risk sites correspond roughly to the mask areas of the face (see Figure 1). The middle-risk and low-risk sites correspond roughly to the middle-risk and low-risk divisions listed in the algorithms (see BCC-A and SCC-A). In addition, 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 middle-risk locations were 10 mm or more in diameter.

These criteria based on size and location are also more or less in agreement with similar work performed at the national level for the Health Care Financing Administration (HCFA). The HCFA work defined what constitutes high-risk tumors appropriate for Mohs micrographic surgery.
Clinical Borders and Primary Versus Recurrent Disease

The risk factors of well-defined versus ill-defined clinical tumor borders and primary versus recurrent disease have been extensively documented in the biomedical literature.\(^{15,20,21}\)

Immunosuppression

Settings of immunosuppression, such as organ transplantation\(^{22,23}\) as well as long-term use of psoralen and ultraviolet A light (PUVA),\(^{24,25}\) significantly increase the incidence of squamous cell cancer development. Basal cell carcinoma incidence also increases slightly in these settings.

Although several small anecdotal reports describe aggressive tumor behavior in patients with underlying malignancies or individuals taking immunosuppressive medications for non-oncologic diseases, the best data are from the organ transplant literature. The incidence of metastatic squamous cell cancer is significantly greater in this population than in individuals who have not received a transplant.\(^{12,26}\) Uncertainty remains whether this is simply because of a greater number of tumors per patient or actually reflects more aggressive tumor behavior at the biological level. Because, collectively, organ transplant recipients have worse outcomes, these patients (see SCC-D) and their neoplasms are designated as high risk.

Actually, very little published data suggest basal cell cancers are more likely to recur or metastasize when they develop in immunosuppressed individuals.\(^ {27,28}\) The only evidence supporting this view includes a few anecdotal clinical reports and several studies documenting laboratory evidence of immunosuppression in these patients. Nevertheless, because of this evidence and the NCCN Panel members’ own anecdotal experiences, the panel decided to classify both basal cell and squamous cell cancers that develop in settings of immunosuppression as potentially high-risk tumors.

Site of Prior Radiotherapy

“Tumors developing in sites of prior radiotherapy” refer to primary non-melanoma skin cancers arising in areas within radiation fields given previously for benign conditions. All recurrent tumors, irrespective of prior therapy, have already been defined as high risk. Again, only a few articles in the biomedical literature support prior radiotherapy for benign conditions as a risk factor for non-melanoma skin cancer recurrence or metastasis.\(^ {29-31}\) However, the NCCN panel consensus was this is a valid risk factor.

Additional Clinical Risk Factors for Squamous Cell Carcinoma

The NCCN panel identified a few additional clinical parameters that increase the risk of squamous cell cancer only (see SCC-A) as follows:

Site of a Chronic Inflammatory Process. A substantial body of biomedical literature has documented increased rates of metastasis for cutaneous squamous cell cancers arising in the setting of chronic scarring.\(^ {12}\)

Symptoms of Neurologic Involvement. In 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.\(^ {32}\) Any suggestion of neurologic involvement in the region of a squamous cell cancer should place that tumor in a high-risk category.

Rapidly Growing Tumor. Only one article in the biomedical literature documents rapid growth of a cutaneous squamous cell...
cancer 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.

**Young Age Is Not a Clinical Risk Factor**

Young age (typically, younger than 40 years) is generally viewed as a clinical risk factor for aggressive non-melanoma skin cancer behavior. However, the NCCN panel decided that young age is not a risk factor, which was a difficult decision. The published biomedical literature does not strongly support “young age” per se as a risk factor. Leffell and colleagues documented an increased percentage of basal cell cancer with aggressive histologic growth patterns in young persons. However, this histologic feature is already a separate risk factor in the algorithm.

The features of 54 basal cell cancers in young patients referred for Mohs surgery were compared with similar tumors in 1050 older patients. Tumor location, histology, and clinical morphology did not differ appreciably between the two groups. In fact, initial lesion and final defect sizes were statistically smaller in the younger patient group. In a study from the United Kingdom, 39 young basal cell cancer patients were followed for a minimum of 5 years; four tumors were incompletely excised; two recurred and one metastasized. Another study observed a higher number of recurrent tumors in younger women referred for Mohs surgery than in other demographic groups. Finally, two more recent studies found no difference in either recurrence rates or presence of aggressive histologic subtypes in younger versus older patients with basal cell skin cancer.

The NCCN Panel decided, taken together, these studies do not support the suggestion that young age, in and of itself, is a high-risk factor for non-melanoma skin cancer behavior. Any tumor showing an aggressive histologic growth pattern, regardless of the patient’s age, becomes a high-risk tumor based on that histology.

**Pathologic Risk Factors for Non-Melanoma Skin Cancer**

**Basal Cell Skin Cancer**

**Histologic Subtypes.** Histologic subtyping of basal cell cancer as a predictor of risk of recurrence is a well-established concept. The subtypes encompassed by the term “aggressive growth pattern”—including the micronodular, infiltrative, sclerosing, and morpheaform (or desmoplastic) patterns—are more likely to recur than the nodular and superficial basal cell cancers.

**Squamous Cell Skin Cancer**

**Histologic Subtypes.** The NCCN Panel elected to include the entity “basosquamous carcinoma” (also sometimes called “metatypical basal cell cancer”) under the category of squamous cell cancer rather than basal cell cancer. Some basosquamous tumors probably represent collision tumors in which a basal cell cancer and a squamous cell cancer developed in close proximity to one another. Others possibly represent biopsied regions of a true basal cell cancer that are inflamed and have undergone squamous metaplasia. Nevertheless, several studies suggest basosquamous carcinoma has a metastatic capacity more like squamous cell cancer than basal cell cancer. For this reason, the panel felt these tumors are best conceptualized as squamous cell cancers until other, more instructive, data become available.

**Perineural Involvement.** Perineural involvement poses a greatly increased risk of recurrence, whether the tumor is a basal cell or squamous cell cancer, and an increased risk of metastasis for
squamous cell cancer. Although perineural involvement is uncommon in any non-melanoma skin cancer, it develops much more frequently in squamous cell than in basal cell cancer.

**Degree of Differentiation.** In their extensive meta-analysis of risk factors for local recurrence and metastasis of squamous cell cancer, Rowe and colleagues found that patients with well-differentiated tumors fared significantly better than those patients with poorly differentiated lesions. Although Broders originally divided squamous cell cancers histologically into four groups or grades, the modern trend has been to reduce the divisions to two groups: (1) well-differentiated, and (2) moderately differentiated, poorly differentiated, or undifferentiated. The NCCN Panel has adopted this modern approach in these guidelines.

**Other Histologic Parameters.** The panel members discussed whether any other histologic parameters should be included as risk factors for squamous cell cancer (see SCC-A) beside the degree of differentiation and perineural involvement.

*Included Parameters:* After some discussion, the NCCN Panel elected to maintain the histologic subtypes of adenoid (or acantholytic) and adenosquamous (or mucin-producing) squamous cell cancer as markers for an increased risk of recurrence or metastasis. Again, few studies document the prognostic significance of these subtypes. Even so, because these tumors probably 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.

One histologic feature reported in the biomedical literature is the presence of desmoplasia. In a study from Germany, desmoplastic cutaneous squamous cell cancer was shown to pose a greatly increased risk of both recurrence and metastasis. After some discussion, the panel elected to include this histologic subtype as a risk factor for aggressive squamous cell cancer behavior.

Finally, a small, somewhat older, body of biomedical literature found an association between invasion of squamous cell cancer into the deep reticular dermis or subcutaneous fat (corresponding to a Clark level IV or V melanoma) and aggressive behavior. Several more studies have suggested squamous cell tumor depth, as measured in millimeters (similar to Breslow’s original work with melanoma), may also have prognostic value. Although there was some discussion, a meta-analysis of squamous cell cancer risk factors for recurrence and metastasis found both types of depth measurements have prognostic value. Therefore, the panel decided to include these two risk factors and used the division points determined by Rowe and colleagues in the algorithm (see SCC-A).

One final note should be made regarding squamous cell cancer histology. The panel elected to include full-thickness atypia, or “squamous cell cancer in situ,” in the algorithm. Although the risk of metastasis from in situ disease is negligible, the risk of recurrence--as with the superficial form of basal cell cancer---depends on the presence or absence of any of the risk factors listed in the algorithm (see SCC-A).

*Excluded Parameters:* The presence or absence of an infiltrative component at the advancing border of a squamous cell tumor was one parameter the NCCN Panel discussed. Some authors have advocated this parameter as a risk factor. However, the pathologists on the panel believe this feature usually correlates well with the degree of differentiation, and it is a descriptive term...
not routinely applied to squamous cell cancer. Consequently, this parameter was excluded.

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 squamous cell cancer behavior. However, the panel decided this indirect association did not warrant the listing of spindle cell squamous cell cancer as a separate risk factor.

**Identification and Management of Patients at High Risk for Squamous Cell Skin Cancer**

The NCCN Panel developed recommendations for the identification and management of patients at high risk for squamous cell skin cancer (see SCC-D). Two members of the International Transplantation Skin Cancer Collective assisted the NCCN Panel in this process and provided expert input. Certain populations of individuals, chiefly those with the nevoid basal cell carcinoma syndrome, are at risk for the development of multiple basal cell cancers; however, the panel felt that the existing basal cell cancer algorithm provides reasonably adequate guidance for care of these patients.

**Clinical Presentation and Workup**

On clinical presentation of the patient with a suspicious lesion, workup of both basal cell and squamous cell cancers begins with a history and physical examination. For basal cell cancer, the emphasis is on a complete skin examination. For squamous cell cancer, the emphasis is on a complete skin and regional lymph node examination. A full skin examination is recommended, because individuals with a skin cancer often have additional, concurrent precancers or cancers located at other, usually sun-exposed, skin sites. These individuals are also at increased risk of developing cutaneous melanoma. A skin biopsy is then performed on any suspicious lesion. The biopsy should include reticular dermis if the lesion is suspected to be more than a superficial process. This procedure is preferred, because an infiltrative histology may sometimes be present only at the deeper, advancing margins of a tumor, and superficial biopsies will frequently miss this component. Skin lesions in high-risk populations (see SCC-D) may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. In patients with squamous cell cancer, the presence of a palpable regional lymph node should prompt a fine-needle aspiration (FNA) for diagnosis. If the aspiration is positive, imaging should be done as clinically indicated. If the aspiration is negative, an open biopsy should be performed. Uncommonly, skin cancers may present with the appearance of deep extension, for example, into bone or the orbit. In such cases, preoperative imaging studies may be useful to help assess the extent of soft tissue or bony involvement.

**Selection of Therapy**

The algorithms list all of the therapies currently used to treat localized non-melanoma skin cancer, including surgical techniques (ie, curettage and electrodesiccation, excision with postoperative margin assessment [POMA], Mohs surgery or excision with “complete circumferential peripheral and deep-margin assessment” [CCPDMA]) and radiation therapy (RT). For basal cell carcinoma, surgery and radiotherapy appear to be the most effective treatments; in an evidence-based review of the literature, the best results were obtained with surgery. In patients with low-risk squamous cell
carcinoma in situ (Bowen disease) or superficial basal cell carcinoma, where surgery or radiation is contraindicated, local therapy (5-fluorouracil, imiquimod, PDT) may be considered even though the cure rate may be lower (see BCC-B and SCC-B).

**Curettage and Electrodesiccation**

The curettage and electrodesiccation technique is deemed effective for low-risk tumors with two caveats. The first caveat states that this technique should not be used to treat hair-bearing sites because of the risk that a tumor, which extends down follicular structures, might not be adequately removed.

The second caveat states that if the subcutaneous layer is reached during the course of surgery, then surgical excision must be performed instead of curettage and electrodesiccation. This change in therapy is necessary, because the effectiveness of the curettage and electrodesiccation technique rests on the ability of the clinician to distinguish between firm, normal dermis and soft tumor tissue when using a sharp curette. Because subcutaneous fat is even softer than tumor tissue, the ability of the curette to distinguish and, therefore, to selectively and completely remove tumor cells, disappears.

**Excision With Postoperative Margin Assessment**

Another therapeutic option for both basal cell and squamous cell cancers is POMA, consisting of standard surgical excision followed by postoperative pathologic assessment of margins. The clinical margins chosen by the panel for low-risk tumors are based on the work of Zitelli and colleagues. Their analysis indicated the excision of basal cell or squamous cell tumors less than 2 cm in diameter and clinically well circumscribed should result in complete removal (with a 95% confidence interval) if 4-mm clinical margins are taken. Any peripheral rim of erythema around a squamous cell cancer must be included in what is assumed to be the tumor.

The panel expanded the clinical margins for squamous cell cancers; the margins are 4 to 6 mm because of this issue and concerns about achieving complete removal. The indications for this approach were also expanded to include: (1) re-excision of low-risk primary basal cell and squamous cell cancers located on the trunk and extremities (area L regions) if positive margins are obtained after an initial excision with POMA, and (2) primary excision of larger tumors located in L regions deemed high risk because of their size, if 10-mm margins can be taken.

If lesions can be excised with the recommended margins, then side-to-side closure, skin grafting, or secondary intention healing (ie, all closures do not rotate tissue around and alter where residual "seeds" of tumor might be sitting) are all appropriate reconstructive approaches. However, if tissue rearrangement or skin graft placement is necessary to close the defect, the group believes intraoperative surgical margin assessment is necessary.

**Mohs Surgery or Excision With Intraoperative Frozen Section Assessment**

Either Mohs surgery or excision with CCPDMA using intraoperative frozen section (IOFS) assessment is the recommended therapeutic approach for all high-risk tumors. It should be noted that IOFS is not acceptable as an alternative to Mohs surgery unless it includes a complete assessment of all deep and peripheral margins. The descriptive term CCPDMA underscores the panel's belief that intraoperative assessment of all tissue margins is the key to complete tumor removal. Mohs surgery is preferred because of its documented efficacy. If Mohs surgery is unavailable, complete tissue margin assessment must still be performed in another fashion.
Consequently, the emphasis is placed on CCPDMA. For certain high-risk squamous cell lesions, sentinel lymph node mapping may be considered, although the benefit of this technique has yet to be proven.

**Radiation Therapy**

The role of RT was probably the single largest source of disagreement among the NCCN Panel of experts. The panel was initially divided into two groups on this issue: (1) the radiation oncologists wanted to use this therapy for almost all tumors, whereas (2) the surgeons did not want to use RT.

A large biomedical literature review was performed and circulated among the participants, followed by a panel discussion of the evidence. A reasonable consensus was achieved after the surgeons realized that, *when properly applied*, RT can result in very good cure rates and excellent cosmesis. The radiation oncologists agreed in order to achieve those cure rates and cosmesis, RT *must be properly applied*. In other words, the details of RT are important and need to be included in the algorithms.

The panel consensus is that adequate training in the techniques of Mohs micrographic surgery and RT are essential to achieve high cure rates when treating non-melanoma skin cancers. If either of these approaches is inappropriately or inadequately applied and performed, less than optimal cure rates will result.

The size and location criteria for RT were expanded to include tumors in high-risk locations up to 15 mm in diameter and tumors in middle-risk locations up to 20 mm in diameter. The low-risk regions of the trunk and extremities are not usually treated with RT; the genitalia, hands, and feet are also excluded. Verrucous carcinoma is excluded, because several reports in the biomedical literature document an increased metastatic risk after RT in patients with this generally low-grade malignancy. RT is also contraindicated in genetic conditions predisposing to skin cancer (e.g., xeroderma pigmentosum) and connective tissue diseases (e.g., lupus, scleroderma).

To assist users of the guidelines, the panel arrived at several principles of primary treatment for both basal cell and squamous cell cancer (see BCC-B and SCC-B). These principles were developed to suggest the importance of customizing any and all therapeutic approaches to the particular factors and to the individual needs of each patient. Specifics about the application of RT, including caveats regarding different types of therapeutic radiation and total doses and fractionation ranges, are shown in the algorithms (see BCC-C and SCC-C).

Finally, all of the panel members agreed RT is generally most appropriate in older individuals because of a tendency for cosmesis to wane and a risk of additional non-melanoma skin cancer to develop within a radiation field, typically after 10 to 20 years. However, the definition of “older” varied somewhat. Everyone agreed 55 years of age was an acceptable middle ground in terms of a cut off for the use of radiotherapy in most instances. Again, the principles of primary treatment of basal cell and squamous cell cancers (see BCC-B and SCC-B) were developed to address this issue.

**Further Points About Choosing Therapy and Adjuvant Treatment**

Several additional, relatively small points about therapy need to be mentioned:

- If a squamous cell cancer extends down into the parotid fascia (i.e., into the parenchyma), a superficial parotidectomy needs to be performed.
If any non-melanoma skin cancer shows evidence of substantial perineural involvement (ie, involvement of more than just a few small sensory nerve branches), postoperative radiotherapy should be considered.

If tissue margins are positive after Mohs surgery or a CCPDMA equivalent of a skin cancer, the case should be presented to a multidisciplinary tumor board and clinical trials should be considered (see BCC-3 and SCC-3).

Patients with positive findings on either FNA or open biopsy of a lymph node should receive regional lymph node dissection. A palpable intraparotid mass, in the presence of a facial tumor, should be treated with superficial parotidectomy. In both settings, adjuvant radiotherapy should be considered if more than one lymph node greater than 3 cm in diameter is present, or if there is any evidence of extracapsular spread. Specifics about the application of RT (including caveats regarding different types of therapeutic radiation, total doses, and fractionation ranges) are shown in the algorithms (see BCC-C and SCC-C).

Suggestions for the care of patients at high risk for squamous cell cancer are listed in the algorithm (see SCC-D).

Follow-Up and Recurrence

Two well-established points about patients with non-melanoma skin cancer underlie the follow-up schedules. One point is that 30% to 50% of these patients will develop another non-melanoma skin cancer during a 5-year follow-up period. They are also at increased risk of developing cutaneous melanoma. Therefore, continued long-term surveillance of these patients is essential, as is patient education about the values of sun protective behavior and regular self examination of the skin (see BCC-4 and SCC-5). A second point is that 70% to 80% of all cutaneous squamous cell cancer recurrences develop within 2 years of the initial therapy. Therefore, close follow-up of these patients during this time period is critical.

Finally, for the management of local tumor recurrence or regional metastasis of squamous cell cancer, the algorithm directs clinicians to follow the appropriate pathways for primary treatment. The case should be presented to a multidisciplinary tumor board and clinical trials should be considered if the following develops: (1) any form of basal cell metastasis, or (2) a regional recurrence of squamous cell cancer or the development of distant disease.
Basal Cell and squamous cell carcinomas that develop in the high-risk mask area of the face are more likely to recur and metastasize than those that develop on the trunk and extremities.

References


