National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Squamous Cell Skin Cancer

Version 1.2016

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Discussion

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NCCN Guidelines Panel Disclosures

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Clinical Trials: 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 Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2016 Updates Squamous Cell Skin Cancer

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Updates in Version 1.2016 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2015 include:

Squamous Cell Skin Cancer

SCC-2

- For "Primary treatment of low-risk squamous cell skin cancer" under "Curettage and electrodesiccation":
  - Bullet "1" statement: "In non-hair bearing areas" was revised: *"Excluding terminal hair-bearing areas, such as scalp, pubic, axillary regions, and beard area in men"*
  - Bullet "2" statement: "If adipose reached, surgical excision should generally be performed", an arrow was added pointing directly to "Standard excision".

SCC-A

- In table of "Risk Factors for Local Recurrence or Metastases" under "Pathology":
  - Statement revised: "Adenoid (acantholytic), adenosquamous (showing mucin production), or desmoplastic *or basosquamous (metatypical)* subtypes"
  - Statement revised: "Perineural, *lymphatic*, or vascular involvement"
- Footnote "4" added to "Area M <10 mm" under "Low Risk", removed from "Area H ≥6 mm" under "High Risk" , and modified: "Location independent of size may constitute high risk. ~~in certain clinical settings~~."

SCC-B

- Under "Principles Of Treatment For Squamous Cell Skin Cancer" for bullet "1" statement modified: "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~~."

SCC-D (1 of 3)

- Under " Identification And Management Of High-Risk Patients", "Definition":
  - Bullet "1", sub-bullet "2": statement modified: "Other settings of immunosuppression (eg, lymphoma, *chronic lymphocytic leukemia,* drug-induced, HIV, ~~etc~~.)"
  - Bullet "4" statement modified: "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."*

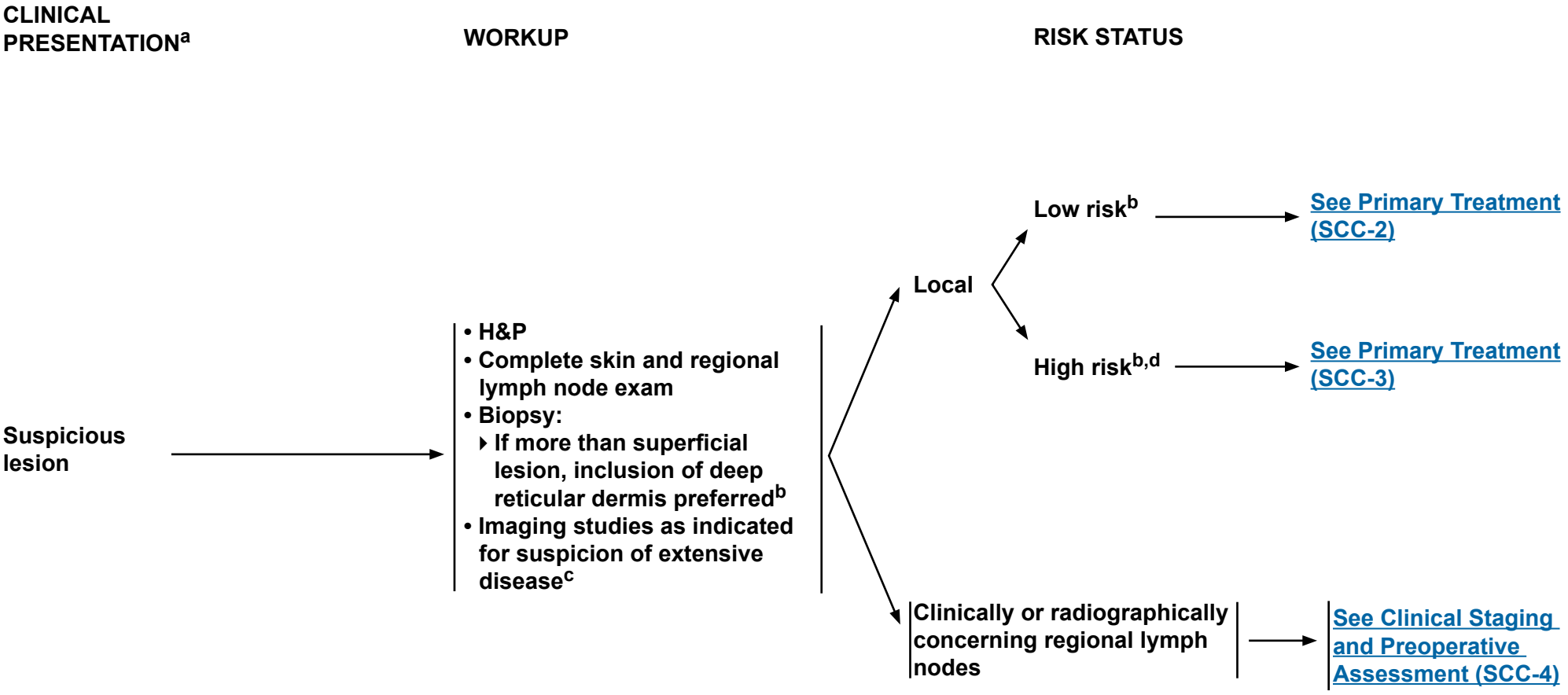
SCC-D (2 of 3)

- Under " Identification And Management Of High-Risk Patients" for "Treatment of Skin Cancers":
  - Bullet "4" modified: "Compared to the ~~normal~~ *low-risk* population, radiation therapy is used more frequently as an adjuvant therapy and for perineural disease."
  - Bullet "5" modified: "Satellite lesions *and* ~~(~~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~~. *multidisciplinary tumor board consultation.*"

SCC-D (3 of 3)

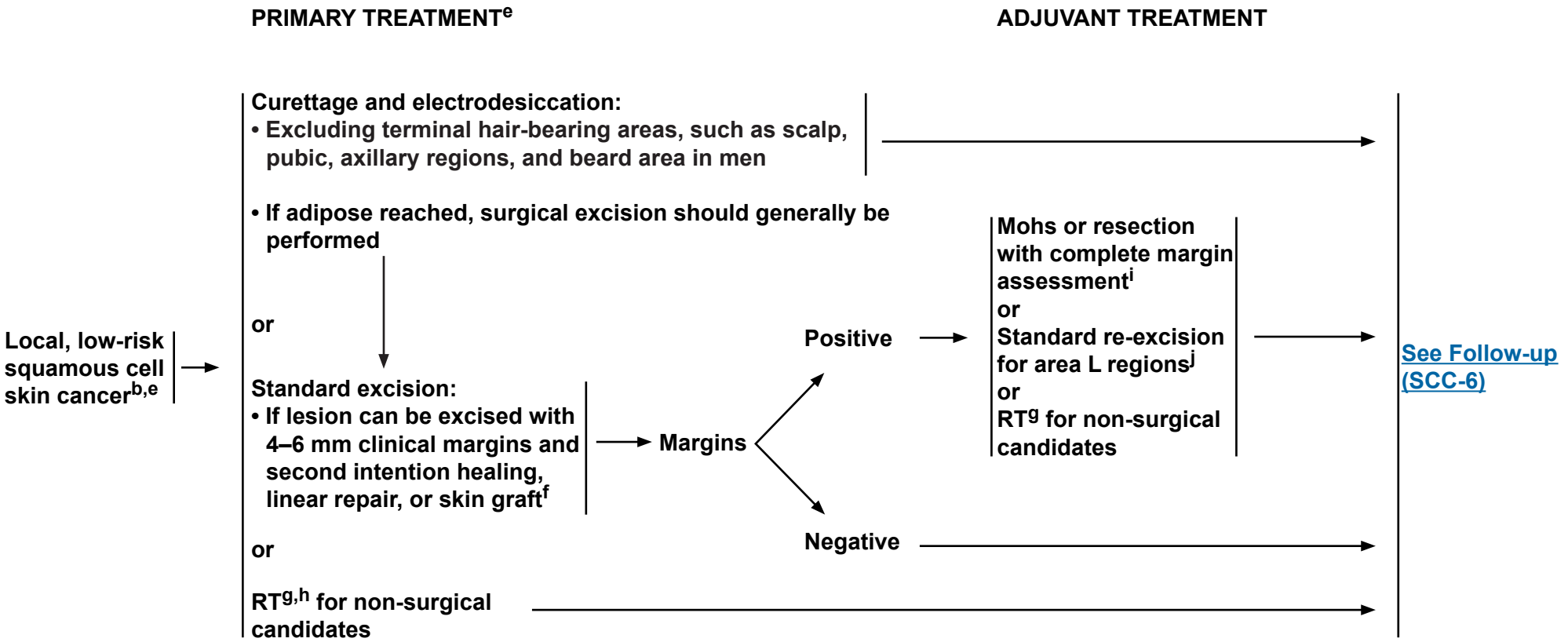
- Under "Identification And Management Of High-Risk Patients" for "Prevention", bullet "1" modified: "Use of oral retinoids (acitretin, isotretinoin) has been effective in reducing the development of ~~precancers~~ *actinic keratoses* and skin cancers in some high-risk patients. Side effects may be significant. 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."

UPDATES



[a]Including basosquamous carcinoma and squamous cell skin cancer in situ (showing full-thickness epidermal atypia, excluding actinic keratoses).
[b]See Risk Factors for Local Recurrence or Metastases (SCC-A).
[c]Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI is preferred.
[d]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.



[b] See Risk Factors for Local Recurrence or Metastases (SCC-A).
[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[f] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[g] See Principles of Radiation Therapy Squamous Cell Skin Cancer (SCC-C).
[h] RT is often reserved for patients over 60 years because of concerns about long-term sequellae.
[i] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs surgery.
[j] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See SCC-A)

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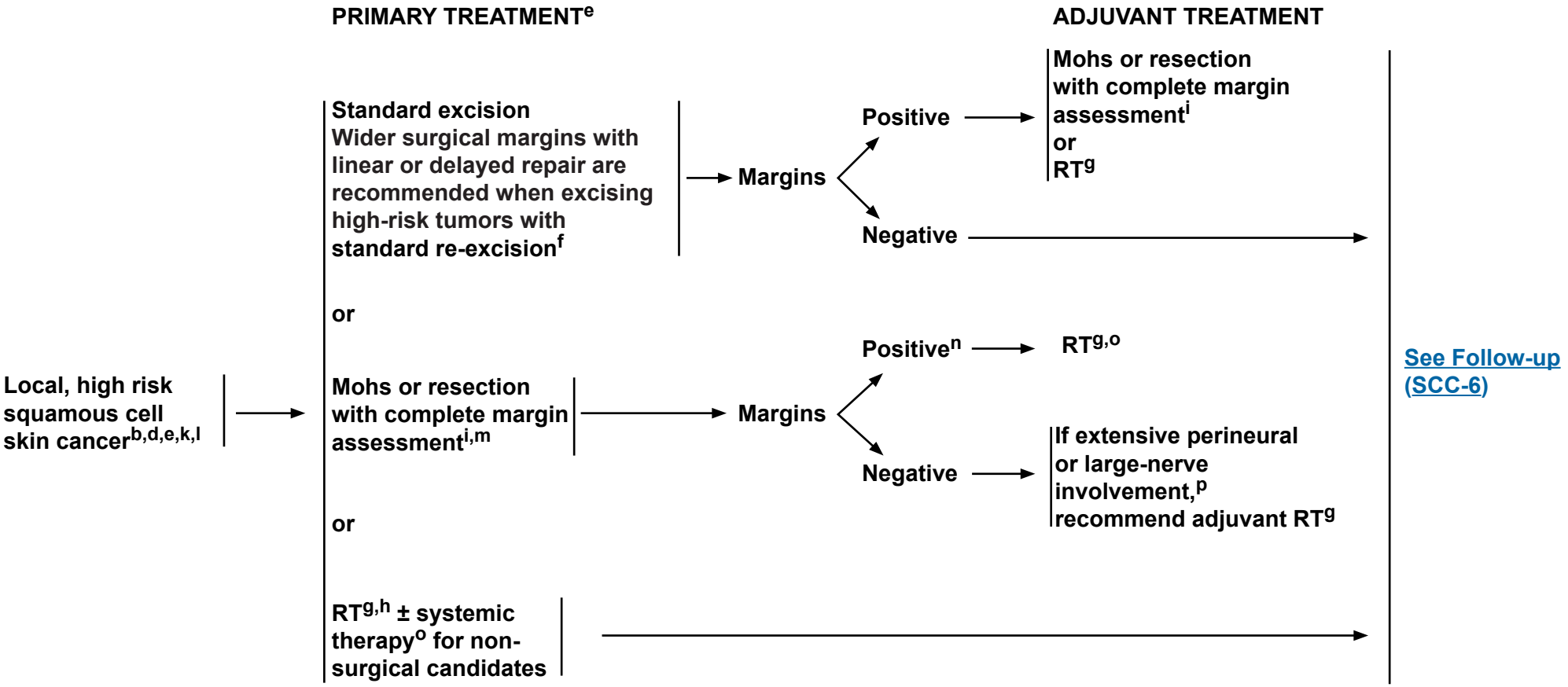

[b] See Risk Factors for Local Recurrence or Metastases (SCC-A).
[d] Any high-risk factor places the patient in the high-risk category.
[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[f] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[g] See Principles of Radiation Therapy Squamous Cell Skin Cancer (SCC-C).
[h] RT is often reserved for patients over 60 years old because of concerns about long-term sequelae.
[i] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs surgery.
[k] In certain high-risk lesions consider sentinel lymph node mapping, although the benefit of this technique has yet to be proven.
[l] For complicated cases, consider multidisciplinary tumor board consultation.
[m] If invasion to parotid fascia, superficial parotidectomy.
[n] Negative margins unachievable by Mohs surgery or more extensive surgical procedures.
[o] Consider multidisciplinary consultation to discuss chemoradiation or clinical trial. RT may be supplemented by chemotherapy in select patients. See NCCN Guidelines for Head and Neck Cancers.
[p] If large nerve involvement is suspected, consider MRI to evaluate extent and base of skull involvement or intracranial extension.

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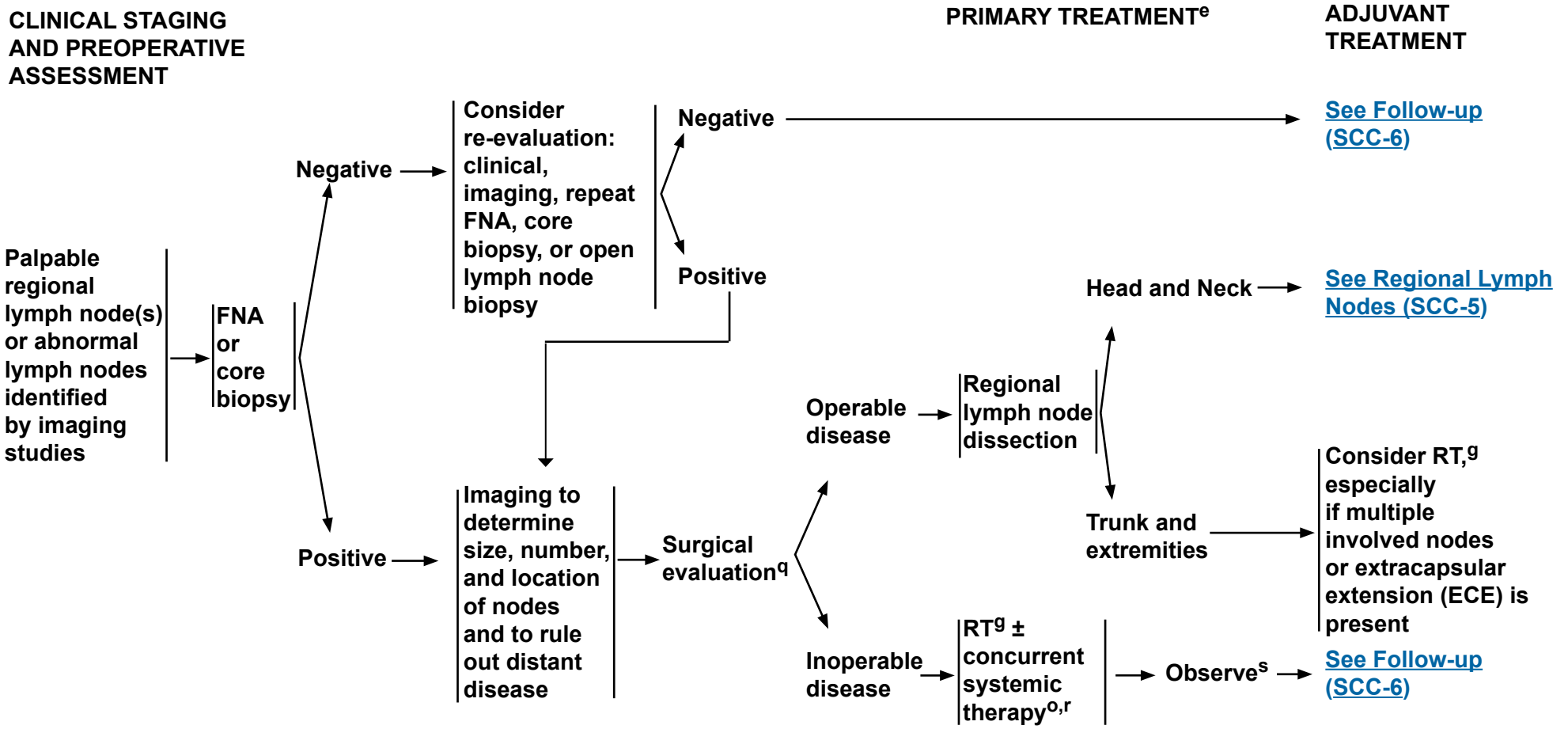

[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[g] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-C).
[o] Consider multidisciplinary consultation to discuss chemoradiation or clinical trial. RT may be supplemented by chemotherapy in select patients. See NCCN Guidelines for Head and Neck Cancers.
[q] Regional lymph node dissection is preferred, unless the patient is not a surgical candidate.
[r] Multidisciplinary consultation recommended. Consider systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas. See NCCN Guidelines for Head and Neck Cancers.
[s] Re-evaluate surgical candidacy for post-radiation lymph node dissection as indicated.

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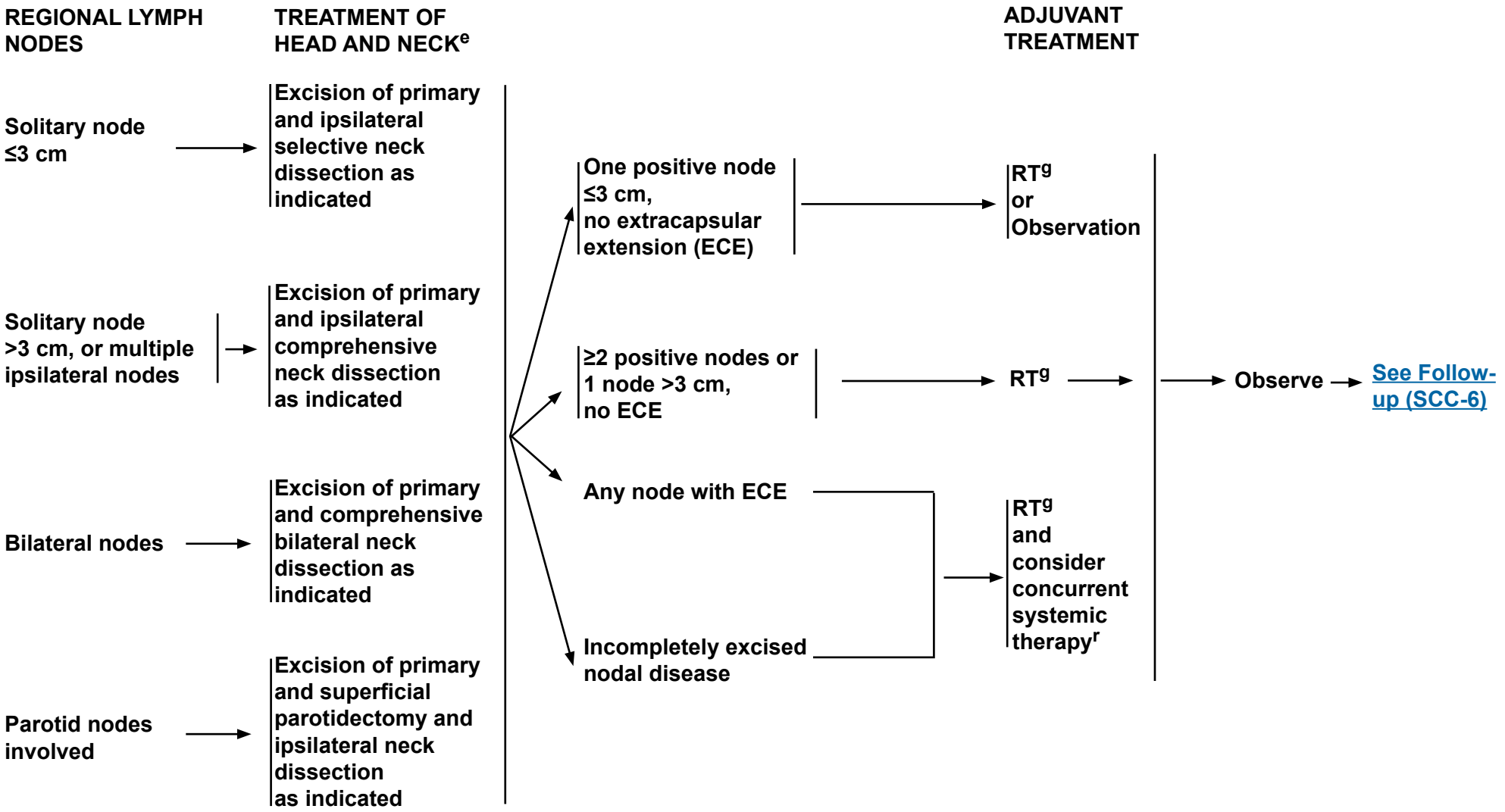


[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[g] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-C).
[r] Multidisciplinary consultation recommended. Consider systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas. See NCCN Guidelines for Head and Neck Cancers.

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.

FOLLOW-UP

Local disease:

H&P[t,u]
Every 3–12 mo for 2 y, then every 6–12 mo for 3 y, then annually for life

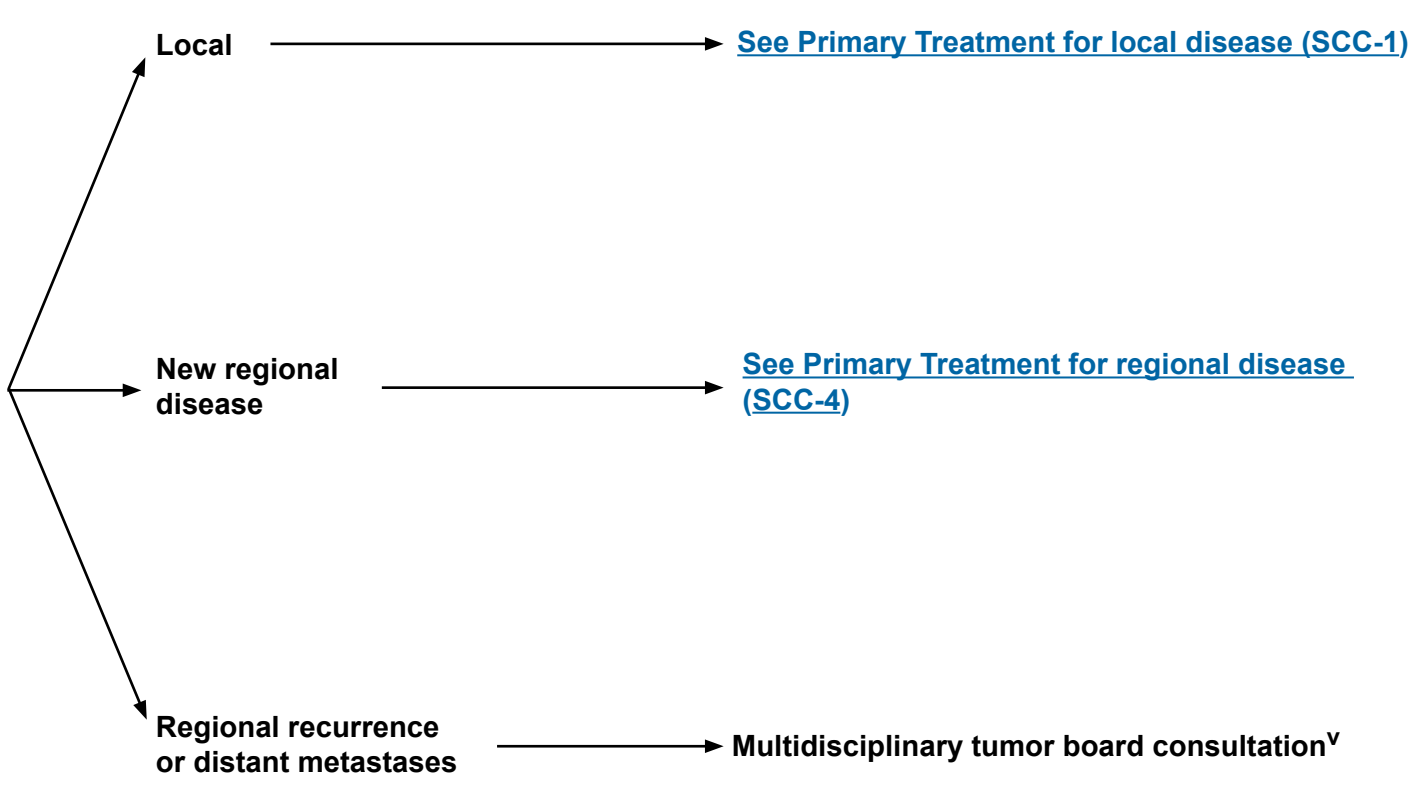
- **Patient education**
  - **Sun protection**
  - **Self examination of skin**

Regional disease:

H&P[t,u]
Every 1–3 mo for 1 y, then every 2–4 mo for 1 y, then every 4–6 mo for 3 y, then every 6–12 mo annually for life

- **Patient education**
  - **Sun protection**
  - **Self examination of skin**

RECURRENCE/DISEASE PROGRESSION



[t]Including complete skin and regional lymph node exam.
[u]Frequency of follow-up should be adjusted based on risk.
[v]Clinical trials are recommended for metastatic cutaneous squamous cell carcinoma. If the patient is a solid organ transplant recipient receiving immunosuppressive therapy, consider dose reduction of the immunosuppressive agent(s) and/or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors where appropriate. Cisplatin, either as a single agent or combined with 5FU, and EGFR inhibitors (eg, cetuximab), have each occasionally produced useful responses, but data supporting efficacy are limited.

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RISK FACTORS FOR LOCAL RECURRENCE OR METASTASES

H&P	Low Risk	High Risk
Location/size[1]	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm[4]	Area M ≥10 mm
	Area H <6 mm[4]	Area H ≥6 mm
Borders	Well-defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT or chronic inflammatory process	(-)	(+)
Rapidly growing tumor	(-)	(+)
Neurologic symptoms	(-)	(+)
Pathology		
Degree of differentiation	Well or moderately differentiated	Poorly differentiated
Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic or basosquamous (metatypical) subtypes	(-)	(+)
Depth[2,3]: Thickness or Clark level	<2 mm or I, II, III	≥2 mm or IV, V
Perineural, lymphatic, or vascular involvement	(-)	(+)

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

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, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

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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.**
- **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 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.**

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PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER

Primary Tumor[1]	Dose Time Fractionation Schedule
Tumor Diameter	Examples of Dose Fractionation and Treatment Duration
<2 cm	64 Gy in 32 fractions over 6–6.4 weeks 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥2 cm	66 Gy in 33 fractions over 6–6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant	50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks

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

ECE= Extracapsular extension

- **Protracted fractionation is associated with improved cosmetic results.**
- **Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, scleroderma).**

[1]Field 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 90% 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.

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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 (eg, 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 (eg, extension beyond cutaneous structures, perineural involvement, large and poorly differentiated, having ≥3 risk factors for recurrence) (See Risk Factors for Local Recurrence or Metastases [SCC-A])
- 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 continued on next page

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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 electrodesiccation.
  - 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.

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Identification and Management continued on next page

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.

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Staging

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
Anatomic location	Primary site ear
	Primary site non-hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated

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

Continue

Table 1 Continued

American Joint Committee on Cancer (AJCC)

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

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T Any	N3	M0
	T4	N Any	M0
	T Any	N Any	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/20/14

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.

Table of Contents

Overview

Basal cell and squamous cell skin cancers, collectively known as non-melanoma skin cancers (NMSCs), are the most common cancer in the United States. It is estimated that more than 3.5 million cases of NMSC were diagnosed in 2006; this exceeds the incidence of all other cancers combined.[1] Furthermore, the incidence of this common malignancy is rising rapidly.[2] Basal cell carcinomas (BCCs) are about four to five times more common than squamous cell carcinomas (SCCs). Although rarely metastatic, BCC and SCC 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 in the Medicare population exceeds $400 million.[3,4] However, NMSCs generally have a good prognosis.

A number of risk factors are associated with NMSCs.[5,6] The most recognized environmental carcinogen is sunlight. Evidence reveals that cumulative exposure to the sun is strongly correlated to SCC, but its relation with BCC appears more complex. Fair-skinned individuals who have received too much sun exposure are at the greatest risk for these cancers. Most of these tumors develop on sun-exposed skin sites, especially the head and neck area (80% of all cases). Radiation exposure, especially at a young age, is also associated with an increased risk for developing NMSC.[7,8]

Actinic keratoses are sun-induced precancerous lesions, while Bowen's disease refers to SCC in situ.[9-11] Both lesions, if left untreated, can progress to invasive SCC with the potential for metastasis.

Experts agree that public education on skin cancer prevention should be promoted, although studies that reliably evaluate net benefits of preventive measures are sorely needed.[12,13] Until then, all patients should be made aware of the various resources that discuss skin cancer prevention. Some of the useful resources are listed below:

- Skin cancer prevention and early detection. American Cancer Society. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003184-pdf.pdf
- SPOT skin cancer. American Academy of Dermatology. Available at: http://aad.org/spot-skin-cancer
- Prevention Guidelines. Skin Cancer Foundation. Available at: http://www.skincancer.org/prevention

Genetics

Extensive research has led to advances in the understanding of the genetics of NMSCs. The sonic hedgehog signaling pathway has emerged as playing a pivotal role in the pathogenesis of BCC.[14] Mutations in the *PTCH1* (patched 1) gene on chromosome 9q, which codes for the sonic hedgehog receptor, are the underlying cause of nevoid BCC syndrome, and are present in approximately 90% of sporadic BCCs. Specific ultraviolet (UV)-induced mutations in the tumor suppressor gene *p53* appear to be a common event in NMSC development.[15] Mutations in several oncogenes (eg, *ras* and *fos*) have also been identified. However, in NMSC development, the role any specific oncogene plays is unclear.[5]

Finally, certain genetic syndromes greatly predispose affected individuals to NMSC formation, such as albinism (in which skin pigment is absent), xeroderma pigmentosum (in which defects exist in UV light-induced unscheduled DNA repair), and nevoid BCC syndrome. Certain settings of immunosuppression (most notably, organ

transplantation) also predispose affected individuals, particularly to SCC. A transplant registry audit held in the United Kingdom reported a 13-fold increase in 10-year incidence of NMSC in transplant recipients compared to the general population.[16]

Clinical Presentation and Workup

On clinical presentation of the patient with a suspicious lesion, workup of both BCC and SCC begins with a history and physical examination. For BCC, the emphasis is on a complete skin examination. For SCC, 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.[17] A skin biopsy is then performed on any suspicious lesion. The biopsy should include deep 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.[18,19] Skin lesions in high-risk populations may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. Imaging studies can be done in all patients as clinically indicated when extensive disease such as bone involvement, perineural invasion, deep soft tissue involvement, or lymphovascular invasion (for SCC) is suspected. MRI is preferred over CT scan if perineural disease is suspected because of its higher sensitivity.

In patients with SCC, the presence of a palpable regional lymph node or abnormal lymph nodes identified by imaging studies should prompt a fine-needle aspiration (FNA) for diagnosis (see *Regional Lymph Node Involvement in SCC*).

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.

Risk Stratification

The NCCN Panel examined risk factors for BCC and SCC associated with recurrence and metastasis. These are listed in table format in the algorithm. If any high-risk feature is present, the patient should be managed according to the high-risk treatment pathway.

The most recent version of the AJCC staging system for SCC reflects many but not all of the features that the NCCN Panel has incorporated to designate high-risk tumors.[20,21] Alternative staging systems have been proposed to more accurately define high-risk groups.[22,23]

After workup, a risk assessment of NMSC should be performed to determine the treatment plan. For SCC, patients should also be evaluated for lymph node involvement (see *Regional Lymph Node Involvement in SCC*).

Common Risk Factors for BCC and SCC

Location and Size

Location has been known to be a risk factor for NMSC recurrence and metastasis for many years.[24,25] 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.[26,27] Size also has been shown to be a risk factor for NMSC recurrence.[28-31] Various different divisions have been used; the most common likely has been greater than or less than 2 cm in diameter.

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.[32,33] 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.

These criteria are 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.[34] More recently, the American Academy of Dermatology (AAD) in collaboration with American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery developed an appropriate use criteria (AUC) document in the treatment of cutaneous neoplasms.[35] This was based on 270 clinical scenarios including 69 BCCs and 143 SCCs. Areas of the body are described in detail in the algorithm sections *Risk Factors for Recurrence*.

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 literature.[29,30,36]

Immunosuppression

Settings of immunosuppression, such as organ transplantation[37] and long-term use of psoralen and UV A light (PUVA),[38,39] significantly increase the incidence of SCC development. BCC incidence also increases slightly in these settings. Immunosuppression is one key prognostic factor for metastasis in a prospective study by Brantsch and colleagues.[40]

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).[41] 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.[42] 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. Because organ transplant recipients have collectively worse outcomes, these patients and their neoplasms are designated as high risk.

Limited data suggest BCCs are more likely to recur or metastasize when they develop in immunosuppressed individuals.[43,44] 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.

Site of Prior Radiotherapy

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. Data from older studies support prior radiotherapy for unrelated (frequently benign) conditions as a risk factor for NMSC recurrence or metastasis.[45-47]

Perineural Involvement

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.[5,29] Although perineural involvement is uncommon in any NMSC (2%–6%), it develops much more frequently in SCC than in BCC.[48] It is associated with other risk factors including recurrent tumors, high grade, and larger lesion size.[48] 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 and recurrence-free survival.[49] If large nerve involvement is suspected, MRI should be considered to evaluate extent and rule out skull involvement.[50] 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.[23,51]

Degree of Differentiation

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.[29] Another cohort study of 315 patients also associated differentiation grade with overall survival.[49] Eroglu and colleagues reported differentiation to be a significant risk factor of recurrence in an analysis of 1039 patients.[52] Although Broders originally divided SCC histologically into four groups or grades in 1920, 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 this guideline.[21,23]

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. Leffell and colleagues documented an increased percentage of BCC with aggressive histologic growth patterns in young persons.[53] However, this histologic feature is already a separate risk factor in the algorithm.

The features of 54 BCC in young patients referred for Mohs surgery were compared with similar tumors in older patients.[54] 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 BCC patients were followed for a minimum of 5 years;[55] 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.[56] Finally, two more recent studies found no difference in either recurrence rates or presence of aggressive histologic subtypes in younger versus older patients with BCC.[57,58] Taken together, these studies do not support that young age, in and of itself, is a high-risk factor for NMSC behavior.

Pathologic Risk Factors for BCC

Histologic subtyping of BCC as a predictor of risk of recurrence is a well-established concept.[5] The subtypes encompassed by the term “aggressive growth pattern” including micronodular, infiltrative, sclerosing, and morpheaform (or desmoplastic) patterns are more likely to recur than the nodular and superficial BCC. Non-aggressive subtypes include the keratotic variant, infundibulocystic variant, and fibroepithelioma of Pinkus.

Basosquamous Carcinoma

Basosquamous carcinomas are tumors of which one part has the histologic appearance of a BCC and another that of a SCC. Some basosquamous tumors are the result of a BCC colliding with an adjacent SCC. Others represent truly biphenotypic tumors, many of which may have started as BCC, but have subsequently undergone prominent partial squamous metaplasia.[59] It seems that the risk for metastasis of these tumors is determined by the squamous component. Data suggest that basosquamous carcinomas have a metastatic capacity that is more similar to that of SCC than BCC.[60]

Additional Risk Factors for SCC

The NCCN Panel identified a few additional clinical parameters that increase the risk for SCC as follows:

Site of a Chronic Inflammatory Process

A substantial body of literature has documented increased rates of metastasis for cutaneous SCC arising in the setting of chronic scarring.[61,62]

Rapidly Growing Tumor

Only one article in the literature documents rapid growth of a cutaneous SCC as a risk factor for increased metastasis and even death.[63] Nevertheless, the NCCN Panel Members unanimously agreed this is a rare, albeit definite, clinical setting indicative of high-risk behavior.

Neurologic Symptoms

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.[64] Any suggestion of neurologic involvement in the region of a SCC should place that tumor in a high-risk category.

Histology

The histologic subtypes of 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.[65-67] 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.[40,68] A recent review of 72 patients with desmoplastic SCC reported a high rate of recurrence of 80%.[69]

Although the risk of metastasis from SCC in situ (full-thickness atypia) is negligible, the risk of recurrence, as with the superficial form of BCC, depends on the presence or absence of any of the risk factors listed in the algorithm.

Depth

Brantsch and colleagues[40] 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, and 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.[19] 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.[19,40] A meta-analysis of SCC risk factors for recurrence and metastasis found that both types of depth measurements have prognostic value.[29] Both tumor thickness and level have been included in the T classification of the most recent AJCC staging for SCC.[21]

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.[19] 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 SCC. 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 SCC behavior.[70] However, the panel decided this indirect association did not warrant the listing of spindle cell SCC as a separate risk factor.

Patients at High Risk of Developing SCC

Individuals with an immunocompromised status, such as solid organ transplant recipients, or those with rare genetic disorders such as xeroderma pigmentosum are at high risk of developing multiple SCCs. Clinicians are advised to follow the algorithm section *Identification and Management of High-risk Patients* for detailed guidance on the treatment of precancers and skin cancers for these patients.

Actinic keratoses, a premalignant skin condition, are most commonly treated with cryotherapy, topical treatment with 5-FU or imiquimod, PDT, or C and E.[9,71-75] Methyl aminolevulinate (MAL) PDT was found to be as effective as cryotherapy for the treatment of actinic keratoses and SCC in situ in randomized clinical trials.[76-78] Other treatments that may be considered include topical diclofenac (category 2B),[79,80] chemical peels, and ablative skin resurfacing.

Destructive techniques that can be used to treat multiple lesions in a single visit may be preferable for individuals who rapidly develop multiple lesions. One feasible strategy for organ transplant recipients is dose reduction of immunosuppressive therapy and/or the use of mTOR inhibition. In the case where surgery is impractical due to high SCC burden, oral capecitabine has been suggested in the transplantation setting, although toxicity is a concern.[81]

Oral retinoids have been found to be effective in reducing the development of pre-cancers and skin cancers in some high-risk patients.[82-84] Side effects may be significant. In addition, these agents are teratogenic and must be used with extreme caution in women of child-bearing age.

Local Treatment for BCC and SCC

Localized BCC and SCC are most commonly treated with surgery. Traditional techniques are mostly supported by older studies, and data from prospective trials with long-term follow-up is scant. In an evidence-based review of the literature, the best results were obtained with surgery.[85] However, consideration of function, cosmetic outcome, and patient preference may lead to the choice of radiation therapy (RT) as primary treatment in order to achieve optimal overall results.

Curettage and Electrodesiccation

Curettage and electrodesiccation (C&E) is the process of alternatively scraping away tumor tissue with a curette down to a firm layer of normal dermis and denaturing the area by electrodessication. Up to 3 cycles may be performed in a session. Although a fast and cost-effective technique for superficial lesions, it does not allow histologic margin assessment. Overall 5-year cure rates reported for BCC and SCC are 92% and 96%, respectively.[86,87] However, recurrence rates can be high for high-risk locations (21%) and high-risk histologic subtypes (27%).[88,89]

This technique is deemed effective for low-risk tumors with three caveats.[33,89] First, this technique should not be used to treat areas with terminal hair growth such as the scalp or beard area in males due to the risk that a tumor extending down follicular structures might not be adequately removed.

Second, if the subcutaneous layer is reached during the course of surgery, then surgical excision should generally be performed instead. This change in therapy is necessary as the effectiveness of the C&E 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 adipose is even softer than tumor tissue, the ability of the curette to distinguish and, therefore, to selectively and completely remove tumor cells, disappears.

Third, if curettage has been performed based only on the appearance of a low-risk tumor, biopsy results of the tissue taken at the time of curettage should be reviewed to make sure that there are no high-risk pathologic features that would require additional therapy.

Excision with Postoperative Margin Assessment

Another therapeutic option for both BCC and SCC is excision with postoperative margin assessment (POMA), consisting of standard surgical excision followed by postoperative pathologic evaluation of margins. This technique has been reported to achieve 5-year disease-free rates of over 98% for BCC and 92% for SCC.[87]

The clinical margins chosen by the panel for low-risk tumors are based on the work of Zitelli and colleagues.[90,91] Their analysis indicated that excision of BCC or SCC 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 SCC must be included in what is assumed to be the tumor. The panel expanded the clinical margins for SCC; 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 re-excision of low-risk primary BCC and SCC located on the trunk and extremities excluding pretibia, hands, feet, nail units, and ankles (area L regions) if positive margins are obtained after an initial excision with POMA.

If lesions can be excised with the recommended margins, then linear closure, skin grafting, or secondary intention healing (ie, 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 before closure.

As noted below, excision with comprehensive intraoperative margin control is the preferred surgical technique for high risk BCC and SCC. However, if standard excision with POMA is used for treatment of a

high-risk tumor due to patient-related clinical circumstances or other variables, wider surgical margins than those recommended for low risk lesions must be taken and increased recurrence rates should be expected.

Mohs Surgery or Excision with Intraoperative Frozen Section Assessment

Mohs surgery is the preferred surgical technique for high-risk BCC and SCC because it allows intraoperative analysis of 100% of the excision margin. A meta-analysis associated Mohs surgery with a 5-year disease-free survival rate of 99% for BCC and 97% for SCC.[29,92] A more recent prospective randomized trial by Mosterd and colleagues[93] from The Netherlands indicates significantly lower recurrence rates for recurrent facial BCC treated with Mohs surgery compared to standard excision. The study failed to demonstrate a significant difference in recurrence rates for primary BCC between treatment groups. However, due to broad variability of surgical technique and margin assessment in the standard excision group, the findings are difficult to generalize.[94]

Excision with complete circumferential peripheral and deep-margin assessment (CCPDMA) using intraoperative frozen section (IOFS) assessment is acceptable as an alternative to Mohs surgery provided 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 for high-risk tumors.

Radiation Therapy

Although surgery is the mainstay of local treatment for NMSC, patient preference and other factors may lead to the choice of RT as primary therapy.[95] Two meta-analyses reported 5-year recurrence rates of 8.7% and 10% after RT on primary BCC and SCC, respectively.[29,36] A randomized study in 347 patients receiving either surgery or RT as primary treatment of BCC found RT to result in higher recurrence rates than surgery (7.5% vs. 0.7%).[96] When compared to cryotherapy in another randomized study of 93 patients with BCC, RT was associated with lower recurrence rates (4% vs. 39%).[97] Specifics about the application of RT, including total doses and fractionation ranges, are described under *Principles of Radiation Therapy* in the algorithm. Verrucous carcinoma is excluded, because several reports in the 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 (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, lupus, scleroderma).

Intensity-modulated RT (IMRT) has been gaining wide use in recent years for the concurrent treatment of the primary skin tumor and the draining lymphatic beds. The panel emphasized the importance of proper support and training by medical physicists in using this technology as primary treatment. Special attention is warranted to ensure adequate surface dose to the target area.

Radiation is an effective treatment option for selected patients with Bowen's disease who have large or multiple lesions and those who refuse surgery.[98]

RT is often reserved for patients older than 60 years because of concerns about long-term sequelae.[86]

The value of postoperative radiation in reducing the rate of recurrence in high-risk patients has been widely accepted.[95] The NCCN Panel recommends adjuvant radiotherapy for any NMSC that shows evidence of substantial perineural involvement (ie, involvement of more than just

a few small sensory nerve branches or large nerve involvement).[48] In select patients, local control approaches 100% with postoperative radiotherapy.[64] Adjuvant RT should also be considered if tissue margins are positive after Mohs surgery or CCPDMA.

Two randomized trials on mucosal SCC demonstrated superior locoregional control and progression-free survival in combining postoperative radiation with concurrent cisplatin compared to radiation alone, although adverse events also increased.[99,100] These results lend support to chemoradiation for SCC of the skin in select patients. An analysis of the trials revealed microscopically involved surgical margins and extracapsular extension (ECE) as the only risk factors for which additional chemotherapy is beneficial.[101]

Superficial Therapies

Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical.[102] Superficial therapies include topical treatment with 5-FU or imiquimod, photodynamic therapy (PDT), and cryotherapy.

Imiquimod was found to be effective for treating multiple, superficial BCC and SCC in situ in randomized studies.[103-106] A prospective trial reported a 84% 5-year disease-free rate in superficial BCC.[106]

Cryosurgery, which destroys tumors cells by freeze-thaw cycles, has demonstrated a 5-year disease-free survival rate of 99% for NMSC in a review of 2932 cases treated by a single clinician.[107]

PDT involves the application of a photosensitizing agent on the skin followed by irradiation with a light source. In one randomized study with long-term follow-up, more patients with nodular BCC treated with methyl aminolevulinate (MAL) PDT had an excellent or good cosmetic outcome compared to those treated with surgery, even though surgery was superior to PDT in terms of efficacy.[108] A review of clinical trials reported cure rates between 70% to 90% by PDT for patients with NMSC not amenable to excision.[109] Currently, PDT is being utilized at some NCCN Member Institutions for premalignant or superficial low-risk lesions on any location on the body, although response rates may be higher on the face and scalp.[74,75,110] A randomized trial of 60 patients with superficial BCC demonstrated similar 5-year recurrence rates with cryotherapy (20%) or PDT (22%).[111]

Although MAL is an approved photosensitizer for PDT, it is no longer produced in the United States.

NCCN Recommendations

For patients with SCC presenting palpable or abnormal lymph nodes, please see *Regional Lymph Node Involvement in SCC*.

Low-Risk NMSC

Primary treatment options for low-risk BCC and 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 POMA with 4-mm margins for BCC and 4- to 6-mm margins for SCC, and with reconstruction techniques such as linear closure, secondary intention healing, or skin graft; and 3) RT for non-surgical candidates, generally limited to those over 60 years of age because of long-term toxicity.

If margins are positive after excision, patients should receive adjuvant therapy. Surgery (Mohs surgery, resection with CCPDMA, or re-excision with POMA for area L regions) is the preferred choice, while radiation may be administered to non-surgical candidates.

The NCCN Panel discussed the use of alternative therapies as first-line treatment in patients with low-risk, shallow NMSCs such as SCC in situ (Bowen's disease) or superficial BCC. These include 5-FU, imiquimod, PDT with porfimer sodium or amino levulinic acid, or vigorous cryotherapy. Limited data suggest that the cure rate of these approaches may be lower compared to Mohs surgery.[110,112] On the other hand, panelist experience indicated that they may be effective for anatomically challenging locations, and recurrences are often small and manageable. Panelists agreed that these therapies may be considered for superficial NMSCs based on patient preference.

High-Risk NMSC

Options for high-risk lesions include: 1) Mohs surgery or resection with CCPDMA; 2) excision with POMA with wider surgical margins and primary or delayed repair; and 3) 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.

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 Mohs surgery or resection with CCPDMA, or receive 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.[113] The survival benefits of sentinel lymph node biopsy remain unclear.

Residual Disease in BCC

For patients with residual BCC where further surgery and radiation are contraindicated, the NCCN Panel recommends consideration of vismodegib or clinical trials. See *Systemic Therapy* for details on vismodegib. Panelists emphasized that treatment decisions should be made with multidisciplinary board consultation.

Regional Lymph Node Involvement in SCC

For patients with SCC, regional nodal involvement significantly increases the risk of recurrence and mortality.[114] Nodal metastasis also commonly coincides with other adverse histopathologic findings such as lymphovascular invasion, poor differentiation, and perineural invasion.[115] About 60% to 82% of patients presenting with nodal disease show involvement in the parotid gland, while cervical neck node disease without parotid invasion is observed in 18% to 41% of cases.[6]

Data on SCC with nodal metastasis are limited to single-center case reviews. Lymph node dissection plus adjuvant RT with or without concurrent chemotherapy is currently the standard of care. A retrospective study of 167 patients with metastatic disease to nodes in the head and neck found decreased locoregional recurrence (20% vs. 43%) and improved 5-year disease-free survival (73% vs. 54%) with the addition of adjuvant RT to surgery compared to surgery alone.[116] Similarly, in a single-institution analysis involving 51 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).[117] Overall and disease-free survival were also

improved by the addition of adjuvant radiation in another study of 122 patients with SCC metastasized to cervical lymph nodes.[118] Systemic therapy has been reported to yield response in 72% of patients with SCC not amenable to local therapy in a review of 28 observational studies.[119]

Parotid involvement, as direct extension from an overlying cutaneous SCC, is a poor prognostic factor for SCC.[120,121] 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.[122] The 5-year overall survival rate of patients treated by parotidectomy and adjuvant RT is 72%.[123]

NCCN Recommendations

Patients with palpable or suspicious lymph nodes on imaging tests should receive a fine-needle biopsy or core biopsy. A negative initial biopsy should be confirmed by re-biopsy and/or re-evaluation.

If there are positive findings on either FNA or open biopsy of a lymph node, the preferred treatment is regional lymph node dissection. Patients who had undergone dissection of nodes in the trunk and extremities should consider RT if multiple nodes are involved or if ECE is present. Dosage information can be found in the algorithm.

For patients with nodal metastasis to the head and neck, adjuvant treatment options are based on both the number of positive nodes and presence or absence of ECE. Postoperative radiation is recommended in all cases, although observation is a reasonable alternative for patients with only one small (≤3 cm) node and no ECE. Patients with ECE or incompletely excised nodes are at high risk of recurrence. They should receive adjuvant RT and also consider chemoradiation depending on individual toxicity tolerance.

Radiation with or without concurrent chemotherapy is an alternative when surgery is not initially feasible; however, patients should be re-evaluated for surgical candidacy for neck dissection after radiation.

Recurrence and Metastasis

Systemic Therapy

BCC

Recent FDA approval of the new agent vismodegib, a first-in-class Hedgehog pathway inhibitor, provided another option for patients who have exhausted surgical and radiation options for treating advanced BCC. Approval was based on a multicenter, single-arm, two-cohort, open-label, phase II trial enrolling 104 patients.[124] About 95% of patients were previously treated with surgery, RT, and/or systemic therapies. Objective response was recorded in 43% and 30% of patients with locally advanced and metastatic disease, respectively, with median response duration of 7.6 months. Adverse events with over 30% incidence included muscle spasms, alopecia, taste loss, weight loss, and fatigue. Twenty-six patients (25%) experienced serious adverse effects. An 18-month update presented in abstract form confirmed prolonged responses. Median duration of response was 14.7 months for metastatic BCC and 20.3 months for locally advanced BCC.[125]

Due to the rarity of advanced cases, the literature on chemotherapy for BCC is limited to case reports.[126-128]

SCC

Cutaneous SCC with distant metastasis, while rare, is more common than metastatic BCC. A 10-year cohort study involving 985 patients with SCC found a 3.7% risk of metastasis and 2.1% risk of disease-specific death. Unfortunately, scant evidence is available regarding systemic therapy for the condition.[129] There are no prospective phase III studies

available. Cisplatin either as a single agent or combined with 5-FU has occasionally produced useful responses, but data supporting efficacy are limited. 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.[130] One of the 11 patients experienced a complete response. Twelve patients with only regional lymph node metastases were treated and 3 had either a partial (2) or complete (1) response. This lends some credence to a cisplatin-based regimen. Other studies are retrospective and most are anecdotal.[129,131]

Some have advocated using therapies useful in metastatic squamous cell head and neck cancer for patients with metastatic cutaneous SCC.[132] 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.[133-138] 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.[139]

Neoadjuvant systemic therapy in preparation for subsequent surgery and/or radiation is generally not considered useful for metastatic disease with the possible exception of a few regional nodes.[140-142]

NCCN Recommendations

For the management of local tumor recurrence, the algorithm directs clinicians to follow the appropriate pathways for primary treatment. Complicated high-risk tumors, regional recurrence, or the development of distant disease should be managed by a multidisciplinary tumor board.

Although the behavior of cutaneous BCC is characteristically indolent, the disease does rarely metastasize to distant sites. In that instance vismodegib or clinical trial should be considered. Panels agreed that many patients with metastatic basosquamous carcinoma will also likely respond to vismodegib.

Patients with metastatic SCC should receive appropriate therapy. Although the NCCN Panel encourages participation in a clinical trial, unfortunately such trials are scarce. Often even large centers don't open trials for rare diseases because of the costs involved. Possible agents include cisplatin monotherapy, cisplatin plus 5-FU, or epidermal growth factor receptor (EGFR) inhibitors such as cetuximab. If the patient is a solid organ transplant recipient taking immunosuppressive therapy, one should consider reducing the doses of immunosuppressive agents where appropriate or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors.[143]

Follow-Up

Two well-established points about patients with NMSC underlie the follow-up schedules. One point is that 30% to 50% of these patients will develop another NMSC within 5 years.[144] This represents a 10-fold increase in risk compared to the general population.[145] They are also at increased risk of developing cutaneous melanoma.[17] Therefore, continued long-term surveillance of these patients is essential, as is patient education about the values of sun protection and regular self-examination of the skin. A second point is that 70% to 80% of all cutaneous SCC recurrences develop within 2 years of the initial therapy.[146] Therefore, close follow-up of these patients during this time period is critical.

NCCN Recommendations

The frequency of follow-up should be based on risk. Detailed guidelines on follow-up schedules can be found in the algorithm.

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