National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Basal Cell and Squamous Cell Skin Cancers

Version 1.2013

NCCN.org

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NCCN Guidelines Version 1.2013 Panel Members
Basal and Squamous Cell Skin Cancers

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Discussion

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NCCN Guidelines Panel Disclosures

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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 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 1.2013 Updates Basal Cell and Squamous Cell Skin Cancers

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Summary of the changes in the 1.2013 of the NCCN Basal Cell and Squamous Cell Skin Cancers Guidelines from the 2.2012 version include:

Basal Cell Skin Cancer

BCC-1

- Footnote "b" was revised: Extensive disease includes deep structural involvement such as bone, ~~or~~ perineural disease, and deep soft tissue. If perineural disease is suspected, MRI is preferred". (Also for SCC-1)

BCC-2

- Primary Treatment (Also for SCC-2):
  - C&E; Second bullet: Clarified as "If ~~fat~~ adipose reached, surgical excision..."
  - Excision with POMA: Clarified as "...~~side-to-side~~ linear repair, or skin graft".
- Adjuvant Treatment after "Excision with POMA"; Margins; Positive: The recommendation changed to "RT for non-surgical candidates". (Also for SCC-2)
- Footnote "h" was revised: "Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles) (See BCC-A)." (Also for SCC-3)

BCC-3

- Last column changed to "...consider multidisciplinary tumor board consultation ~~+ therapy~~ (consider vismodegib or clinical trials)".
- Footnote "j" is new to the algorithm: "If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy."
- The following footnote was removed "Consider clinical trials (preferred) or vismodegib. Combination chemotherapy with cisplatin- or carboplatin-based doublets has produced responses".

BCC-4

- Regional or distant metastases: "Multidisciplinary tumor board consultation ~~+ therapy~~ (consider vismodegib or clinical trials)".

BCC-A---Risk Factors For Recurrence

- Area M: Revised to include the "pretibia". (Also for SCC-A)

BCC-B---Principles of Treatment for Basal Cell Skin Cancer

- Fourth bullet: "Methyl aminolevulinate [MAL]" was removed from the list of photodynamic therapies (Also for SCC-B). Although FDA approved, this therapy is no longer being distributed in the United States.

Squamous Cell Skin Cancer

SCC-3

- Footnote "n" is new to the algorithm: "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."
- Footnote "o" was revised "If large nerve involvement is suspected, consider MRI to evaluate extent and ~~rule out~~ base of skull involvement or intracranial extension."

SCC-4

- Operable disease; Regional lymph node dissection; Trunk and extremities; Adjuvant Treatment was revised: "...especially if multiple involved nodes or ~~extensive~~ extracapsular extension (ECE) is present"
- Footnote "q" was revised: "~~Concurrent chemotherapy: Cisplatin 100 mg/m^2 every 3 weeks or cisplatin weekly at 30 mg/m^2.~~ 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".

SCC-6

- Regional recurrence or distant metastases: Recommendation changed to "Multidisciplinary tumor board consultation ~~+ therapy~~".

SCC-D---Identification and Management of High-Risk Patients

Page 2 of 3

- Treatment of Precancers: First bullet; First arrow: "Cryosurgery" changed to "Cryotherapy".
- Treatment of Skin Cancers:
  - Third bullet was revised: "...en bloc excision and ~~split thickness skin~~ grafting have been used with efficacy.
  - Fourth bullet was revised: "...radiation therapy is used more frequently as an adjuvant therapy and for perineural disease, ~~and less frequently for the treatment of primary tumors~~"
  - Sixth bullet was revised: "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.

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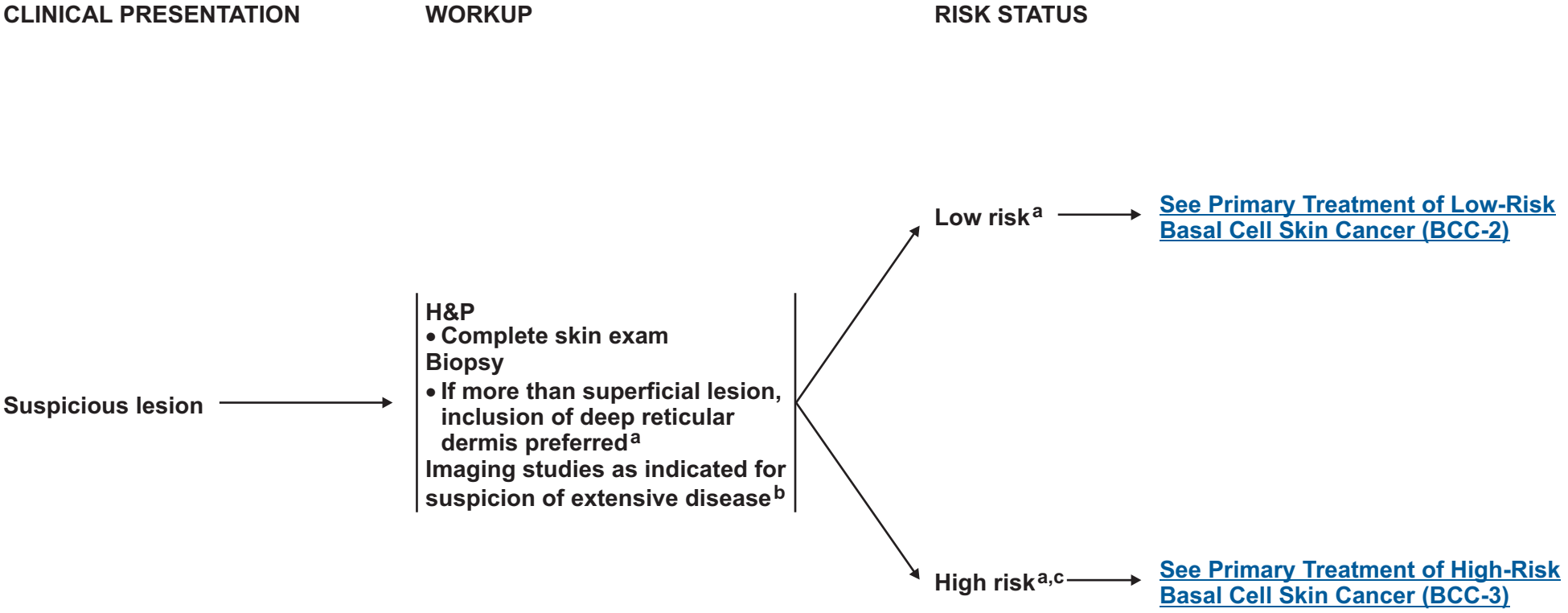

[a] See Risk Factors for Recurrence (BCC-A).
[b] Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI is preferred.
[c] Any high-risk factor places the patient in the high-risk category.

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.

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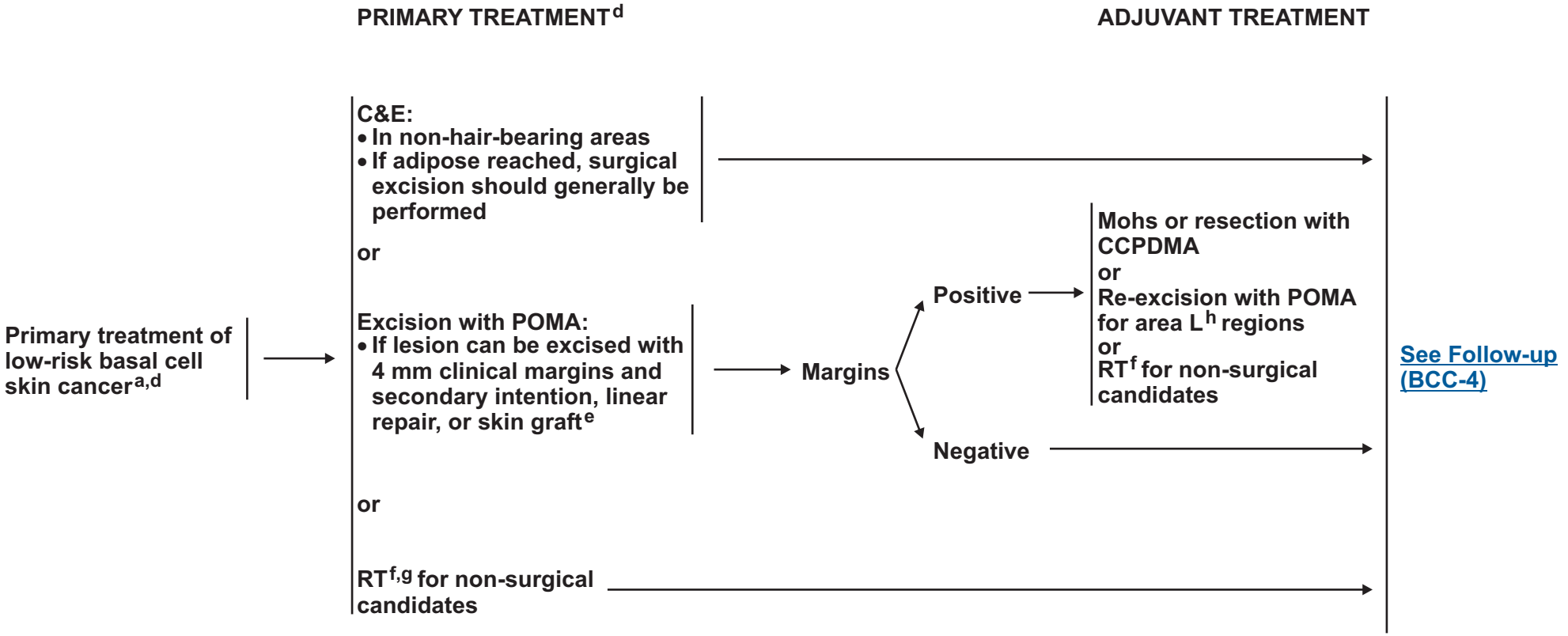

[a] See Risk Factors for Recurrence (BCC-A).
[d] See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f] See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g] RT generally reserved for patients over 60 y because of concerns about long term sequellae.
[h] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See BCC-A)

C&E= curettage and electrodesiccation

POMA= postoperative margin assessment

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

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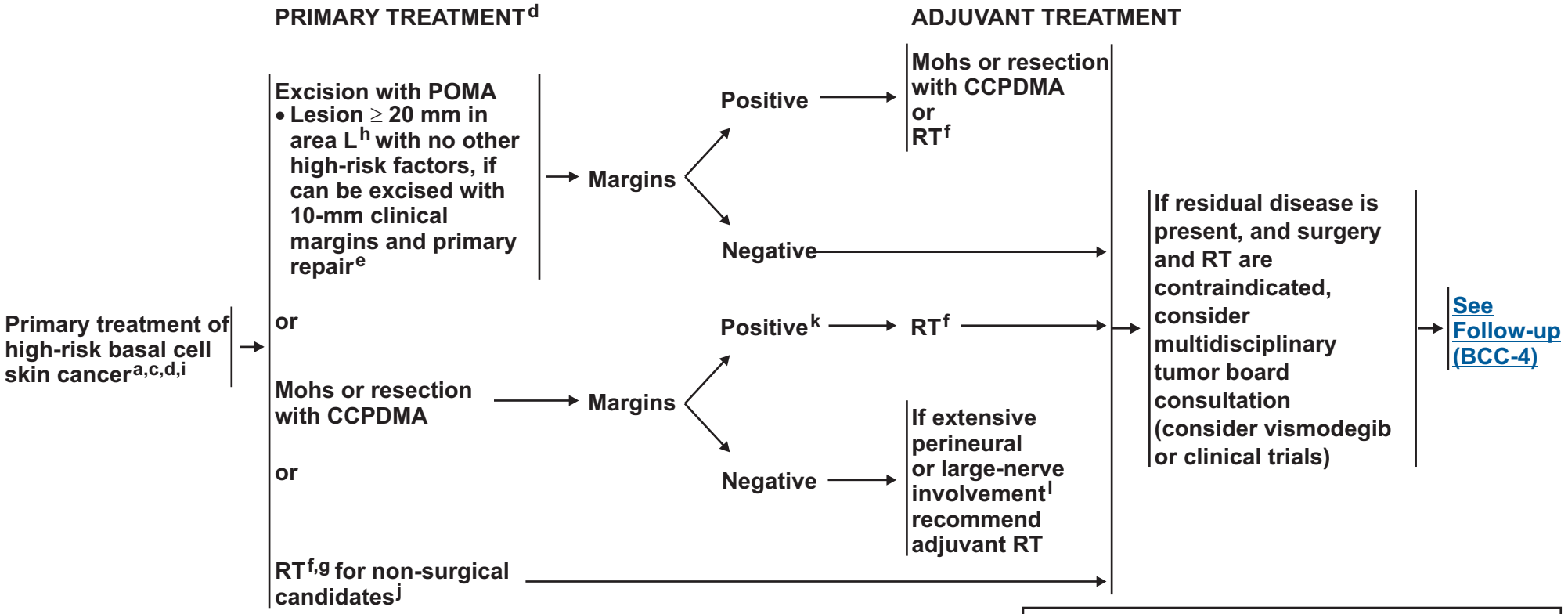

POMA= postoperative margin assessment

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

[a] See Risk Factors for Recurrence (BCC-A).
[c] Any high-risk factor places the patient in the high-risk category.
[d] See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f] See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g] RT generally reserved for patients over 60 y because of concerns about long term sequellae.
[h] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See BCC-A)
[i] For complicated cases, consider multidisciplinary tumor board consultation.
[j] If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.
[k] Negative margins unachievable by MOHS surgery or more extensive surgical procedures.
[l] If large nerve involvement is suspected, consider MRI to evaluate extent and rule out skull involvement.

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FOLLOW-UP

RECURRENCE

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

Patient education:
- **Sun protection**
- **Self-examination**

Local → **Follow Primary Treatment Pathways (BCC-1)**

Regional or distant metastases → **Multidisciplinary tumor board consultation (consider vismodegib or clinical trials)**

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RISK FACTORS FOR RECURRENCE

H&P	Low Risk	High Risk
Location/size	Area L < 20 mm	Area L ≥ 20 mm
	Area M < 10 mm	Area M ≥ 10 mm
	Area H < 6 mm[1]	Area H ≥ 6 mm[1]
Borders	Well defined	Poorly defined
Primary vs. Recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology		
Subtype	Nodular,[2] superficial	Aggressive growth pattern[3]
Perineural involvement	(-)	(+)

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).
(Connolly SM, Baker DR, Coldiron BM, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery.Dermatol Surg 2012;38:1582-1603).

[1]Location independent of size may constitute high risk in certain clinical settings.
[2]Low risk histologic subtypes include nodular, superficial and other non-agressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[3]Having morpheaform, sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor. For basosquamous (metatypical) lesions, see NCCN Squamous Cell Skin Cancer Guidelines.

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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 is contraindicated or impractical, topical therapies such as 5-fluorouracil, imiquimod, photodynamic therapy (eg, amino levulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rate may be lower.**

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PRINCIPLES OF RADIATION THERAPY FOR BASAL CELL SKIN CANCER

Dose and Field Size

Tumor Diameter	Margins	Examples of Electron Beam Dose and Fractionation
< 2 cm	1 - 1.5 cm[1]	64 Gy in 32 fractions over 6 - 6.4 weeks[2] 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	1.5 - 2 cm[1]	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

- **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]When using electron beam, wider field margins are necessary than with orthovoltage x-rays due to the wider beam penumbra. 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. Appropriate medical physics support is essential.

[2]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.

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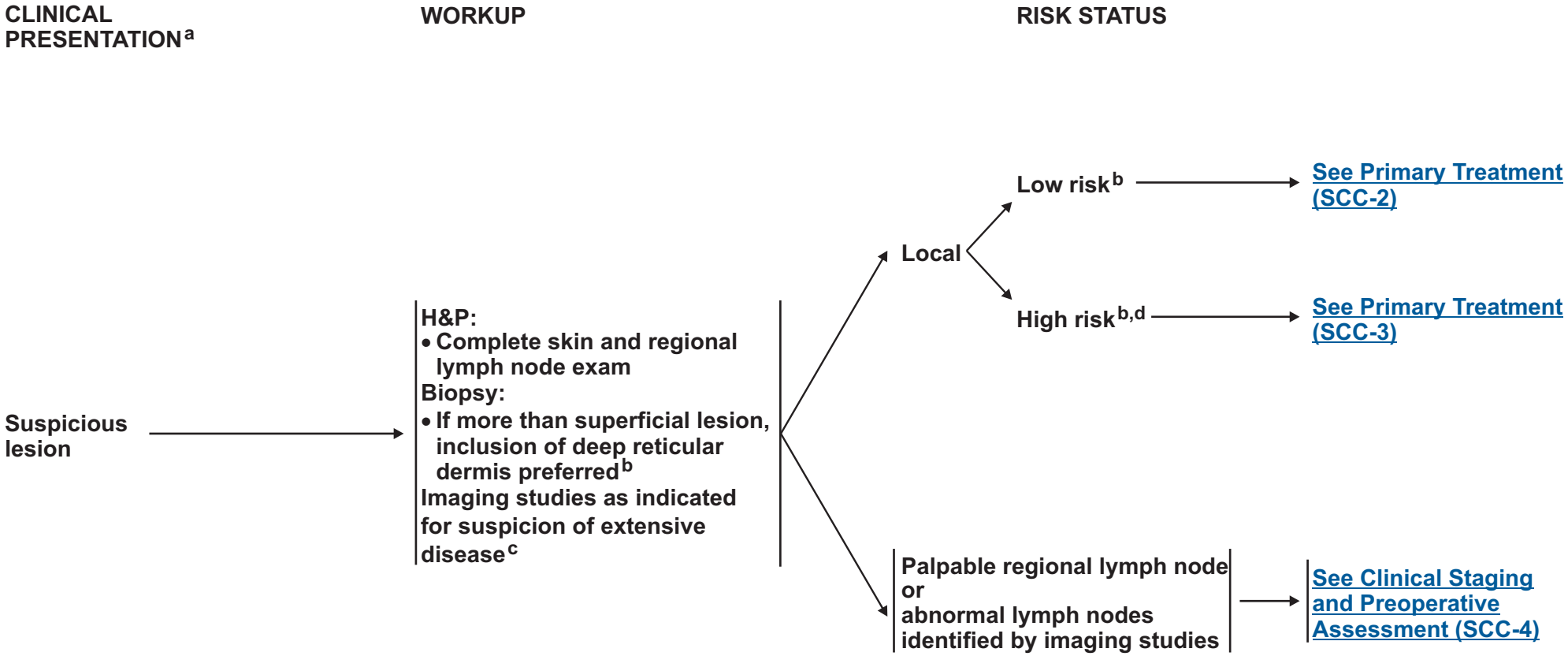

[a] Including basosquamous carcinoma and squamous cell skin cancer in situ (showing full-thickness epidermal atypi, excluding actinic keratoses).
[b] See Risk Factors for Recurrence (SCC-A).
[c] Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue.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

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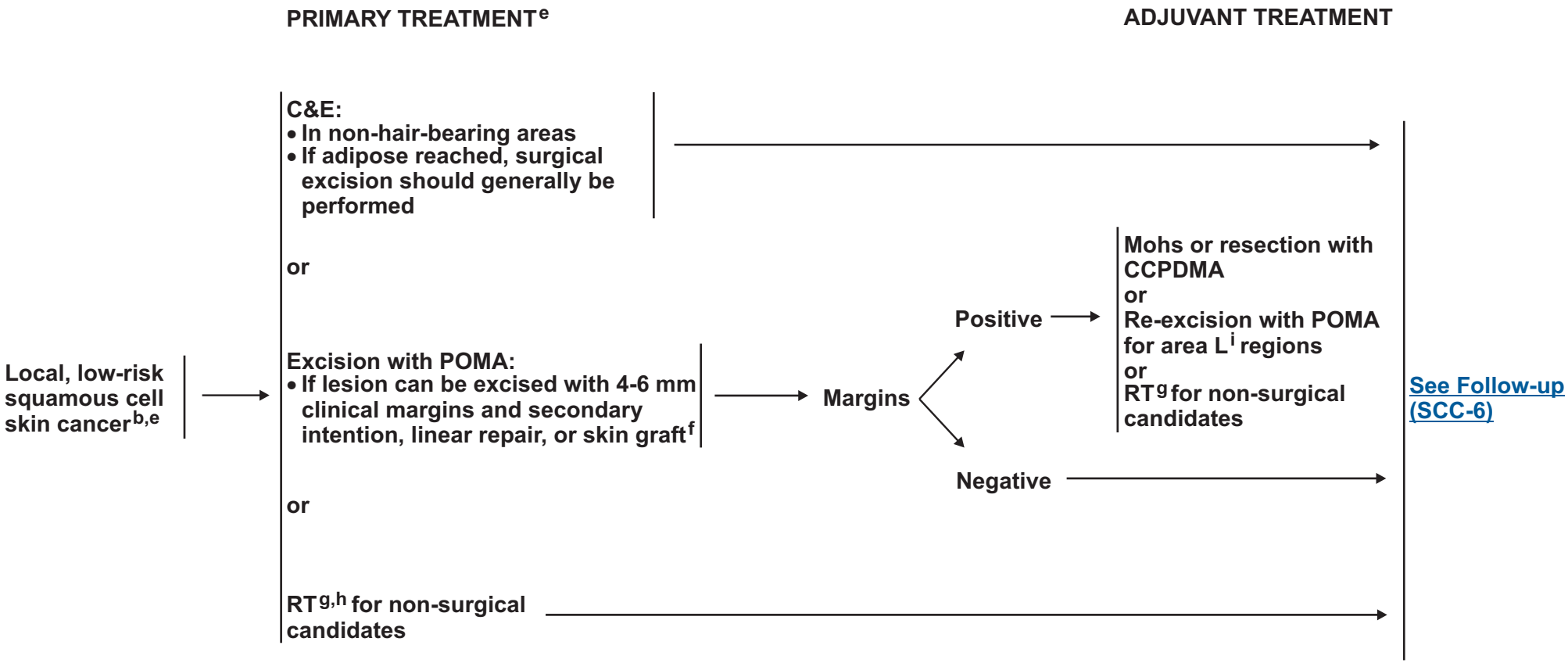

[b] See Risk Factors for Recurrence (SCC-A).
[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[f] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[g] See Principles of Radiation Therapy Squamous Cell Skin Cancer (SCC-C).
[h] RT generally reserved for patients over 60 y because of concerns about long-term sequellae.
[i] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See SCC-A)

C&E= curettage and electrodesiccation

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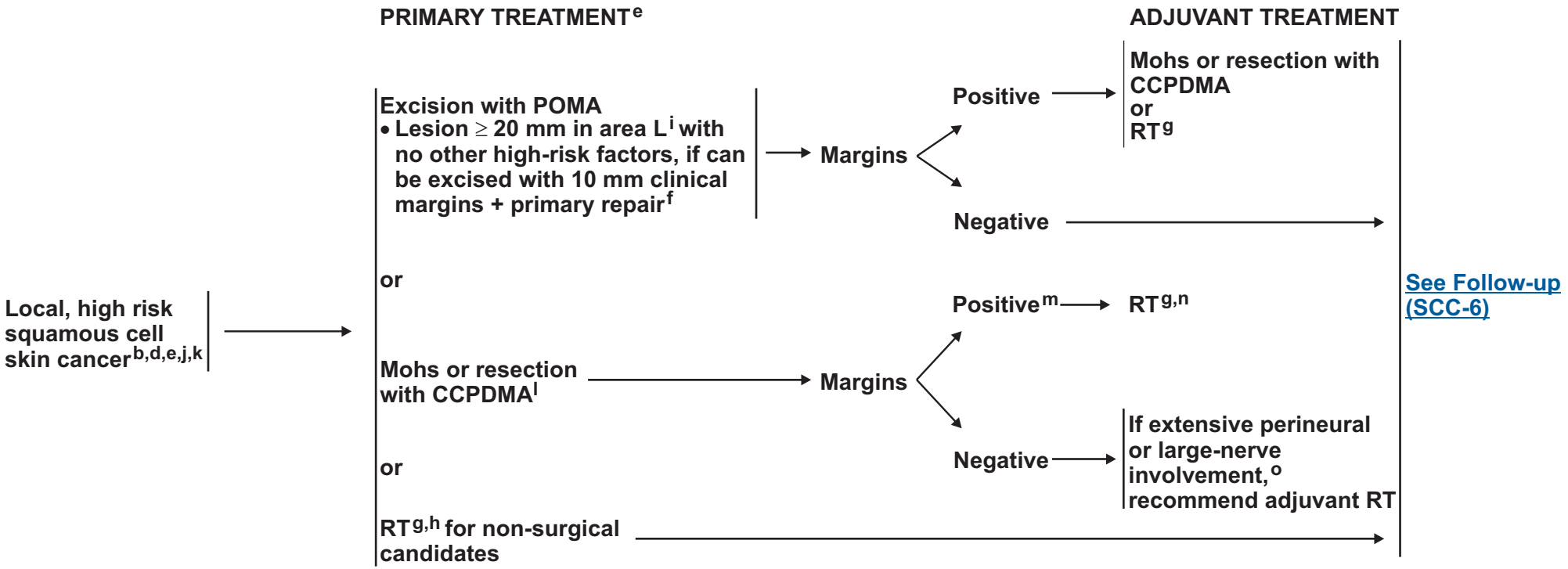

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[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[f] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[g] See Principles of Radiation Therapy Squamous Cell Skin Cancer (SCC-C).
[h] RT generally reserved for patients over 60 y because of concerns about long term sequelae.
[i] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See SCC-A)
[j] In certain high-risk lesions consider sentinel lymph node mapping, although the benefit of this technique has yet to be proven.
[k] For complicated cases, consider multidisciplinary tumor board consultation.
[l] If invasion to parotid fascia, superficial parotidectomy.
[m] Negative margins unachievable by MOHS surgery or more extensive surgical procedures.
[n] 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.
[o] If large nerve involvement is suspected, consider MRI to evaluate extent and base of skull involvement or intracranial extension.

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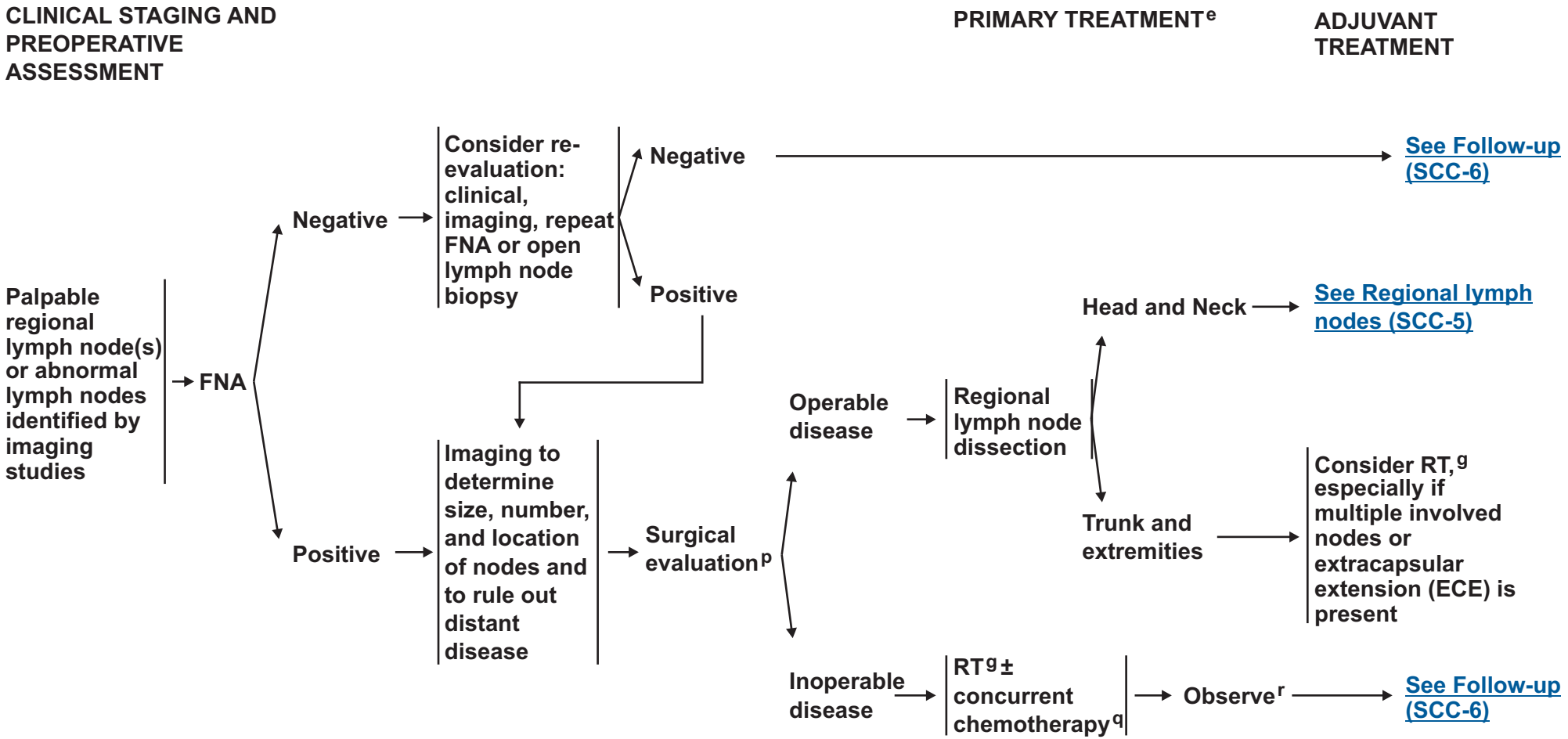

[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[g] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-C).
[p] Regional lymph node dissection is preferred, unless the patient is not a surgical candidate.
[q] Multidisciplinary consultation recommended. Consider systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas. See NCCN Guidelines for Head and Neck Cancers.
[r] Re-evaluate surgical candidacy for post-radiation lymph node dissection as indicated.

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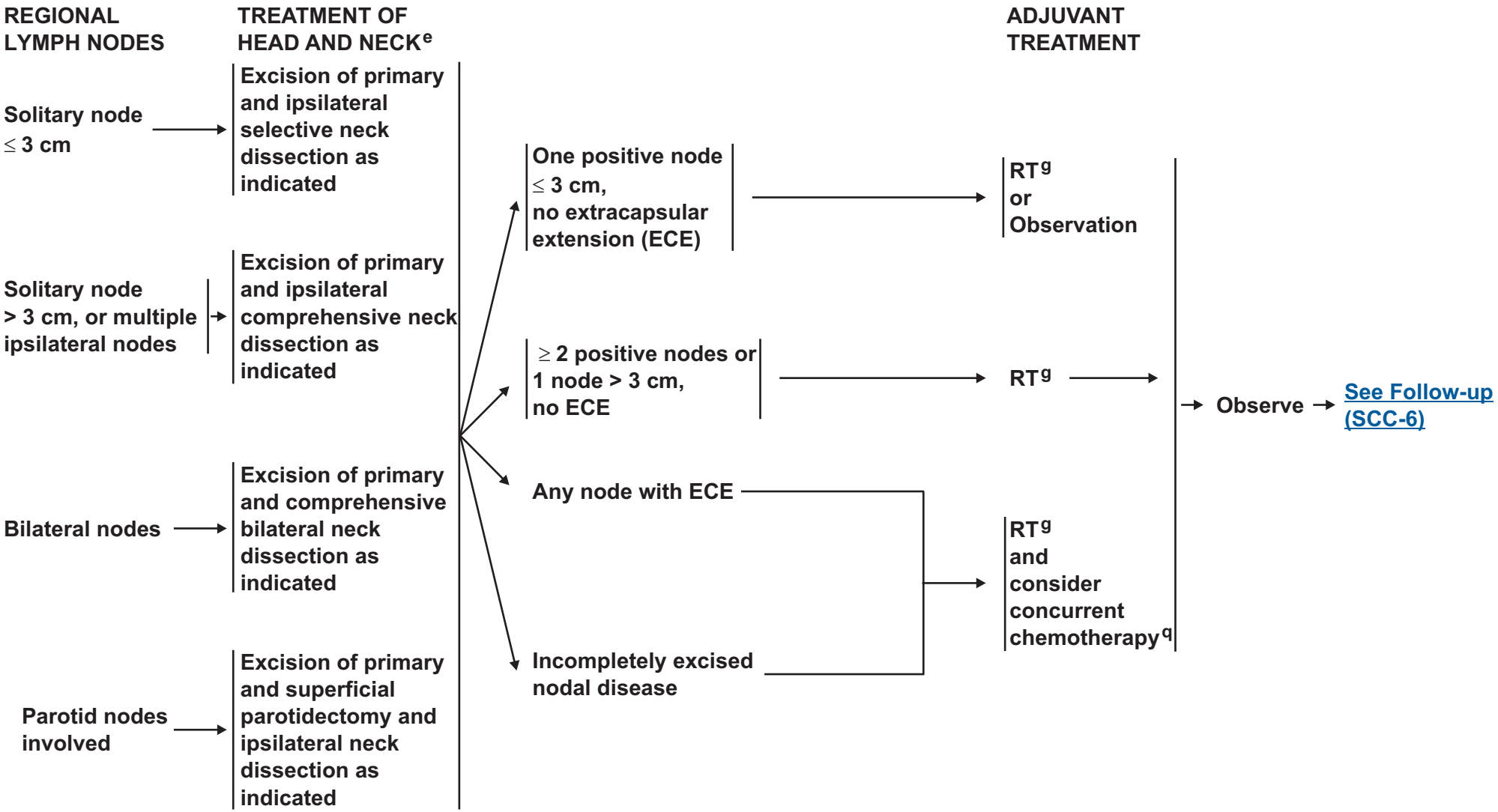

[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[g] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-C).
[q] Multidisciplinary consultation recommended. Consider systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas.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

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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.

FOLLOW-UP

Local disease:

- **H&P[q]**
  Every 3-6 mo for 2 y,
  then every 6-12 mo for 3 y,
  then annually for life

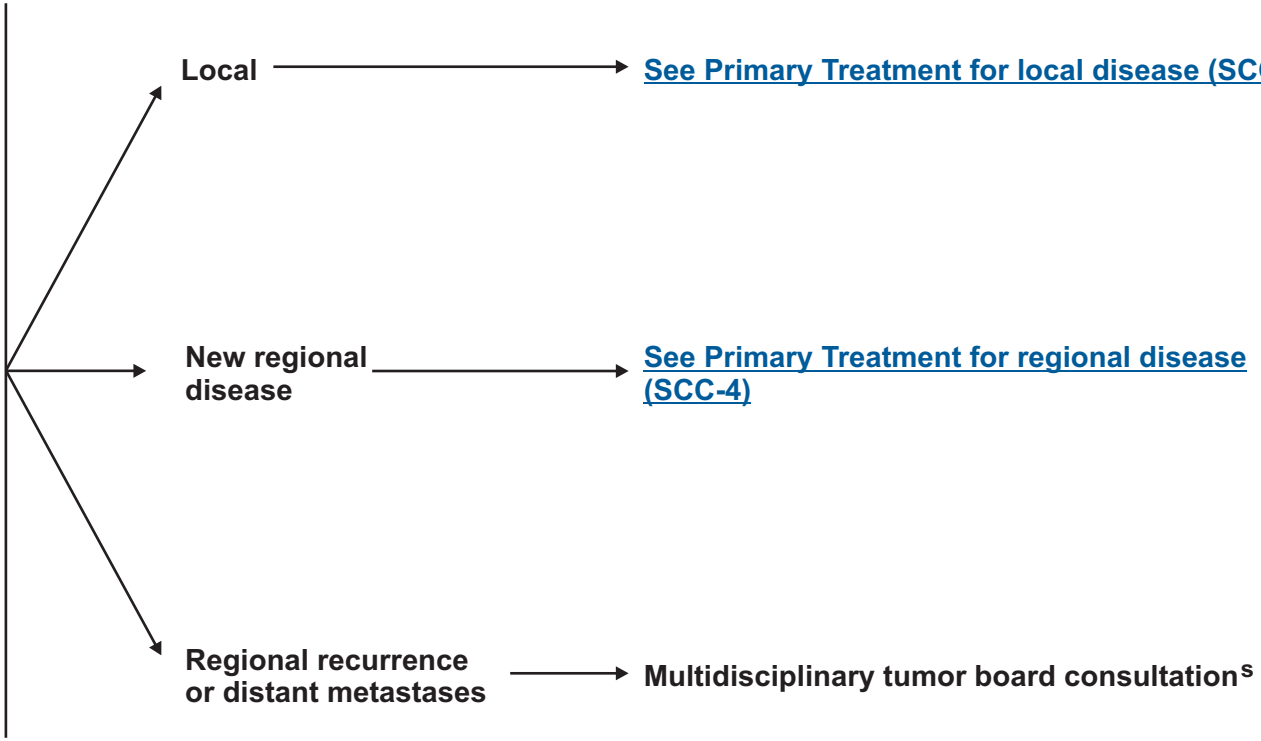
- **Patient education**
  - **Sun protection**
  - **Self examination of skin**

Regional disease:

- **H&P[r]**
  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



[r]Including complete skin and regional lymph node exam.

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

RISK FACTORS FOR RECURRENCE

H&P	Low Risk	High Risk
Location/size[1]	Area L < 20 mm	Area L ≥ 20 mm
	Area M < 10 mm	Area M ≥ 10 mm
	Area H < 6 mm[3]	Area H ≥ 6 mm[3]
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 differentiated	Moderately or poorly differentiated
Adenoid (acantholytic), adenosquamous (showing mucin production), or desmoplastic subtypes	(-)	(+)
Depth: Thickness[2] or Clark level	< 2 mm or I, II, III	≥ 2 mm or IV, V
Perineural or vascular involvement	(-)	(+)

[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, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).
(Connolly SM, Baker DR, Coldiron BM, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery.Dermatol Surg 2012;38:1582-1603).

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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 or impractical, topical 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	**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.

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.

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 (eg, 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 continued on next page

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.

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 & electrodessication.
  - Other modalities that may be considered include diclofenac (category 2B), 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, 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 normal population, radiation therapy is used more frequently as an adjuvant therapy and for perineural disease.
- 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 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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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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 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.

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.

Staging

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Cutaneous Squamous Cell Carcinoma (cSCC) and Other Cutaneous Carcinomas (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 features*

T3 Tumor with invasion of maxilla, mandible, orbit, or temporal bone

T4 Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

*Excludes cSCC of the eyelid

** High-risk features for the primary tumor (T) staging

Depth/invasion	> 2 mm thickness
	Clark level ≥ IV
	Perineural invasion
Anatomic	Primary site ear
location	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) and Other Cutaneous Carcinomas (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 and 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 03/12/12

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.

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Overview

Basal cell and squamous cell skin cancers, collectively known as non-melanoma skin cancers (NMSC), are the most common cancer in the United States. It is estimated that more than two million cases of NMSC were diagnosed in 2010; this exceeds the incidence of all other cancers combined.[1] Furthermore, the incidence of this common malignancy is rising rapidly.[2] Basal cell carcinomas (BCC) are about four to five times more common than squamous cell caricnomas (SCC). 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.[9,10] Bowen's disease refers to SCC in situ lesions that occur predominantly in older persons.[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:

- "Safe-Sun" Guidelines. American Academy of Family Physicians, 2000. (http://www.aafp.org/afp/20000715/375ph.html).
- Skin protection from ultraviolet light exposure: American College of Preventive Medicine Practice Policy Statement. Washington, DC: American College of Preventive Medicine. (http://www.acpm.org/skinprot.htm).
- Centers for Disease Control and Prevention. Preventing skin cancer: findings of the Task Force on Community Preventive Services on reducing exposure to ultraviolet light. (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5215a1.htm).

Genetics

Extensive research has led to advances in the understanding of the genetics of NMSCs. The sonic hedgehog signalling pathway has emerged as playing a pivotal role in the pathogenesis of BCC.[14] Mutations in the PTCH (patched) gene on chromosome 9q, which codes for the sonic hedgehog receptor, are the underlying cause of nevoid basal cell caricnoma syndrome, and are frequently present in sporadic BCC. Specific 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 ultraviolet light-induced unscheduled DNA repair), and nevoid BCC syndrome. Certain settings of immunosuppression (most notably, organ

transplantation) also predispose affected individuals. 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]

Steps in Developing the Guidelines

In developing the practice guidelines for the treatment of NMSC, the NCCN panel initially limited the algorithms to BCC and SCC, which account for most of the NMSCs.[17] Algorithms for rare forms of NMSCs - Merkel cell carcinoma and dermatofibrosarcoma protuberans - were later developed as a supplement (see NCCN Merkel Cell Carcinoma Guidelines and NCCN Dermatofibrosarcoma Protuberans Guidelines). Because more than 95% of BCC and SCC only involve local disease, the panel decided to expand the American Joint Committee on Cancer (AJCC) staging system[18] to develop a more comprehensive stratification system. This would reflect clinically relevant “levels” or “tiers of difficulty” involved in treating primary tumors. The most recent version of the AJCC staging system for SCC reflects many but not all of the features that the NCCN panel have incorporated to designate high-risk tumors.[18,19]

The NCCN panel examined risk factors for BCC and SCC 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 BCC and for SCC.

Clinical Risk Factors

Several clinical risk factors apply to both BCC and SCC. These risk factors include tumor location and size, the status of tumor borders, whether the tumor is primary or recurrent, certain settings of immunosuppression, 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 NMSC recurrence and metastasis for many years.[20,21] Stated in general terms, both BCC and SCC that develop in the head and neck area are more likely to recur than are those carcinomas developing on the trunk and extremities. SCC 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 (Figure 1).[22,23] Size also has been shown to be a risk factor for NMSC recurrence.[24-27] 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 and Cancer Unit of the New York University (NYU) School of Medicine. This review, published in 1991, evaluated a database containing information on 5755 BCC.[28,29] Of the 5755 BCC 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 (Figure 1). The middle-risk and low-risk sites correspond roughly to the middle-risk and low-risk divisions listed in the algorithms. 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 locations are also more or less in agreement with similar work performed at the national level for the Centers for Medicare and Medicaid Services (CMS).[30] The CMS 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.[25,26,31]

Immunosuppression

Settings of immunosuppression, such as organ transplantation[32] as well as long-term use of psoralen and ultraviolet A light (PUVA),[33,34] significantly increase the incidence of squamous cell cancer development. BCC 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 (reviewed by Euvrard et al).[35] A recent 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.[36] 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 organ transplant recipients have collectively worse outcomes, these patients and their neoplasms are designated as high risk.

Actually, very little published data suggest BCC are more likely to recur or metastasize when they develop in immunosuppressed individuals.[37,38] 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 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 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 NMSC recurrence or metastasis.[39-41] However, the NCCN panel consensus was this is a valid risk factor.

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 squamous cell cancer.[5,25] Although perineural involvement is uncommon in any NMSC, it develops much more

frequently in squamous cell than in BCC. In a prospective cohort study of 315 patients with cutaneous squamous cell cancer of the head and neck, Kyrgidis and colleagues identified perineural involvement as a factor associated with lower overall survival and recurrence-free survival.[42] If large nerve involvement is suspected, MRI should be considered to evaluate extent and rule out skull involvement.[43]

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.[25] Similar results were reported by Kyrgidis et al.[42] 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-differentiated; (2) moderately differentiated, poorly differentiated, or undifferentiated.[44] The NCCN Panel has adopted this modern approach in this guideline.

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 NMSC 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 BCC with aggressive histologic growth patterns in young persons.[45] 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.[46] 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;[47] 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.[48] 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.[49,50]

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 NMSC 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 NMSC

Histologic Subtypes

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 the micronodular, infiltrative, sclerosing, and morpheaform (or desmoplastic) patterns are more likely to recur than the nodular and superficial BCC. Other non-aggressive subtypes include the keratotic variant, infundibulocystic variant, and fibroepithelioma of Pinkus.

SCC

The NCCN Panel elected to include the entity “basosquamous carcinoma” under the category of squamous cell cancer rather than BCC. 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 squamous cell cancer. Others represent truly biphenotypic tumors, many of which may have started as BCC, but have subsequently undergone prominent partial squamous metaplasia.[51] 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 squamous cell cancer than BCC.[52] For this reason, the panel felt these tumors are best conceptualized as SCC until other, more instructive, data become available.

Additional Clinical Risk Factors for SCC

The NCCN panel identified a few additional clinical parameters that increase the risk of squamous cell cancer only as follows:

Site of a Chronic Inflammatory Process

A substantial body of biomedical literature has documented increased rates of metastasis for cutaneous SCC arising in the setting of chronic scarring.[53,54]

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.[55] Nevertheless, the NCCN panel members unanimously agreed this is a rare, albeit definite, clinical setting indicative of high-risk behavior.

Neurological 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.[56] Any suggestion of neurologic involvement in the region of a squamous cell cancer should place that tumor in a high-risk category.

Other Histologic Parameters

The panel members discussed whether any other histologic parameters should be included as risk factors for squamous cell cancer 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. Only a few older studies document the prognostic significance of these subtypes.[57-59] 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 studies from Germany, desmoplastic cutaneous squamous cell cancer was shown to pose a greatly increased risk of both recurrence and metastasis.[60,61] A recent review of 72 patients with desmoplastic SCC reported a high rate of recurrence of 80%.[62] 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.[44] 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.[44,60] 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.[25] Therefore, the panel decided to include these two risk factors and used the division points determined by Rowe and colleagues in the algorithm.

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 BCC, depends on the presence or absence of any of the risk factors listed in the algorithm.

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.[44] 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.[63] 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 SCC

The NCCN Panel developed recommendations for the identification and management of patients at high risk for squamous cell skin cancer. Two members of the International Transplantation Skin Cancer Collaborative 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 BCC; however, the panel felt that the existing BCC algorithm provides reasonably adequate guidance for care of these patients.

Oral retinoids have been found to be effective in reducing the development of pre-cancers and skin cancers in some high-risk patients.[64-66] Side effects may be significant. Oral retinoids are teratogenic and must be used with extreme caution in women of child-bearing age.

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 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.[67] 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.[44,68] 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, or lymphovascular invasion (for SCC) is suspected.

In patients with squamous cell cancer, 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. For lymph nodes in the head and neck region where aspiration is negative, consider re-evaluation with imaging, repeat FNA, or open lymph node biopsy. Any positive findings should be followed by imaging to determine the size, number, and location of abnormal lymph nodes, and to rule out distant disease. For lymph nodes in the trunk or extremity region 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 Primary Therapy

Basal and SCC are most commonly treated with surgery or radiation. In an evidence-based review of the literature, the best results were obtained with surgery.[69] However, consideration of function, cosmetic outcome and patient preference may lead to the choice of radiation therapy as primary treatment in order to achieve optimal overall results. The algorithms list all of the therapies currently used to treat localized NMSC, 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]), radiation therapy (RT) and superficial therapies.[70,71]

To assist users of the guidelines, the panel arrived at several principles of primary treatment for both basal cell and squamous cell cancer. 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. In certain high-risk patients, increased surveillance and prophylactic measures may be warranted. Specifics about the application of RT, including caveats regarding different types of therapeutic radiation and total doses and fractionation ranges, are described under “Principles of Radiation therapy” in the algorithm.

Curettage and Electrodesiccation

The curettage and electrodesiccation technique is deemed effective for low-risk tumors with three caveats.[29,72] 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 should generally 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.

The third caveat states that 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 pathological features that would require additional therapy.

Excision with Postoperative Margin Assessment

Another therapeutic option for both BCC and SCC is excision with 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.[73,74] 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 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 the following:

- Re-excision of low-risk primary BCC and SCC located on the trunk and extremities (area L regions) if positive margins are obtained after an initial excision with POMA.
- 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 before closure.

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.[25,75,76] 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, sentinal 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.[25,28,31,39,77-102] 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 NMSCs. If either of these approaches is inappropriately or inadequately applied and performed, less than optimal cure rates will result.

The panel has also included radiation therapy as an option for non-surgical candidates, but it is generally reserved for older patients over 60 years because of concerns about long terms sequelae.[71] RT is delivered in fractional doses involving orthovoltage x-rays or electron-beam. Protracted fractionation is associated with improved cosmetic results. Wider field margins are necessary when using electron beam therapy than with orthovoltage x-rays. Tighter field margins are possible when using electron beam therapy adjacent to critical structures. 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 intermediate-risk locations up to 20 mm in diameter. 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 (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, lupus, scleroderma).

Intensity modulated radiation therapy is gaining wide use in recent years. The panel emphasized the importance of proper support and training by medical physicists in using this new 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.[103]

Brachytherapy has recently been suggested as an option for the management of SCC. Support comes from older studies that showed efficacy especially for anatomically challenging sites such as the nose.[94,104,105] A few institutions are beginning to use brachytherapy for unresectable cases, but this technique requires special equipment and expertise and is therefore not widely used.

Superficial Therapies

Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical.[106] Superficial therapies include topical treatment with 5-fluorouracil or imiquimod, photodynamic therapy (PDT) and cryotherapy. PDT involves the application of a photosensitizing agent on the skin followed by irradiation with 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.[107] Currently, PDT is being utilized at NCCN 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.[108-110]

In patients with low-risk shallow cancers, such as SCC in situ (Bowen's disease) or low-risk superficial BCC, topical therapies such as 5-fluorouracil, imiquimod, PDT (MAL, porfirmer sodium or topical amino levulinic acid), or vigorous cryotherapy may be considered even though the cure rate may be lower.[70,110] Imiquimod was found to be effective for

treating multiple, superficial basal cell skin cancers and SCC in situ in randomized studies.[111-113]

Actinic keratoses are most commonly treated with cryotherapy, topical treatment with 5-fluorouracil or imiquimod, PDT, or curettage and electrodessication.[9,108,109,114-116] MAL PDT was found to be as effective as cryotherapy for the treatment of actinic keratoses and SCC in situ in randomized clinical trials.[117-119] Other treatments that may be considered include topical diclofenac (category 2B),[120,121] chemical peels, and ablative skin resurfacing.

Regional Lymph Node Dissection

For patients with SCC, regional nodal involvement significantly increases the risk of recurrence and mortality.[122] If there are positive findings on either FNA or open biopsy of a lymph node, the preferred treatment is regional lymph node dissection following the corresponding pathway for the head and neck region or the trunk and extremity region. Radiation with or without concurrent cisplatin therapy is an alternative when surgery is not initially feasible; however, patients should be re-evaluated for surgical candidacy for neck dissection after radiation.

Parotid involvement is a poor prognostic factor for SCC.[123,124] 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.[125]

Adjuvant radiation with or without concurrent chemotherapy is often required following lymph node dissection (see discussion below).

Adjuvant Treatment

The value of postoperative radiation in reducing the rate of recurrence in high risk patients has been widely accepted. 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). In select patients, local control approaches 100% with postoperative radiotherapy.[56] Adjuvant radiation therapy should also be considered if tissue margins are positive after Mohs surgery or a CCPDMA equivalent of a skin cancer.

Adjuvant RT should be considered for all patients with regional disease of the trunk and extremities who have undergone lymph node dissection, especially in cases of ECE or multiple involved nodes. For patients with nodal involvement in the head and neck region, postoperative radiation is recommended in all cases,[126,127] although observation is a reasonable alternative for patients with only one small node and no extracapsular spread. Dosage information can be found in the algorithm.

Despite resection followed by RT, high-risk patients suffer locoregional recurrence, distant metastasis, and 5-year survival rates of 30%, 25%, and 40%, respectively.[128] Two randomized trials on mucosal squamous cell tumors demonstrated superior locoregional control and progression-free survival in combining postoperative radiation with concurrent cisplatin compared to radiation alone, although adverse events also increased.[129,130] These results lend support to chemoradiation for squamous carcinomas 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.[131] Since margin assessment is not typically performed for neck dissections, concurrent chemotherapy should be considered in patients with ECE. Patients with incompletely excised nodes are at high risk of recurrence and may also consider chemoradiation depending on individual toxicity tolerance.

Residual Disease (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.[132] 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.

For patients with residual BCC where further surgery and radiation are contraindicated, the NCCN panel recommends consideration of clinical trial (preferred) or vismodegib. Combination chemotherapy containing cisplatin or carboplatin is also an option. Panelists emphasized that treatment decisions should be made following multidisciplinary board consultation.

Follow-Up and Recurrence

Two well established points about patients with NMSC underlie the follow-up schedules. One point is that 30-50% of these patients will develop another NMSC within 5 years[133]; that represents a 10-fold increase in risk compared to the general population.[134] They are also at increased risk of developing cutaneous melanoma.[67] 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 70-80% of all cutaneous squamous cell cancer recurrences develop within 2 years of the initial therapy.[135] Therefore, close follow-up of these patients during this time period is critical. Two phase II studies are underway to study the efficacy of gefinitib in the treatment of recurrent and metastatic SCC of the skin. Detailed guidelines on follow-up schedules can be found in the algorithm.

Finally, 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 and clinical trials should be considered.

Metastatic Disease

BCC

Although the behavior of cutaneous BCC is characteristically indolent, the disease does rarely metastasize to distant sites. In that instance systemic therapy is indicated. Clinical trials (preferred) or vismodegib is recommended. Platinum-based chemotherapy is also an option as published experiences report that responses are not unusual and occasional complete responses have been observed in the metastatic setting.[136-138]

SCC

Cutaneous squamous cell cancer with distant metastases, while rare, is more common than metastatic BCC, but little information is available regarding systemic therapy for the condition.[139] There are no prospective phase III studies available, and only one prospective phase II study. The preference is, again, participation in a clinical trial, although such trials are scarce. Often even large centers don't open trials for rare diseases because of the costs involved.

If the patient is a solid organ transplant recipient taking immunosuppressive therapy, one should consider, where appropriate, reduction of the doses of the immunosuppressive agents or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors.[140]

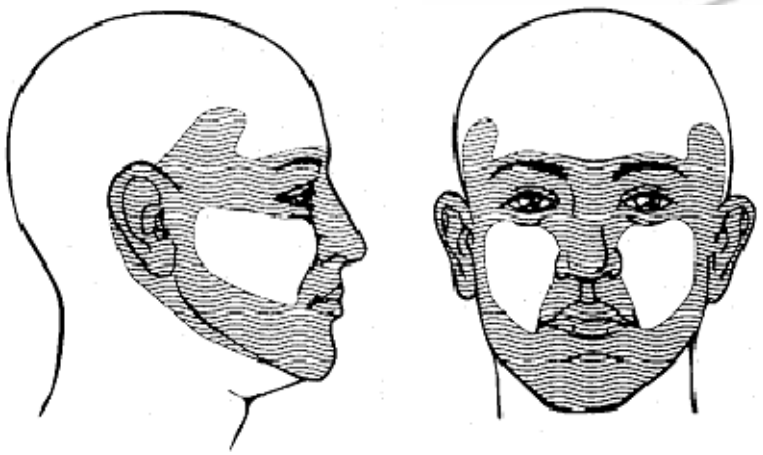
Cisplatin either as a single agent or combined with 5-FU has occasionally produced useful responses, but data supporting efficacy are limited. In the only phase II study of biochemotherapy with interferon alfa, cis-retinoic acid and cisplatin, 35 patients were assessed for response, of which 11 had distant metastases.[141] 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 leads some credence to an effect of a cisplatin-based regimen. Other studies are retrospective and most are anecdotal.[139,142]

Some have advocated using therapies useful in metastatic squamous cell head and neck cancer for patients with metastatic cutaneous squamous cell cancer.[143] 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.[144-149] The low toxicity profile of cetuximab holds an advantage over the toxic cisplatin regimen.

Neo-adjuvant 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.[150-152]

Figure 1. High-risk mask area of the face.

BCC and SCC 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.



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