Evidence-Based Medicine: Facial Skin Malignancy

Matthew L. Iorio, M.D.
Ryan P. Ter Louw, M.D.
C. Lisa Kauffman, M.D.
Steven P. Davison, D.D.S., M.D.

Washington, D.C.

Learning Objectives: After studying this article, the participant should be able to: 1. Identify common precancerous and malignant cutaneous growths of the head and neck. 2. Recommend surgical treatment, including margins, based on consensus guidelines. 3. Counsel patients as to available evidence for expected recurrence, follow-up, and morbidity.

Summary: Skin lesion excision is the most common procedure performed by plastic surgeons. Because of the cumulative risk factors of sun and carcinogen exposure, the head and neck are the most frequently affected regions of the body. Timely diagnosis and treatment are critical for preventing continued spread and metastasis, and it is incumbent on the treating physician to make the appropriate recommendations for surgical margin and the possibility of adjuvant therapy to prevent recurrence and optimize long-term survival. As clinical guidelines are developed from ongoing outcome studies, new generations of treatment recommendations are continuously in development. Therefore, a systematic review of the most relevant guidelines and clinically rigorous studies was performed with a summarization of treatment recommendations for the following: actinic keratosis, Bowen disease (squamous cell in situ), basal cell carcinoma, squamous cell carcinoma, malignant melanoma, and Merkel cell carcinoma of the head and neck. (*Plast. Reconstr. Surg.* 132: 1631, 2013.)

Cutaneous malignancies are the most frequent type of cancer in the world, with over 2 million people affected yearly.[1] Not unexpectedly, then, cutaneous lesion removal is the most common procedure performed by plastic surgeons, with in excess of 4 million excisions performed annually.[2] In many cases, surgical excision allows for both a tissue diagnosis and definitive treatment in a single stage.

Ideally, the resection margin of a suspicious lesion is a planned area of tissue excision that is clinically and histologically free of cellular atypia characteristic of the central lesion (Table 1).[3–17] Because of discontinuous disease infiltration and frequent atypia at the perimeter of malignant lesions, additional tissue resection may represent a balance between decreased local recurrence and improved patient survival while avoiding excessive scarring or functional compromise. The subsequent recommendations for optimal treatment and surgical margin management continue to evolve based on inferences from outcome data and clinical observation.

It is the goal of this Maintenance of Certification module to review the characteristics of the most common head and neck cutaneous malignancies and to summarize the available guidelines and outcome studies for optimum patient counseling and treatment.

ACTINIC KERATOSIS

Clinical Characteristics

Actinic keratosis is the most common precancerous lesion of the epidermis. Resulting from chronic sun exposure, it presents as a scaly, hyperkeratotic plaque on sun-exposed areas of fair-skinned individuals. The hallmark histologic character is atypical keratinocytes located within the basal layers of the skin. These lesions have a

From the Department of Plastic Surgery, Georgetown University Hospital; Georgetown Dermatology; and DAVinci Plastic Surgery.
Received for publication April 2, 2013; accepted May 14, 2013.

DOI: 10.1097/PRS.0b013e3182a8085f

Disclosure: *The authors have no financial interests in any of the products or techniques mentioned and have received no external support related to this study.*

Table 1. Margin Recommendation with Current Level of Evidence for the Reviewed Head and Neck Cutaneous Malignancies

	Breslow Depth (mm)	Recurrence Risk	Excision Margin	Level of Evidence
Recurrent actinic keratosis[3,4]		High	4 mm/Mohs*	V
Bowen disease[5]		Low	4 mm/Mohs	II
Squamous cell carcinoma[6]		Low	4 mm	II
		High	6 mm/Mohs	II
Basal cell carcinoma[7–9]		Low	3 mm	III
		High	4 mm/Mohs	II
Merkel cell carcinoma[10]		High	1 cm/XRT	II
Melanoma[11–17]	In situ		5 mm/Mohs	II
	≤1.0		1 cm	III
	1.01–2.0		1 cm†	III
	>2.0		2 cm	I
	>4.0		≥2 cm	II

XRT, radiotherapy.
*Recurrent actinic keratosis previously treated with nonsurgical modalities harbor increased risk of occult squamous cell carcinoma.
†For an intermediate thickness melanoma characterized by an aggressive histologic subtype or ulceration, a wider minimum excision margin at 2 cm is recommended.

variable clinical course, with interval remission or malignant transformation. Treatment is based on the lifetime risk of malignant transformation into squamous cell carcinoma at 6 to 10 percent.[3]

Treatment Guidelines

Nonsurgical therapies include cryosurgery, 5-fluorouracil, imiquimod, and photodynamic therapy, all of which attempt to eliminate potential malignant transformation and eliminate the pruritus and burning frequently associated with the lesions.[4] Perrett et al. prospectively evaluated photodynamic therapy versus topical 5-fluorouracil for immunocompromised patients with actinic keratoses. At 1, 3, and 6 months, photodynamic therapy was superior to 5-fluorouracil in achieving complete resolution of lesions, 88 percent versus 11 percent, respectively.[18] For photodynamic therapy, the lesion should be pretreated with 5-aminolevulinic acid 3 hours before illumination with either a red (630 to 700 nm) or blue (400 to 470 nm) light source. Both 5-fluorouracil and photodynamic therapy leave the patient with a diffuse, erythematous healing patch over the affected area for 1 week. In comparison, cryosurgery with liquid nitrogen has a reported clearance rate of 98 percent.[4]

Surgical treatment of actinic keratoses is an option with larger lesions and should be reserved for rapidly changing lesions or those that fail topical treatment. On older patients with diffuse actinic damage, mild actinic changes may be present at the margins of any excision, even if the visible central clinically evident actinic keratosis is excised microscopically. *Because of the high rate of incipient squamous cell carcinoma in recalcitrant or recurrent actinic keratoses, resection margins should be based on an early squamous cell carcinoma diagnosis at 4 mm.*[3,19]

BOWEN DISEASE

Clinical Characteristics

Bowen disease, also known as squamous cell carcinoma in situ, is another premalignant lesion secondary to chronic sun exposure. Bowen disease of the head and neck most commonly presents in the auricular, nasal, and perioral regions. Lesions arise as erythematous scaly plaques that exhibit slow growth and surface fissures.[20] Although Bowen disease and actinic keratosis are clinically difficult to differentiate, the hallmark microscopic feature of Bowen disease is normal basal cells, and slow lateral extension frequently allows atypical cells to be found beyond the periphery of clinical margins. The lifetime risk of Bowen disease transforming into squamous cell carcinoma is 3 to 8 percent.[5,20]

Treatment Guidelines

Bowen disease is frequently treated nonsurgically, and excisional studies are limited. *However, the current margin for surgical excision of large, invasive, or recurrent Bowen disease is 4 to 6 mm.* Common nonsurgical modalities include 5-fluorouracil, photodynamic therapy, and cryotherapy. Topical 5-fluorouracil can be applied twice daily for 4 to 8 weeks until superficial erosion or ulceration is present. Subclinical margins should also be treated with wide local application around the lesion. Imiquimod is another once-daily topical treatment for Bowen disease, based on the up-regulation of the cellular immune response and interferon alpha. After 16 weeks of topical

imiquimod treatment, 73 percent of patients are disease free according to posttreatment biopsy results[7]; however, cryotherapy and photodynamic therapies have improved recurrence rates at 10 percent and 12 percent, respectively.[20,21]

Regarding excision, a prospective study by Leibovitch et al. examined 270 cases of Bowen disease, 93 percent of which were located on the head and neck. Following treatment with Mohs excision, 20 percent had subclinical extension greater than 2 cm. At 5 years, primary Bowen disease had a recurrence rate of 2.5 percent and secondary recurrent Bowen disease had a recurrence rate of 9 percent.[5]

BASAL CELL CARCINOMA

Clinical Characteristics

Basal cell carcinoma is the most common cutaneous malignancy on the face, and 85 percent of all basal cell carcinomas occur on the head and neck. The annual incidence of basal cell carcinoma is 146 per 100,000 (Fig. 1). Clinical subtypes include nodular, superficial spreading, pigmented, and sclerosing morpheaform. Basal cell carcinomas are characterized by slow growth with rare metastasis, but incomplete resection or delayed diagnosis can lead to further tissue involvement[7] (Fig. 2). Basal cell carcinoma is more likely to appear on the upper lip, whereas squamous cell carcinoma has a predilection for the lower lip (Table 2).

Trichoepithelioma is a neoplasm that has a clinical appearance similar to that of basal cell carcinoma, with flesh-colored papules occurring either in groups or as solitary lesions. Typically occurring in childhood, lesions may increase in number with age as firm papules or nodules along the face, nose, and eyelids (Fig. 3). Originating from the hair germ, trichoepithelioma can be identified as poorly differentiated hamartomas and nests of basaloid cells. This is distinct from basal cell carcinoma, as trichoepithelioma exhibits rare ulceration, a well-circumscribed base, and rare inflammatory cell infiltrates.[22] In isolated cases, surgical excision should include the hair follicle within the deep dermis to minimize recurrence, although malignant degeneration is exceedingly rare.

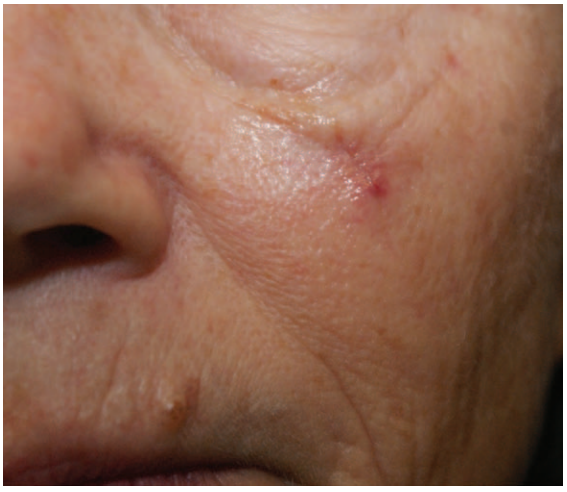

Fig. 2. Basal cell carcinoma of the left cheek.

Treatment Guidelines

Several nonsurgical options for basal cell carcinoma exist, albeit with a frequently higher

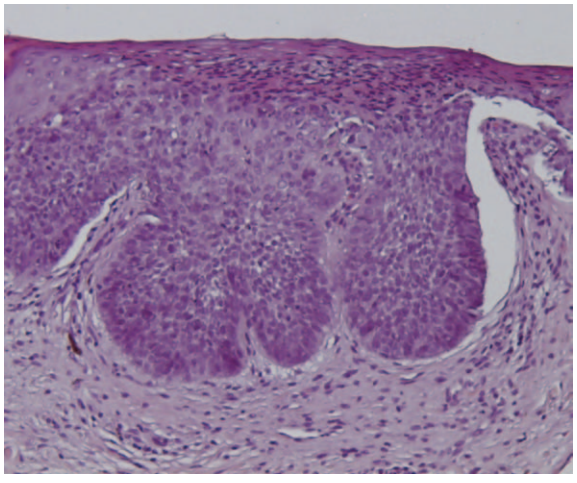

Fig. 1. Basal cell carcinoma section demonstrating basaloid tumor lobules arising from the epidermis with peripheral palisading and stromal retraction.

Table 2. Risk Assessment for Basal Cell Carcinoma Recurrence*†

	Low Risk	High Risk
Location		
Area M	<10 mm	≥10 mm
Area H	<6 mm	≥6 mm
Border	Well defined	Irregular
Primary	Yes	Recurrent
Immunosuppression	No	Yes
Prior field irradiation	No	Yes
Subtype	Nodular, superficial	Morpheaform, sclerosing, micronodular
Perineural involvement	No	Yes

*Adapted from National Comprehensive Cancer Network Basal Cell and Squamous Cell Skin Cancers. Basal cell and squamous cell skin cancers. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2004;2:6–27.

†Area M includes the cheek, forehead, scalp, and neck. Area H includes the "mask areas" of the face, with central face, eyebrow/eyelid, nose, lip, chin, mandible, periauricular area, and ear.

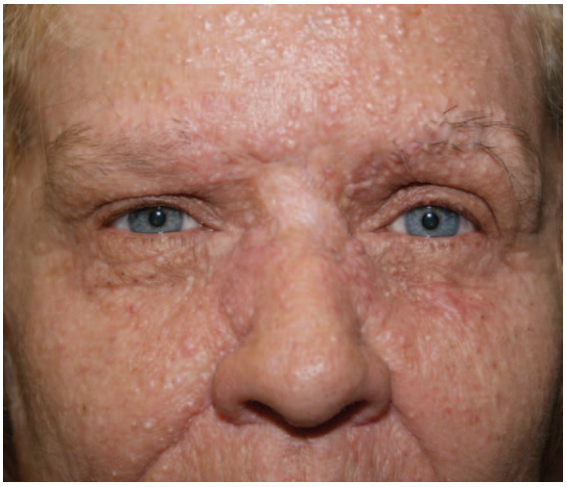

Fig. 3. Diffuse trichoepitheliomas associated with Brooke-Spiegler syndrome.

recurrence. Chren et al. evaluated 1488 nonmelanoma skin cancers treated with destruction with electrodesiccation and curettage, versus standard excision or Mohs excision. At 5-year follow-up, a recurrence rate of 4.9 percent was found following destruction, compared with 3.5 percent and 2.1 percent in the excision and Mohs cohorts, respectively.[23] Mosterd et al. evaluated photodynamic therapy compared with a 3-mm surgical excision in 149 patients. At 36-month follow-up, treatment failure within 5 mm of the original lesion was noted in 2.3 percent of the surgical excision group and 30.3 percent of the photodynamic therapy group ($p < 0.001$).[8]

Carbon dioxide laser offers another method of treatment, but recurrence rates may be dependent on the method of application. In a single-pass application, Adams and Price found a 50 percent recurrence rate in 24 lesions.[24] This outcome differs significantly from the experience of Iyer et al., who used a 500-mJ pulse set at 10 Hz, with two to eight passes per lesion. Sixty-one lesions were treated, with a recurrence rate of 3.2 percent. It should be stressed that the surrounding margin should be included in the treatment field for adequate destruction of the lesion.[25]

Surgical treatment with wide local excision or Mohs surgery is the standard for minimizing recurrence. A previous recommendation for a 4-mm margin to treat a low-risk lesion was based on a review of 117 well-demarcated basal cell carcinomas that were excised in 2-mm increments, and the 4-mm margin demonstrated a 95 percent clearance rate.[26,27] However, in a much larger systematic review of 89 articles evaluating 16,066 lesions, pooled-data analysis found average recurrence rates for 5-, 4-, 3-, and 2-mm surgical margins at 0.39, 1.62, 2.56, and 3.96 percent, respectively. *Therefore, 3 mm may represent the optimum margin for 95 percent clearance in well-demarcated, small, nonmorpheaform basal cell carcinomas (Table 3).*[7]

In high-risk lesions, Mohs surgery has demonstrated improved recurrence rates. This was evidenced by a prospective trial comparing Mohs to surgical excision that demonstrated a significant decrease in recurrence for 204 aggressive subtype or recurrent basal cell carcinomas when Mohs surgery was used ($p = 0.015$).[28] However, when Mohs surgery was compared with 3-mm excision in 408 primary lesions, no statistical difference in recurrence was noted at the 2-year follow-up, although Mohs surgery was associated with a smaller final defect size and higher operative cost ($p < 0.001$), indicating that Mohs surgery should be reserved for high-risk or recurrent lesions[9] (Fig. 4).

SQUAMOUS CELL CARCINOMA

Clinical Characteristics

Squamous cell carcinomas of the head and neck account for 75 percent of all cutaneous

Table 3. Basal Cell Carcinoma Recommended Resection Margins, Nonsurgical Therapies, and Adjuvant Treatments

	Resection Margin	Nonsurgical Therapy	Adjuvant Therapy
Tis (in situ)	3 mm/Mohs	PDT, 5-FU, imiquimod, carbon dioxide laser, cryosurgery, electrodesiccation	XRT
T1 (<2 cm) (tumor with <2 high risk factors)	3 mm/Mohs	PDT, 5-FU, imiquimod, carbon dioxide laser, cryosurgery, electrodesiccation	XRT
T2 (>2 cm) (tumor with >2 high risk factors)	4 mm/Mohs	Surgical excision preferred	XRT, platinum-based chemotherapy
T3 (invasion of maxilla, mandible, orbit, temporal bone)	Abnormality cleared resection; frozen section margin	Surgical excision preferred	XRT, platinum-based chemotherapy, vismodegib
T4 (skeletal invasion or perineural invasion at skull base)	Abnormality cleared resection; frozen section margin	Surgical excision preferred	XRT, chemotherapy, vismodegib

XRT, radiotherapy; PDT, photodynamic therapy; 5-FU, 5-fluorouracil.

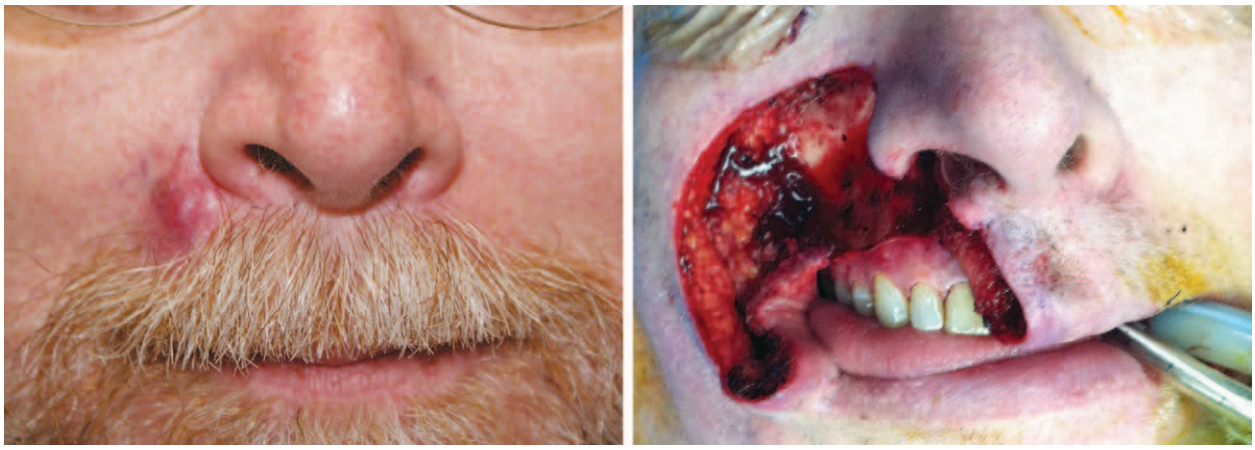

Fig. 4. (*Left*) Recurrent basal cell carcinoma of the right nasolabial fold. (*Right*) Wide resection of the recurrent tumor, with histologic perineural invasion and tumor invasion through the subcutaneous tissue into the superficial musculature.

squamous cell carcinomas. Typically more aggressive in invasion and metastasis than basal cell carcinoma, ultraviolet radiation exposure, fair skin, and immunosuppression are known risk factors.[29] Squamous cell carcinoma has a variable clinical appearance that includes patches, plaques, ulcers, nodules, and even exophytic tumors. Histologic features of squamous cell carcinoma include full-thickness loss of polarity, with islands and strands of tumor extending into the dermis, and aggressive forms often invading into neurovascular structures (Fig. 5). Tumor location can be influential, with squamous cell carcinoma of the lip having the most metastatic potential, followed by squamous cell carcinoma of the ear, non–sun-exposed sites, and squamous cell carcinoma arising from irradiation, thermal injury, or chronic wounds (i.e., Marjolin ulcer)[30] (Fig. 6).

Given the cumulative effect of risk factors typically associated with a squamous cell carcinoma, patients have a 30 to 50 percent chance of developing a second primary tumor within 5 years (10 times higher than the general population), and if recurrence develops, 70 to 80 percent will recur within 2 years of initial treatment[31] (Table 4). Brantsch et al. prospectively evaluated 615 patients with squamous cell carcinoma at an average follow-up of 43 months. Tumors less than 2.0 mm in thickness did not metastasize, whereas 4 percent of tumors 2.1 to 6.0 mm in thickness and 16 percent of tumors greater than 6.0 mm metastasized.[32] Following multivariate analysis, other key indicators for potential metastasis included immunosuppression (hazard ratio, 4.32; 95 percent CI, 1.62 to 11.52; $p = 0.0035$) and lesions on the ear (hazard ratio, 3.61; 95 percent CI, 1.51 to 8.67; $p = 0.0040$).

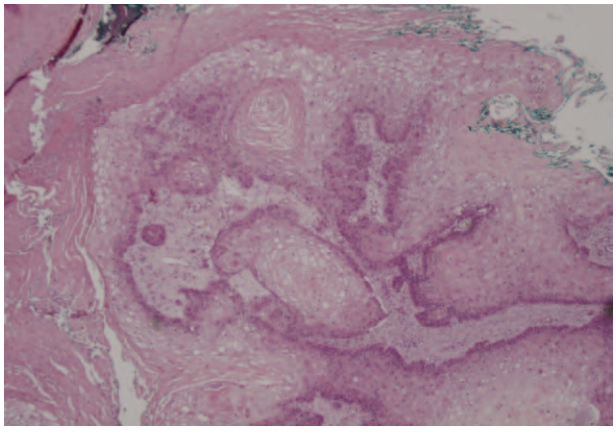

Fig. 5. Squamous cell carcinoma section demonstrating epithelioid tumor islands within the dermis showing focal keratinization.

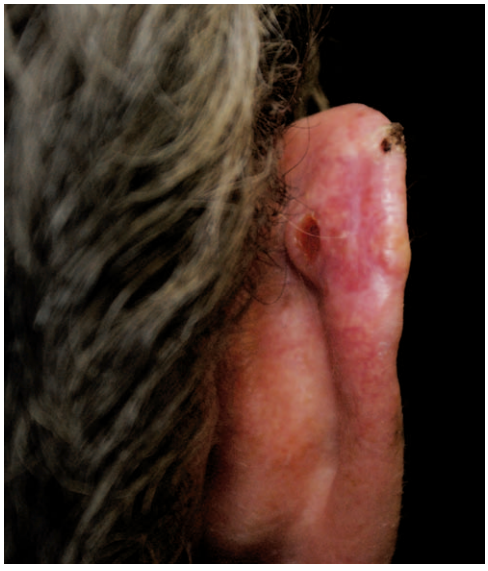

Fig. 6. Squamous cell carcinoma of the helical rim.

Table 4. Recommended Resection Margins, Nonsurgical Therapies, Adjuvant Treatments, and Lymph Node Sampling Criteria for Squamous Cell Carcinoma*

	Resection Margin	Nonsurgical Therapy	Adjuvant Therapy	Regional Lymph Node Sampling†
Tis (in situ)	4 mm/Mohs	5-FU, PDT, cryotherapy, imiquimod, XRT	—	No
T1 (<2 cm) (tumor with <2 high risk factors)	4 mm/Mohs	XRT	XRT	No
T2 (>2 cm) (tumor with >2 high risk factors)	6 mm/Mohs	Surgical excision preferred	XRT, chemotherapy	Yes
T3 (invasion of maxilla, mandible, orbit, temporal bone)	Abnormality cleared resection; frozen section margin	Surgical excision preferred	XRT, chemotherapy	Yes
T4 (skeletal invasion or perineural invasion at skull base)	Abnormality cleared resection; frozen section margin	Surgical excision preferred	XRT, chemotherapy	Yes

XRT, radiotherapy; PDT, photodynamic therapy; 5-FU, 5-fluorouracil.
*Squamous cell carcinoma disease-free survival rates are 86% for stage I, 55% for stage II, and 47% for stage III.
†High-risk lesions suggested for sentinel node lymph node biopsy include size >2 cm, depth >8 mm, immunosuppression, perineural invasion, or poor differentiation.

A variant of squamous cell carcinoma is basosquamous carcinoma. Frequently, these lesions represent an overlap of synchronous squamous cell and basal cell carcinomas, as both lesions share similar cumulative risk profiles. However, some lesions do represent a basal cell that has undergone partial squamous metaplasia (Fig. 7). In either case, the risk and incidence of metastasis is most dependent on the squamous cell component, and treatment guidelines should therefore mirror the recommendations for squamous cell carcinoma.[33,34]

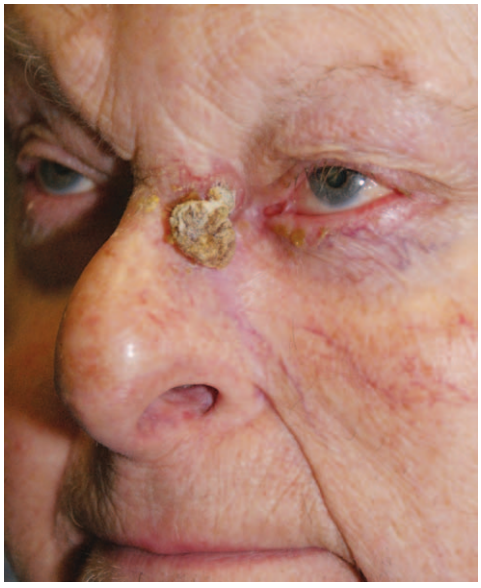

Fig. 7. Ulcerated basosquamous cell carcinoma of the nose. Subsequent pathologic examination revealed dermal infiltration by islands of basaloid cells, many enclosing central foci of keratin and concentric layers of squamous cells.

Treatment Guidelines

Lesion diameter and depth of invasion are prognostic for overall risk of recurrence and metastasis. Lesions larger than 2 cm are twice as likely to recur (15.2 percent versus 7.4 percent) and three times as likely to metastasize (30.3 percent versus 9.1 percent) compared with smaller lesions.[6] Lesions that have invaded into subcutaneous tissue or involve a depth greater than 4 mm have a metastatic rate of 45.7 percent, as compared with 6.7 percent for more superficial squamous cell carcinoma. Recurrence rates for excision of low-risk lesions is 5 to 8 percent, whereas lesions larger than 2 cm commonly recur at 15.7 percent, and poorly differentiated lesions recur as frequently as 25 percent following excision.[6] *"High-risk" lesions, characterized by poor histologic differentiation, periocular/perioral location, or a diameter greater than 2 cm, require a 6-mm margin to clear 95 percent, as compared with only 4 mm in "low-risk" lesions.*[35]

Mohs surgery is advocated for aesthetically sensitive areas and should be considered for lesions at high-risk for recurrence such as those with failed primary treatment, poorly delineated clinical borders, diameters larger than 2 cm, perineural involvement, or critical anatomical locations such as the eyelid (**Level of Evidence: Therapeutic, IV**).[36] Leibovitch et al. prospectively evaluated the 5-year recurrence rate of squamous cell carcinoma treated with Mohs micrographic surgery in 1263 patients and reported a failure rate of 3.9 percent in those that completed follow-up. In comparison with primary excision, Mohs surgery demonstrated an improved recurrence rate in both high- and low-risk lesions ($p < 0.001$).[36]

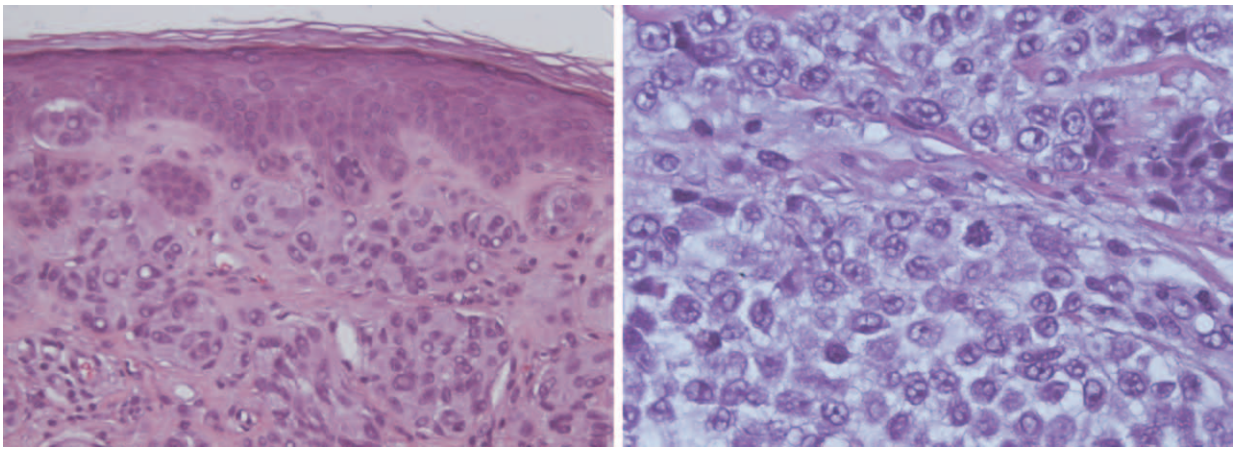

Fig. 8. (*Left*) Low-power section of malignant melanoma that demonstrates sheets of pleomorphic melanocytes. (*Right*) High-power section with occasional mitotic figures within the tumor.

Adjuvant radiotherapy has been used for high-risk lesions that cannot be safely resected or where medical comorbidity precludes resection.[6] The morbidity of head and neck irradiation includes dry mouth, tissue atrophy, esophagitis, and dental carries. Kyrgidis et al. reviewed 315 head and neck squamous cell carcinomas treated by wide local excision and radiation therapy. At 3- and 5-year follow-up, 87 percent and 69 percent were disease free, respectively. Recurrence and survival were improved with postoperative radiotherapy in combination with surgical excision, with a 92 percent reduced risk of recurrence compared with treatment without radiation therapy.[37]

MELANOMA

Clinical Characteristics

The average person in the United States has a one in 55 chance of developing melanoma, an incidence that is markedly increased with heavy sun exposure, as seen in the increased incidence in Australia at one in 29 people.[38] Twenty percent of new melanoma diagnoses originate on the head and neck, and there are four major subtypes, including lentigo maligna, superficial spreading, nodular, and acral lentiginous (Fig. 8). Superficial spreading melanoma is the most common form and is found on the trunk or extremities, whereas acral lentiginous melanomas are found on darker pigmented individuals on the hands, feet, and nail beds. The nodular type is also found on the trunk and extremities with a blue/black hue and a greater tendency for vertical growth. Preoperative planning may be aided through examination of the lesion for birefringence and/or the use of an ultraviolet lamp to define the irregular borders of the lesion.

Lentigo maligna is a subtype of melanoma in situ and occurs most frequently on the face. It is defined by horizontal growth without a pronounced vertical component and atypical melanocytes in the basal epidermis, as compared with the uniform cytologic atypia, melanocyte nesting, and suprabasilar spread seen in other forms of melanoma in situ (Fig. 9). Lentigo maligna has the potential to spread beyond the epidermal basement membrane zone and progress to a more invasive disease known as lentigo maligna melanoma. Lentigo maligna and lentigo maligna melanoma are members of a subclass of cutaneous melanomas and, although only 5 percent of cutaneous melanomas are lentigo maligna melanoma,

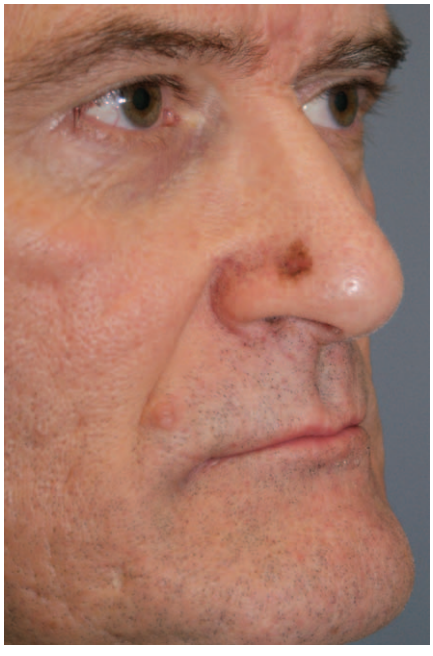

Fig. 9. Lentigo maligna of the right alar rim.

together they account for greater than 50 percent of head and neck melanomas.[39]

Another subtype of malignant melanoma with a distinct clinical presentation is desmoplastic melanoma. Frequently appearing as a nonpigmented plaque or nodule, desmoplastic melanoma is often misdiagnosed as basal cell carcinoma or even a benign lesion at the initial clinical examination, despite a relatively advanced tumor depth according to preliminary biopsy results.[40] Histologically, the lesion is composed of spindle cells surrounded by abundant collagen, and desmoplastic melanoma has a high propensity for local recurrence, with aggressive behavior. Additional testing for the S100 antigen on immunohistochemistry may aid in differentiating the lesion from malignant schwannoma. In a systematic review of 17 studies, 27.2 percent of patients (n = 703) suffered from local tumor recurrence and demonstrated a 5-year overall survival of 75.2 percent. In addition, despite frequent tumor recurrence, nodal metastasis appeared to be less than that for other forms of malignant melanoma at 7.1 percent, suggesting a different natural history for desmoplastic melanoma. In any event, prompt surgical excision is the treatment of choice to prevent recurrence or metastatic disease. Given the aggressive local infiltration and subsequent high risk of recurrence, desmoplastic melanoma may be optimally treated with at least a 1-cm surgical margin of excision.[40]

Staging

In all melanocytic neoplasms, thickness remains the most powerful prognostic indicator and predicts the significant decline in 5- and 10-year survival estimates with increasing thickness.[41] The 96 percent survival rate found in patients with melanomas less than 0.5 mm thick rapidly decreases to a 42 percent 10-year survival in tumors greater than 6 mm thick.[42] Secondary prognostic factors include ulceration, mitotic rate, and regional/distant lymph node metastasis.[42] Pathologic classifications using Clark level have largely fallen out of favor, although some continued application should still be appreciated in the head and neck. The absolute tissue thickness of facial structures such as the upper eyelid may be the best example of this, as an invasion of 0.9 to 1.0 mm may in fact indicate subcutaneous spread and mandate more aggressive treatment.[43]

Second only to tumor thickness in importance, mitotic rate was added in 2009 to the American Joint Committee on Cancer guidelines as a significant prognostic factor.[44] The presence of one or more mitoses per square millimeter will upstage a lesion from T1a to T1b.[45] A review of 13,200 patients with stage 1 or 2 melanoma found that lesions with no identifiable mitoses per square millimeter experienced a 93 percent 10-year survival rate, whereas patient samples with 20 mitoses per square millimeter had a 28 percent survival rate.[45]

Treatment Guidelines

For all cutaneous forms of melanoma, surgical excision is the standard of care, although several alternative modalities have shown benefit when patient comorbidities or other factors preclude surgical treatment. Powell et al. reviewed the use of imiquimod for lentigo maligna in 48 patients. Thirty-seven patients responded to treatment, whereas the remaining 11 demonstrated persistent histologic disease, and one patient developed invasive disease at 49-month follow-up.[46] Radiation therapy is another alternative, although it is associated with local recurrence rates as high as 14 percent, with the majority of recurrences returning at the borders of the irradiation field.[11,47]

Surgical margins for melanoma are based on the Breslow scale or depth of tumor invasion beyond the granular layer of epidermis. Before 1980, the recommended surgical margins were 5 cm, independent of tumor thickness or location.[48] With an increasing amount of patient outcome and recurrence data, the World Health Organization and, later, the American Joint Committee on Cancer, modified these margins based on inferences from ongoing outcome studies (Table 5).[41,42,49,50,55] *Currently, for melanoma in situ and melanoma less than 1 mm in depth, resection margins of 5 mm and 1 cm have been recommended, respectively.*[11] However, multiple studies have demonstrated that 5 mm may be insufficient for extensive in situ lesions such as lentigo maligna because of the poorly defined nature of these lesions and occult extension and/or junctional melanocytic hyperplasia.[12] A prospective study of 161 lentigo maligna lesions excised with mapped serial excision found that 30 percent required a margin wider than 5 mm, and that the margin continued to increase with lentigo maligna melanoma subtypes and recurrent tumors (56 percent).[12]

Although not traditionally recommended for melanoma because of the distortion of frozen specimens and miscalculation of lesion depth, mapped serial excision or Mohs surgery is generating a large amount of data for use in melanoma, particularly for early invasive stages such as in situ disease or lentigo maligna subtypes.[51]

Table 5. Recommended Resection Margins, Nonsurgical Therapies, Adjuvant Treatments, Lymph Node Sampling Criteria, and 5-Year Survival Rates for Malignant Melanoma

		Resection Margin[49]	Nonsurgical Therapy	Adjuvant Therapy	Lymph Node Sampling[41,50,55]	AJCC 5-Year Survival (%)[42]
Tis (in situ)		5 mm, Mohs (9 mm)	Imiquimod (recurrence, 9–25%), XRT (recurrence, 5–14%)	—	No	—
T1 (≤1.0 mm)		1 cm, Mohs (9 mm)	Surgical excision preferred	XRT*, IL-2, dacarbazine	Lesion depth, 0.76–0.86 mm with ulceration or mitosis >1 mm²; all lesions >0.85 mm in depth	
a	No ulceration or mitoses <1 mm²					92
b	Ulceration or mitosis ≥1 mm²					82
T2 (1.01–2.0 mm)		1 cm, Mohs (12 mm)	Surgical excision preferred	XRT, IL-2, dacarbazine, ipilimumab	Yes	
a	No ulceration					92
b	Ulceration					82
T3 (2.01–4.0 mm)		2 cm, Mohs (12 mm)	Surgical excision preferred	XRT, IL-2, dacarbazine, ipilimumab	Yes	
a	No ulceration					79
b	Ulceration					68
T4 (>4.0 mm)		≥ 2 cm, Mohs (>12 mm)	(Surgical excision preferred)	XRT, IL-2, dacarbazine, ipilimumab	Yes	
a	No ulceration					71
b	Ulceration					53

AJCC, American Joint Committee on Cancer; XRT, radiotherapy; IL-2, interleukin 2.
*Radiotherapy can be used as primary treatment for in situ lesions in poor operative candidates or as adjuvant therapy for desmoplastic melanoma. Data do not show improved survival in adjuvant radiotherapy, and it is best used in metastatic disease and palliation.

A prospective series of 1072 patients treated with Mohs surgery found an 86 percent clearance rate with a 6-mm margin and a 98.9 percent clearance rate with a 9-mm margin ($p < 0.001$). *Mohs surgery may be optimal in regions where repeated excision would sacrifice tumor control or aesthetic results, with excisional margins approximating early invasive melanoma for aggressive in situ subtypes*[44–46] (Fig. 10).

In thicker lesions, some controversy exists regarding wide (2 to 3 cm) versus narrow (≤1 cm) margins (**Reference 13, Level of Evidence: Therapeutic, IV**).[13,14] A Cochrane review with meta-analysis of five studies favored wide excision for improved overall survival but was not statistically significant (hazard ratio, 1.04; 95 percent CI, 0.95 to 1.15; $p = 0.40$).[13] This finding was consistent with another systematic review of wide and narrow excision data from 2071 patients that found no significant difference in overall survival or recurrence.[14] Bichakjian et al. reported that there is little evidence to recommend margins wider than 1 cm in primary melanomas 1.0 to 2.0 mm in thickness, based on recurrence or overall survival.[11,13] In contrast, Balch et al. in the Intergroup Trial found a 6- to 8-fold increase in local recurrence in ulcerated lesions. *This evidence supports the recommendation that thin, nonulcerated melanomas 1.0 to 2.0 mm thick should be resected with a 1-cm margin, and that thicker lesions or ulcerated thin lesions are optimally treated with a 2-cm margin.*[14]

The US Intergroup Surgical Trial investigated thicker melanomas at 2 to 4 mm and determined 2-cm margins to be adequate, with larger margins not significantly impacting recurrence rate (**Level of Evidence: Therapeutic, II**).[15] Other randomized studies have investigated the optimal margins on melanomas 2 to 4 mm thick and found that 3 cm margins do not improve the recurrence and disease-free survival rates when compared with 2-cm margins.[16] However, 2 cm appears to be the minimal margin in intermediate thickness melanomas, as demonstrated by Thomas et al., who evaluated

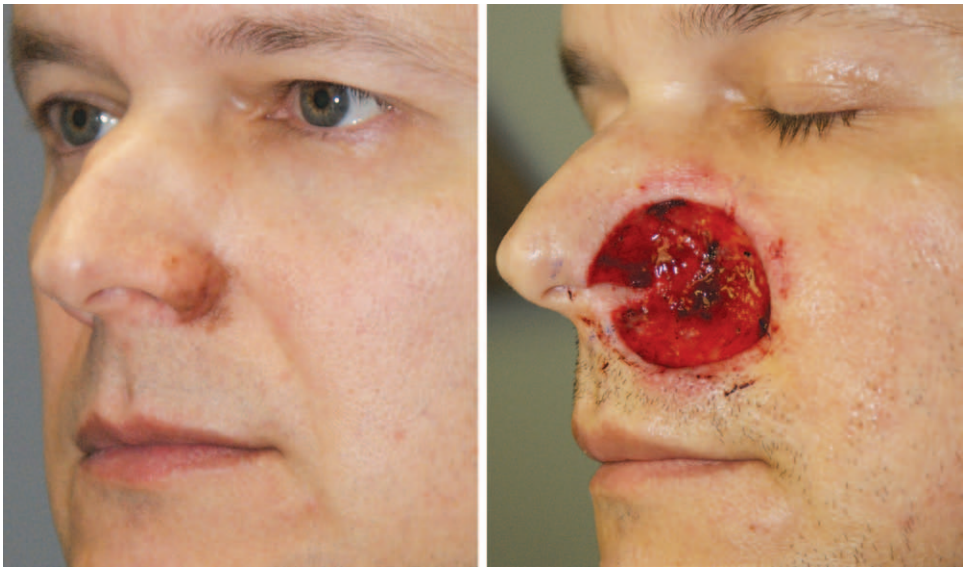

Fig. 10. (*Left*) Melanoma in situ of the left alar rim and nasolabial fold. (*Right*) Resection margin following Mohs excision with 5-mm surgical margins.

900 patients assigned randomly to either a 1-cm or 3-cm margin for melanomas thicker than 2 mm. *A statistically significant increase in local recurrence (hazard ratio, 1.26; 95 percent CI, 1.00 to 1.59; p = 0.05) was found in the narrow margin cohort, evidence that lesions thicker than 2 mm should be resected with at least a 2-cm margin to prevent local recurrence.*[17]

Lymph Node Evaluation

Following the diagnosis of melanoma, a clinical lymph node evaluation should be performed. Occult nodal metastasis is estimated to be as high as 10 to 15 percent in clinically negative nodes, although elective lymphadenectomy is a staging procedure that has limited proven survival benefit and frequent patient morbidity.[54] De Rosa et al. systematically reviewed results of 3400 sentinel node biopsies in the setting of head and neck melanoma, and determined that a sentinel node could be accurately identified in 95 percent of cases. Metastasis was positive in 15 percent of those specimens, and long-term follow-up determined a 13 percent chance of recurrence in the setting of a positive node.[55] *Sentinel lymph node biopsy should be considered for disease staging in lesions 0.76 to 0.85 mm thick with ulceration and greater than one mitoses. Sentinel lymph node biopsy should also be performed for any lesion greater than 0.85 mm in thickness*[41,42] (Table 6). Sentinel lymph node biopsy carries a false-negative rate of 5 to 15 percent; however, biopsy results have proven to be an important independent predictor of survival and further disease progression in patients with clinically negative nodes.[41,50]

Lymph node biopsy may be suboptimal in patients with previous wide resection, or when the draining node is mapped to the parotid gland. Discordant spread and multiple draining lymph node basins often exist, precluding secondary lymph node mapping if not performed concurrently with wide excision. Elective or therapeutic lymph node dissection should be reserved for clinically positive nodes on physical examination or following sentinel lymph node biopsy. Lens et al. performed a literature review of randomized trials evaluating the efficacy of elective lymph node dissection in patients without clinically positive nodal disease and found no added benefit regarding survival.[14] A large, international, randomized trial (Multicenter Selective Lymphadenectomy Trial II) is currently underway to investigate whether positive sentinel node biopsy results warrant an elective node dissection versus nodal basin observation.[50]

Table 6. Guidelines for Sentinel Lymph Node Biopsy in Malignant Melanoma*

Melanoma Thickness	Sentinel Lymph Node Biopsy[41,50,55]
<0.76 mm	No
<0.76 mm; positive ulceration/regression, mitosis >1 mm^2	No
≥0.76 to <0.85 mm; no ulceration/regression, mitosis <1 mm^2	No
≥0.76 to <0.85 mm; positive ulceration/regression, mitosis >1 mm^2	Yes
>0.85 to <1.00 mm	Yes
≥1.00 mm	Yes

*Adapted from Levine SM, Shapiro RL. Surgical treatment of malignant melanoma: Practical guidelines. *Dermatol Clin.* 2012;30:487–501.

Table 7. Recommended Resection Margins, Nonsurgical Therapies, Adjuvant Treatments, Lymph Node Sampling Criteria, and 5-Year Survival Rates for Merkel Cell Carcinoma

	Resection Margin[56,57,60]	Nonsurgical Therapy	Adjuvant Therapy*	Regional Lymph Node Sampling†	AJCC 5-Year Survival (%)[59]‡
Tis (in situ)	1 cm/Mohs	XRT	XRT	Yes	Poorly defined
T1 (<2 cm)	1 cm/Mohs	XRT	XRT, chemotherapy	Yes	60
T2 (2.01–5.0 cm)	2 cm/Mohs	XRT	XRT, chemotherapy	Yes	58
T3 (>5 cm)	2 cm	XRT	XRT, chemotherapy	Yes	49
T4 (invasion of fascia, muscle, or bone)	2 cm	XRT	XRT, chemotherapy	Yes	47

AJCC, American Joint Committee on Cancer; XRT, radiotherapy.
*Merkel cell is a radiosensitive tumor and radiotherapy is recommended for all lesions. Chemotherapy has no randomized data and is indicated only for palliation and distant metastases.
†If results of the sentinel lymph node biopsy are positive, completion lymph node dissection is indicated.
‡Merkel cell carcinoma disease-free survival rates are 81% for stage I, 67% for stage II, 52% for stage III, and 11% for stage IV.

MERKEL CELL CARCINOMA

Clinical Characteristics

Merkel cell carcinoma, a neuroendocrine tumor, is an aggressive form of skin cancer with a high rate of treatment failure and local recurrence.[56] The lesion is typically found in older, immunocompromised, fair-skinned women, with 50 percent of lesions occurring in the head and neck and 5 to 10 percent of those occurring on the eyelids. The cause of the cancer may be secondary to polyomavirus infection in up to 80 percent of cases, and the prevalence of this disease is high in human immunodeficiency virus–positive individuals.[57,58] Merkel cell carcinoma presents as a firm and painless fleshy nodule with a red or blue discoloration, and is likely to occur on sun-exposed areas.[58]

The associated mortality rate is significantly affected by nodal metastasis. Disease-free survival at 5 years with node-negative disease is closer to 83 percent, whereas nodal disease decreases survival at 5 years to 58 percent.[59] The staging system for Merkel cell carcinoma is basic, with 2 cm defined as the difference between stage 1 and stage 2. Nodal or distant metastasis will upstage to stages 3 and 4, respectively.[10] In a review of 251 treated patients using this system, Allen et al.[10] determined that disease stage at presentation can be correlated as an independent predictor of survival (stage I, 81 percent; stage II, 67 percent; stage III, 52 percent; stage IV, 11 percent; $p = 0.001$). In addition, the authors did not find a decreased rate of recurrence with a surgical margin of more than 1 cm (<1 cm, 9 percent; >1 cm, 10 percent; $p = 0.83$).

Treatment Guidelines

The current standard of care for Merkel cell carcinoma is surgical resection with wide location excision or Mohs therapy. *Wide surgical excision margins are recommended, with a 1-cm margin for lesions less than 2 cm in clinical size, and a 2-cm margin for those larger than 2 cm.*[60] In addition, because of the high rate of occult nodal metastasis, sentinel lymph node biopsy is recommended at the time of resection for all tumor sizes (Table 7).

Adjuvant radiotherapy also plays an important role in the management of Merkel cell carcinoma, as it is a very radiosensitive tumor. Following excision, adjuvant radiotherapy following resection has demonstrated a 3.7-fold decrease in recurrence.[60,61] In a multicenter trial, Boyer et al. evaluated marginal recurrence and survival rates in 45 patients that had undergone resection and postoperative radiation therapy compared with resection only. At an average 27.8 months of follow-up, there were four cases (16 percent) of local recurrence in the group that had not received radiotherapy, and none in the combined group ($p = 0.12$).[54]

Steven P. Davison, D.D.S., M.D.
DAVinci Plastic Surgery
3101 New Mexico Avenue NW
Washington, D.C. 20016
davisonplastic@yahoo.com

PATIENT CONSENT

Patients provided written consent for the use of their images.

REFERENCES

1. Jemal A, Saraiya M, Patel P, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. *J Am Acad Dermatol.* 2011;65(Suppl 1):S17–25.e1.
2. American Society of Plastic Surgeons. Procedural statistics. Available at: http://www.plasticsurgery.org. Accessed February 27, 2013.
3. Brodsky J. Management of benign skin lesions commonly affecting the face: Actinic keratosis, seborrheic keratosis, and rosacea. *Curr Opin Otolaryngol Head Neck Surg.* 2009;17:315–320.

4. Martin G. The impact of the current United States guidelines on the management of actinic keratosis: Is it time for an update? *J Clin Aesthet Dermatol.* 2010;3:20–25.
5. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Cutaneous squamous carcinoma in situ (Bowen's disease): Treatment with Mohs micrographic surgery. *J Am Acad Dermatol.* 2005;52:997–1002.
6. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip: Implications for treatment modality selection. *J Am Acad Dermatol.* 1992;26:976–990.
7. Gulleth Y, Goldberg N, Silverman RP, Gastman BR. What is the best surgical margin for a basal cell carcinoma: A meta-analysis of the literature. *Plast Reconstr Surg.* 2010;126:1222–1231.
8. Mosterd K, Thissen MR, Nelemans P, et al. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: Results of a randomized controlled trial. *Br J Dermatol.* 2008;159:864–870.
9. Smeets NW, Krekels GA, Ostertag JU, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: Randomised controlled trial. *Lancet* 2004;364:1766–1772.
10. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: Prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23:2300–2309.
11. Bichakjian CK, Halpern AC, Johnson TM, et al.; American Academy of Dermatology. Guidelines of care for the management of primary cutaneous melanoma: American Academy of Dermatology. *J Am Acad Dermatol.* 2011;65:1032–1047.
12. Huilgol SC, Selva D, Chen C, et al. Surgical margins for lentigo maligna and lentigo maligna melanoma: The technique of mapped serial excision. *Arch Dermatol.* 2004;140:1087–1092.
13. Sladden MJ, Balch C, Barzilai DA, et al. Surgical excision margins for primary cutaneous melanoma. *Cochrane Database Syst Rev.* 2009;(4):CD004835.
14. Lens MB, Dawes M, Goodacre T, Newton-Bishop JA. Elective lymph node dissection in patients with melanoma: Systematic review and meta-analysis of randomized controlled trials. *Arch Surg.* 2002;137:458–461.
15. Balch CM, Soong S, Ross MI, et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial. *Ann Surg Oncol.* 2000;7:87–97.
16. Gillgren P, Drzewiecki KT, Niin M, et al. 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: A randomised, multicentre trial. *Lancet* 2011;378:1635–1642.
17. Thomas JM, Newton-Bishop J, A'Hern R, et al.; United Kingdom Melanoma Study Group; British Association of Plastic Surgeons; Scottish Cancer Therapy Network. Excision margins in high-risk malignant melanoma. *N Engl J Med.* 2004;350:757–766.
18. Perrett CM, McGregor JM, Warwick J, et al. Treatment of post-transplant premalignant skin disease: A randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol.* 2007;156:320–328.
19. Ehrig T, Cockerell C, Piacquadio D, Dromgoole S. Actinic keratoses and the incidence of occult squamous cell carcinoma: A clinical-histopathologic correlation. *Dermatol Surg.* 2006;32:1261–1265.
20. Cox NH, Eedy DJ, Morton CA; Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol.* 2007;156:11–21.
21. Braathen LR, Szeimies RM, Basset-Seguin N, et al.; International Society for Photodynamic Therapy in Dermatology. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. *J Am Acad Dermatol.* 2007;56:125–143.
22. Kechijian P, Connors RC, Ackerman AB. Trichoepithelioma vs. basal-cell carcinoma: Criteria for histologic differentiation. *J Dermatol Surg.* 1975;1:22–23.
23. Chren MM, Linos E, Torres JS, Stuart SE, Parvataneni R, Boscardin WJ. Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol.* 2013;133:1188–1196.
24. Adams EL, Price NM. Treatment of basal-cell carcinomas with a carbon-dioxide laser. *J Dermatol Surg Oncol.* 1979;5:803–806.
25. Iyer S, Bowes L, Kricorian G, Friedli A, Fitzpatrick RE. Treatment of basal cell carcinoma with the pulsed carbon dioxide laser: A retrospective analysis. *Dermatol Surg.* 2004;30:1214–1218.
26. Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. *Arch Dermatol.* 1987;123:340–344.
27. National Comprehensive Cancer Network. National Comprehensive Cancer Network (Web site). Available at: http://www.nccn.org. Accessed March 7, 2013.
28. Mosterd, K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: A prospective randomized controlled trial with 5-years' follow up. *Lancet Oncol.* 2008;9:1149–1156.
29. Morselli P, Zollino I, Pinto V, Brunelli G, Carinci F. Clinical prognostic factors in stage I head and neck squamous cell carcinoma. *J Craniofac Surg.* 2008;19:740–743.
30. Motley R, Kersey P, Lawrence C; British Association of Dermatologists; British Association of Plastic Surgeons. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Plast Surg.* 2003;56:85–91.
31. Shin DM, Maloney ME, Lippman SM. Follow-up and prevention (squamous cell carcinoma). In: Miller SJ, Maloney ME, eds. *Cutaneous Oncology: Pathophysiology, Diagnosis, and Management.* Malden, Mass: Blackwell Science; 1998.
32. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: A prospective study. *Lancet Oncol.* 2008;9:713–720.
33. Garcia C, Poletti E, Crowson AN. Basosquamous carcinoma. *J Am Acad Dermatol.* 2009;60:137–143.
34. Costantino D, Lowe L, Brown DL. Basosquamous carcinoma: An under-recognized, high-risk cutaneous neoplasm. Case study and review of the literature. *J Plast Reconstr Aesthet Surg.* 2006;59:424–428.
35. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 1992;27:241–248.
36. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. *J Am Acad Dermatol.* 2005;53:253–260.
37. Kyrgidis A, Tzellos TG, Kechagias N, et al. Cutaneous squamous cell carcinoma (SCC) of the head and neck: Risk factors of overall and recurrence-free survival. *Eur J Cancer* 2010;46:1563–1572.
38. National Cancer Institute. National Cancer Institute at the National Institutes of Health (Web site). Available at: http://www.cancer.gov. Accessed February 7, 2013.
39. Arlette JP, Trotter MJ, Trotter T, Temple CL. Management of lentigo maligna and lentigo maligna melanoma: Seminars in surgical oncology. *J Surg Oncol.* 2004;86:179–186.

40. Lens MB, Newton-Bishop JA, Boon AP. Desmoplastic malignant melanoma: A systematic review. *Br J Dermatol.* 2005;152:673–678.
41. Levine SM, Shapiro RL. Surgical treatment of malignant melanoma: Practical guidelines. *Dermatol Clin.* 2012;30:487–501.
42. Wisco OJ, Sober AJ. Prognostic factors for melanoma. *Dermatol Clin.* 2012;30:469–485.
43. Esmaeli B, Youssef A, Naderi A, Ahmadi MA, Meyer DR, McNab A; Collaborative Eyelid Skin Melanoma Group. Margins of excision for cutaneous melanoma of the eyelid skin: The Collaborative Eyelid Skin Melanoma Group Report. *Ophthal Plast Reconstr Surg.* 2003;19:96–101.
44. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27:6199–6206.
45. Thompson JF, Soong SJ, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: An analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol.* 2011;29:2199–2205.
46. Powell AM, Robson AM, Russell-Jones R, Barlow RJ. Imiquimod and lentigo maligna: A search for prognostic features in a clinicopathological study with long-term follow-up. *Br J Dermatol.* 2009;160:994–998.
47. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. *Br J Dermatol.* 2002;146:1042–1046.
48. Leiter U, Eigentler TK, Forschner A, et al. Excision guidelines and follow-up strategies in cutaneous melanoma: Facts and controversies. *Clin Dermatol.* 2010;28:311–315.
49. Bricca GM, Brodland DG, Ren D, Zitelli JA. Cutaneous head and neck melanoma treated with Mohs micrographic surgery. *J Am Acad Dermatol.* 2005;52:92–100.
50. Ross MI, Gershenwald JE. Sentinel lymph node biopsy for melanoma: A critical update for dermatologists after two decades of experience. *Clin Dermatol.* 2013;31:298–310.
51. Smith-Zagone MJ, Schwartz MR. Frozen section of skin specimens. *Arch Pathol Lab Med.* 2005;129:1536–1543.
52. Kunishige JH, Brodland DG, Zitelli JA. Surgical margins for melanoma in situ. *J Am Acad Dermatol.* 2012;66:438–444.
53. Bub JL, Berg D, Slee A, Odland PB. Management of lentigo maligna and lentigo maligna melanoma with staged excision: A 5-year follow-up. *Arch Dermatol.* 2004;140:552–558.
54. Davison SP, Clifton MS, Kauffman L, Minasian L. Sentinel node biopsy for the detection of head and neck melanoma: A review. *Ann Plast Surg.* 2001;47:206–211.
55. de Rosa N, Lyman GH, Silbermins D, et al. Sentinel node biopsy for head and neck melanoma: A systematic review. *Otolaryngol Head Neck Surg.* 2011;145:375–382.
56. Boyer JD, Zitelli JA, Brodland DG, D'Angelo G. Local control of primary Merkel cell carcinoma: Review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. *J Am Acad Dermatol.* 2002;47:885–892.
57. Schrama D, Ugurel S, Becker JC. Merkel cell carcinoma: Recent insights and new treatment options. *Curr Opin Oncol.* 2012;24:141–149.
58. Slutsky JB, Jones EC. Periocular cutaneous malignancies: A review of the literature. *Dermatol Surg.* 2012;38:552–569.
59. Smith VA, Camp ER, Lentsch EJ. Merkel cell carcinoma: Identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. *Laryngoscope* 2012;122:1283–1290.
60. Wang TS, Byrne PJ, Jacobs LK, Taube JM. Merkel cell carcinoma: Update and review. *Semin Cutan Med Surg.* 2011;30:48–56.
61. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol.* 2006;142:693–700.