High-Risk Cutaneous Squamous Cell Carcinoma

A Practical Guide for Patient Management

Chrysalyne D. Schmults
Editor

Springer

High-Risk Cutaneous Squamous Cell Carcinoma

Chrysalyne D. Schmults
Editor

High-Risk Cutaneous Squamous Cell Carcinoma

A Practical Guide for Patient Management

Springer

Editor
Chrysalyne D. Schmults, MD, MSCE
Director, Mohs & Dermatologic Surgery Center
Brigham & Women's Hospital
Department of Dermatology
Boston, MA, USA

ISBN 978-3-662-47080-0 ISBN 978-3-662-47081-7 (eBook)
DOI 10.1007/978-3-662-47081-7

Library of Congress Control Number: 2015956335

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer-Verlag GmbH Berlin Heidelberg

To my husband and daughters who have shown great patience with my distraction while editing this book.

Preface

My coauthors and I are happy to bring you this inaugural textbook on high-risk cutaneous squamous cell carcinoma. We feel it is timely in that many advances in defining this entity have occurred in recent years and we're witnessing the beginning of the serious study of this historically understudied disease. If any subsequent editions of this text are released, they will almost certainly contain important advances in prognostic stratification, our understanding of the molecular and genetic underpinnings of aggressive tumor formation and progression, accurate disease staging, and even treatment. Although the study of high-risk cutaneous squamous cell carcinoma is in its infancy, it will not remain there for long. Many distinguished investigators, many of whom are authors of this book, are hard at work to bring new information to light that will ultimately benefit patients who suffer from this difficult disease. Meanwhile, we hope that you will find this a useful compendium of current knowledge.

Boston, MA, USA — Chrysalyne D. Schmults, MD, MSCE

Contents

Contributors

Sarah Tuttleton Arron, MD, PhD Department of Dermatology, University of California, San Francisco, San Francisco, CA, USA

Christian L. Baum, MD Department of Dermatology, Mayo Clinic, Rochester, MN, USA

Travis W. Blalock, MD Department of Dermatology, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA

Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA

John A. Carucci, MD, PhD Ronald O. Perelman Department of Dermatology, New York University Langone Medical Center, New York, NY, USA

Sasha Jenkins Haberle, MD, MPH Department of Dermatology, Dermatologists of Southwest Ohio, INC, Cincinnati, OH, USA

Glenn J. Hanna, MD Department of Medical Oncology and Hematology, Dana Farber Cancer Institute, Boston, MA, USA

Catherine Anne Harwood, BA, MA, PhD, FRCP Centre for Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Royal London Hospital, London, UK

Günther F.L. Hofbauer, MD Dermatologische Klinik, Universitätsspital Zürich, Zürich, ZH, Switzerland

Julie Howle, BSc, MBBS, MS, FRACS, FACS Department of Surgery, Westmead Hospital, Sydney, NSW, Australia

Anokhi Jambusaria-Pahlajani, MD, MSCE Department of Dermatology, Mayo Medical School, Mayo Clinic Florida, Jacksonville, FL, USA

Pritesh S. Karia, MPH Department of Dermatology, Brigham and Women's Hospital, Boston, MA, USA

Jochen H. Lorch, MD, MSc Department of Medical Oncology, Harvard Medical School, Dana Farber Cancer Institute, Boston, MA, USA

Vishal Anil Patel, MD Department of Dermatology, Columbia University/New York Presbyterian, New York, NY, USA

Charlotte Mary Proby, BA, MBBS, FRCP Ninewells Hospital and Medical School, Jacqui Wood Cancer Center, Medical Research Institute, University of Dundee, Dundee, UK

Désirée Ratner, MD Department of Dermatology, Beth Israel Medical Center, St. Luke's Hospital, Roosevelt Hospital, New York, NY, USA

Lauren Rimoin, MD Department of Dermatology, Emory University, Atlanta, GA, USA

Emily Stamell Ruiz, MD Department of Dermatology, Brigham and Women's Hospital, Boston, MA, USA

Thomas Stasko, MD Department of Dermatology, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA

Vitaly Terushkin, MD Ronald O. Perelman Department of Dermatology, New York University Langone Medical Center, New York, NY, USA

Myrto Georgia Trakatelli, MD, PhD Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece

St. Pierre Hospital, Bruxelles, Belgium

Michael Veness, MB, BS, MD (USyd), FRANZCR Westmead Cancer Care Center, Westmead Hospital, Sydney, NSW, Australia

Valerie Yanofsky, BS Ronald O. Perelman Department of Dermatology, NYU-Langone Medical Center, New York, NY, USA

Fiona Zwald, MD, MRCPI Piedmont Transplant Institute, Piedmont Hospital, Atlanta, GA, USA

Part I
Defining the Problem of High-Risk SCC

Chapter 1
Epidemiology and Outcomes of Cutaneous Squamous Cell Carcinoma

Pritesh S. Karia

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common cancer diagnosed among whites in the United States [1]. Whilst most cases are easily cured by surgical removal, a subset termed "high-risk SCC" carries an elevated risk of metastasis and death. High-risk SCC and its associated outcomes have recently been better defined [2, 3]. Tumors with multiple high-risk factors (tumor diameter ≥2 cm, poorly differentiated histology, depth beyond fat, and perineural invasion ≥0.1 mm) have the greatest metastatic potential and result in the majority of SCC deaths.

The lifetime risk of developing SCC is 14 % in men and 9 % in women [4]. SCC causes significant morbidity and mortality among elderly persons however, the incidence of SCC which, is often treated in outpatient settings, is unknown. National cancer registries such as Surveillance, Epidemiology, and End Results do not collect routine incidence and mortality data for SCC. In spite of the paucity of population-based data, several studies have reported an increase of 50–200 % in SCC incidence in the United States over the last three decades [5–7]. With the reported increase in SCC incidence, the incidence of poor outcomes resulting from SCC may be rising as well making SCC a potentially under recognized public health problem.

Incidence

The global age-adjusted incidence of SCC varies according to latitude. Studies have shown that SCC incidence doubles with each 8 to 10° decrease in latitude (proximity to the equator) [5]. Table 1.1 summarizes the age-adjusted SCC incidence among

P.S. Karia, MPH (✉)
Department of Dermatology, Brigham and Women's Hospital, Boston, MA, USA
e-mail: pkaria@partners.org

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_1

Table 1.1 Population-based incidence of cutaneous squamous cell carcinoma by geographic location for white persons

Country	Region	Author (first and last)	Study period	Age adjusted SCC incidence (per 100,000)		
				Men	Women	Overall
Australia	Whole country	Staples, Giles et al. [9]	1985[a]	209.0	122.0	166.0
			1990	338.0	164.0	250.0
			1995	419.0	228.0	321.0
			2002	499.0	291.0	387.0
	Nambour, Queensland	Green, Weedon et al. [10]	1985–1992[a]	1035.0	472.0	–
	Townsville, Queensland	Buettner and Raasch [11]	1996–1997[a]	1332.3	754.8	–
Canada	British Columbia	McLean, Lee et al. [12]	1973[b]	24.4	11.5	–
			1983	35.6	16.9	–
			1993	56.8	26.3	–
			2003	60.3	32.4	–
	Alberta	Jung, Salopek et al. [13]	1988[b]	45.0	22.9	33.0
			1997	63.6	26.2	42.7
			2006	60.2	30.5	43.4
Denmark	Whole country	Magnus [14]	1976–1985[a]	6.7	2.5	–
Finland	Whole country	Hannuksela-Svahn, Pukkala and Karvonen [15]	1956–1960[a]	3.2	1.8	–
			1961–1965	4.2	2.2	–
			1966–1970	3.9	2.3	–
			1971–1975	4.1	2.3	–
			1976–1980	4.6	2.5	–
			1981–1985	5.2	3.3	–
			1986–1990	6.2	3.9	–
			1991–1995	7.2	4.2	–
	Whole country	Magnus [14]	1976–1985[a]	5.6	3.9	–
Germany	Schleswig-Holstein	Katalinic, Kunze and Schafer [16]	1998–2001[a]	11.2	5.3	–
Iceland	Whole country	Magnus [14]	1976–1985[a]	7.1	4.0	–

(continued)

Table 1.1 (continued)

Country	Region	Author (first and last)	Study period	Age adjusted SCC incidence (per 100,000)		
				Men	Women	Overall
Norway	Whole country	Iversen and Tretli [17]	1966–1970[a]	2.9	1.2	–
			1971–1975	4.5	2.1	–
			1976–1980	5.9	2.8	–
			1981–1985	6.6	3.3	–
			1986–1990	7.8	4.1	–
			1991–1995	9.4	5.5	–
	Whole country	Magnus [14]	1976–1985[a]	6.4	3.2	–
Sweden	North coast	Andersson and Wastensson [18]	1970[b]	6.8	6.4	–
	North inland		1970	9.6	1.9	–
	South coast		1970	11.3	4.7	–
	South inland		1970	6.3	6.3	–
	Gothenburg		1970	11.5	3.4	–
	North coast		2007	82.2	40.8	–
	North inland		2007	62.9	35.7	–
	South coast		2007	95.8	68.4	–
	South inland		2007	53.4	36.3	–
	Gothenburg		2007	73.9	45.7	–
	Whole country	Magnus [14]	1976–1985[a]	10.2	4.6	–
Switzerland	Vaud	Levi, Mezzanotte et al. [19]	1976–1985[a]	16.1	7.7	–
United Kingdom	West Glamorgan	Roberts [20]	1988[a]	31.7	6.2	19.0
	South Wales	Holme, Malinovszky and Roberts [21]	1988[a]	22.8	9.3	15.1
			1998	25.2	8.6	15.8
	Scotland	Brewster, Doherty et al. [22]	1992–1994[a]	6.5	18.4	–
			1995–1997	9.4	25.5	–
			1998–2000	8.5	22.6	–
			2001–2003	9.4	24.0	–

(continued)

Table 1.1 (continued)

Country	Region	Author (first and last)	Study period	Age adjusted SCC incidence (per 100,000)		
				Men	Women	Overall
United States	Iowa	Scotto, Kopf and Urbach [6]	1971–1972[b]	50.8	14.3	–
	Minneapolis-St. Paul, MN		1971–1972	36.5	12.3	–
	San Francisco-Oakland, CA		1971–1972	51.7	15.8	–
	Dallas-Fort Worth, TX		1971–1972	144.7	54.4	–
	Seattle, WA	Scotto and Fraumeni [5]	1977–1978[b]	46.6	16.1	–
	Minneapolis-St. Paul, MN		1977–1978	36.6	11.8	–
	Detroit, MI		1977–1978	30.0	11.0	–
	Utah		1977–1978	123.1	45.9	–
	San Francisco-Oakland, CA		1977–1978	56.3	18.4	–
	Atlanta, GA		1977–1978	131.0	52.6	–
	New Orleans, LA		1977–1978	153.4	48.8	–
	New Mexico		1977–1978	98.1	41.7	–
	Rochester, MN	Chuang, Chute et al. [23]	1976–1984[b]	63.1	22.5	38.8
	Rochester, MN	Gray, Roenigk et al. [24]	1985–1992[b]	155.5	71.2	105.6

[a]Adjusted to the world standard population
[b]Adjusted to country/state population

white persons in various geographic areas of the world. There is nearly a 100-fold difference in SCC incidence between the white populations of Australia and northern European countries such as Finland and Denmark. These differences are partly attributed to differences in sun exposure.

A similar pattern of geographic variability exists in the United States. The National Cancer Institute conducted two population-based surveys of NMSC incidence in the 1970s. These surveys which were conducted in ten metropolitan areas with varying sun exposure revealed a north–south SCC incidence gradient. The incidence of SCC increased significantly with increasing sun exposure. The highest SCC incidence was observed in individuals living in southern latitudes such as Atlanta, Georgia (131.0 per 100,000 in men and 52.6 per 100,000 in women), Dallas-Ft. Worth Texas (144.7 per 100,000 in men and 54.4 per 100,000 in women),

and New Orleans, Louisiana (153.4 per 100,000 in men and 48.8 per 100,000 in women) while the lowest SCC incidence was observed in individuals living in northern latitudes such as Minneapolis-St. Paul, Minnesota (36.6 per 100,000 in men and 11.8 per 100,000 in women) and Seattle, Washington (46.6 per 100,000 in men and 16.1 per 100,000 in women) (Table 1.1) [5, 6]. Similarly, a recent study estimating the 2012 incidence of SCC found that the incidence of SCC was about five times higher in southern and central United States (average assumption: 233.3 per 100,000 in men and 83.4 per 100,000 in women) as compared to northern United States (average assumption: 46.3 per 100,000 in men and 15.7 per 100,000 in women). This study also found that deaths from SCC in southern and central United States were as common as deaths from renal and oropharyngeal carcinomas and melanoma [8].

There is a strong association between age and SCC incidence [5, 23, 25–27]. The incidence of SCC in individuals above 65 years of age is 488.9 per 100,000 as compared to 137.5 and 73.9 per 100,000 in individuals 55–64 and 45–54 years of age, respectively [26]. SCC is uncommon in individuals younger than 40 years of age with an annual incidence of 3.9 per 100,000 [28].

The incidence of SCC also varies with ethnicity. A population-based study conducted in an ethnically diverse area of southeastern Arizona showed that the SCC incidence in hispanics (32.9 per 100,000 for men and 13.8 per 100,000 for women) was 11 times lower as compared to the SCC incidence in non-hispanic whites (364.2 per 100,000 in men and 153.5 per 100,000 in women) [29]. Similarly, the age-adjusted incidence of SCC in blacks is low; about 3 per 100,000 [30]. However, blacks are about 8.5 times more likely to develop SCCs in non-sun-exposed sites as compared to whites [31].

Risk Factors

Ultraviolet Radiation

Exposure to UV radiation is the most common cause of SCC. UV radiation is comprised of three distinct sections: UVA (wavelength 320–400 nm), UVB (290–320), and UVC (200–280 nm). UVC radiation is effectively absorbed by the ozone layer before reaching the earth's surface therefore; exposure to UVC radiation mainly occurs through man-made sources. UVA and UVB radiation both reach the earth's surface and have distinct biological effects on SCC formation. UV radiation induces skin cancer by causing DNA damage which if left unrepaired can result in carcinogenic changes through the accumulation of mutations. UVB radiation is principally responsible for SCC formation while UVA radiation, which is 10,000 times less mutagenic, enhances the carcinogenic effects of UVB radiation, adding to the risk of developing SCC [1, 32–35]. The p53 tumor suppressor gene which, plays a significant role in controlling DNA repair mechanisms, is found to be mutated in over half of all SCCs [36–38].

Occupational exposure to UV radiation has been linked to an increased incidence and prevalence of SCC. A meta-analysis investigating the risk of SCC associated with occupational UV exposure found a twofold increased risk of SCC in individuals with occupational UV light exposure as compared to those with no occupational UV light exposure [39]. Similarly, a population-based study exploring the relationship between UVB radiation and SCC prevalence among watermen in Maryland found that those in the upper quartile of cumulative UVB exposure were 3 times more likely to have an SCC as compared to those in the lowest quartile of cumulative UVB exposure [40].

Recreational exposure to UV radiation has also been shown to increase the risk of SCC incidence. A meta-analysis conducted by the International Agency for Research on Cancer to determine the impact of sunbed tanning on SCC risk found a positive association with ever-use of sunbed tanning [41]. Based on the results of this meta-analysis, the International Agency for Research on Cancer formally classified UV radiation from tanning beds as carcinogenic to humans (Group 1) in 2010 [42]. A more recent meta-analysis investigating the association between indoor tanning and NMSC risk found that patients who reported ever use of indoor tanning beds had a 67 % higher risk of SCC as compared to those who reported no use of indoor tanning [43]. A dose-response relationship between the frequency of tanning bed use and SCC risk has also been implicated. Those who use tanning beds 6 or more times a year are more likely to develop SCC as compared to those using tanning beds 3–5 and 1–2 times a year [44]. In 2014, the Food and Drug Administration within the U.S. Department of Health and Human Services issued an order that requires all sunlamp products to include a visible black box warning about skin cancer risks.

Treatment of severe cutaneous psoriasis with orally administered psoralen and UVA radiation (PUVA), although highly effective, has been linked to a significant increase in SCC incidence. A substantial dose-response relationship between PUVA and SCC incidence has been reported [45]. Those exposed to more than 450 treatments of PUVA have a 35-fold increased incidence of SCC as compared to those exposed to fewer than 50 treatments [46]. When compared to an age and gender matched white population sample, the incidence of SCC in patients treated with PUVA is about 30-fold higher [46, 47].

Phenotypic characteristics that predispose individuals to increased sun sensitivity such as eye color, hair color, and skin color also play an important role in mediating SCC risk. Light skin color, red hair, and eye colors other than brown have all been associated with an increased risk of SCC [48, 49]. Skin sensitivity to sunlight as measured by the propensity of the skin to burn on initial exposure to sunlight is significantly associated with SCC incidence. Those who burn, tan and/or peel after exposure to sunlight have a higher risk of developing SCC as compared to those who do not burn [48]. Several case-control studies have also shown strong associations between a history of blistering sunburns and SCC risk though these studies are subject to recall bias [50, 51]. A recent prospective cohort study showed a 25 % increased risk in women with 1–4 blistering sunburns and a 68 % increased risk in women with 5 or more blistering sunburns as compared to women with no blister-

ing sunburns between the ages of 15 and 20 years [52]. Photoprotective measures such as regular sunscreen application have been shown to reduce the occurrence of SCC by about 40 % [53, 54].

Furthermore, studies investigating the effects of migration on the incidence of SCC in Australia have found that SCC was less common in migrants, most of whom were British or northern European in origin, as compared to people born in Australia. Moreover, migrants who arrived in Australia earlier in life or those who had been in Australia for a long time had a higher risk of SCC as compared to migrants who arrived later in life or more recently [45, 49]. These studies suggest that early and cumulative exposure to UV radiation may be the most significant risk factor for SCC development.

Ionizing Radiation

Ionizing radiation has been shown to induce SCC in animals and humans. Patients treated with low-energy ionizing radiation (mainly X-ray) for benign dermatologic conditions such as acne, dermatitis, and hemangiomas have an increased risk of SCC [55]. The most important risk factor in patients with radiation-induced SCC is the total accumulated dose which, is inversely related to the latency period for SCC development. Fair-skinned individuals treated with ionizing radiation are more likely to develop SCC as compared to other skin types suggesting that melanin plays a protective role against ionizing radiation [56]. In addition to therapeutic use, ionizing radiation exposure is prevalent in several occupational groups such as radiologists, uranium miners, and technicians. X-ray exposure has been associated with an increased risk of SCC in children treated with X-rays for tinea capitis or for thymic enlargement [59–61]. Besides X-rays, gamma rays and grenz rays have also been shown to induce SCC formation in animal studies [62].

Immunosuppression

Chronic immunosuppression whether iatrogenic or non-iatrogenic, has been shown to significantly increase SCC incidence. It is well documented that patients with solid organ transplantation and chronic inflammatory disorders are at an increased risk of developing SCC and other cutaneous malignancies. These patients are often placed on multiple immunosuppressive agents which, although life-saving, have been shown to have specific oncogenic properties.

The risk of SCC is particularly high in organ transplant recipients (OTRs) with a 60- to 100-fold increased risk as compared to the general population [63]. Furthermore, OTRs tend to develop multiple and more aggressive SCCs. In heart transplant recipients diagnosed with post-transplant SCC or BCC, the cumulative incidence of developing a subsequent SCC within 5 years is 70 % [64]. In terms of

SCC outcomes, a risk of 13.5 % for local recurrence and 5–8 % for metastasis has been reported in OTRs as compared to 3.0–4.6 % and 3.7–4.0 % in the general population, respectively [2, 3, 65].

The risk of SCC in OTRs is related to the duration and intensity of immunosuppression. In the United States, the cumulative risk of SCC in heart transplant recipients is reported to be 3 %, 21 %, and 35 % at 1, 5, and 10 years post-transplantation, respectively [66]. The cumulative risk of SCC in sunnier countries such as Australia is as high as 45 % 10-years post-transplantation [67, 68]. A high risk of SCC is observed in heart and lung transplant recipients who are maintained on high levels of immunosuppressive drugs while a lower risk is observed in kidney and liver transplant recipients who require lower levels of immunosuppressive drugs [68–70]. In addition, multi-drug regimens are associated with the highest-risk of malignancies [71].

Several studies have also shown that the risk of SCC is related to the type of immunosuppressive regimen. Immunosuppressive drugs such as cyclosporine, azathioprine, and prednisone have been shown to increase SCC incidence in OTRs [72]. A population-based study investigating the risk of SCC in kidney and heart transplant recipients on various long-term immunosuppressive regimens found that those receiving cyclosporine, azathioprine, and prednisone were three times more likely to develop SCC as compared to those receiving azathioprine and prednisone [73]. Conversely, newer immunosuppressive drugs such as sirolimus have been shown to have antineoplastic properties [74, 75]. A recent meta-analysis found that sirolimus-based immunosuppression was associated with a 42 % decline in SCC risk among kidney transplant recipients [76].

The effect of immunosuppressive drugs on SCC incidence may be reversible to some degree. A prospective study examining the efficacy and safety of conversion from calcineurin inhibitors such as cyclosporine and tacrolimus to sirolimus in kidney transplant recipients found that those switched to sirolimus had a significantly lower rate of SCC formation (22 %) as compared to those who continued on calcineurin inhibitors (39 %) [74, 77].

Chronic inflammatory disorders such as systemic lupus erythematosus and inflammatory bowel disease (IBD) have also been linked to a higher incidence of SCC. A population-based study conducted in Sweden found a twofold increased incidence of SCC in patients with systemic lupus erythematosus as compared to the general population [78]. IBD patients have a four to sevenfold increased risk of SCC as compared to individuals without IBD [79]. In addition, IBD patients treated with thiopurines have a fivefold increased risk of SCC as compared to those not treated with thiopurines [79, 80]. Other conditions that impair the immune system including infection with the human immunodeficiency virus (HIV) and chronic lymphocytic leukemia (CLL) are also associated with an increased incidence of SCC. A recent study found that the incidence of SCC in HIV positive individuals was threefold higher as compared to those who were HIV negative [81].

Patients with CLL have an overall greater frequency of SCC and a higher rate of SCC recurrence [82–85]. If they form high-risk SCCs and have a history of advanced CLL, their mortality risk is particularly high. At 12 %, this risk was equivalent to their

risk of dying from CLL in one study. Interestingly, this was true even when adjusted for CLL treatment and remission so that the mortality risk from SCC may remain high even after CLL is in remission [86].

Chronic Inflammation

An increased risk of SCC has been observed in long-standing chronic ulcers, scars, osteomyelitis, sinus tracts, and burns of the skin [1, 87]. Although only 1 % of cutaneous skin cancers arise in chronically inflamed skin, about 95 % of these skin cancers are SCC [88]. SCC arising in previously burned or irradiated skin is also known as Marjolin's ulcer. This form of SCC has been shown to be more aggressive than SCC arising in UV-damaged skin [89].

Arsenic Exposure

Arsenic is a naturally occurring substance that is found in soil and minerals and may thus contaminate well water. Chronic exposure to arsenic has been associated with an increased incidence of SCC, BCC, and other malignancies [90]. A study from Taiwan investigating the association between arsenic ingestion and skin cancer found that areas with high arsenic levels (>0.64 mg/L) in well water had a higher incidence of SCC as compared to areas with low arsenic levels (<0.04 mg/L) [91]. A similar dose-response relationship was also observed for BCC. In addition, a population-based study investigating the risk of skin cancer in relation to toenail arsenic concentrations found that those with arsenic concentrations above the 97th percentile had a twofold higher risk of developing SCC as compared to those with low to moderate levels of arsenic exposure [92].

Exposure to arsenic has also been reported in a wide range of occupations including mining, agriculture, and production of electronic semiconductors. However, studies investigating the link between occupational exposure to arsenic (mainly through inhalation) and skin cancer have yielded inconsistent results [93, 94].

Polycyclic Aromatic Hydrocarbons Exposure

Polycyclic aromatic hydrocarbons (PAH) are a group of chemicals that are formed during incomplete burning of coal, oil, gas, and other organic substances such as tobacco and meat [95]. PAH exposure occurs mainly through inhalation of contaminated air, ingestion of grilled food, and skin contact. Several studies have shown that workers with skin exposure to tar or pitch, shale oil, creosote, asphalt, and chimney soot are at an increased risk of SCC, especially scrotal SCC [96–102].

Family History

Offspring whose parents are diagnosed with SCC at an early age (<40 years) have a twofold increased risk of SCC as compared to those whose parents are not diagnosed with SCC at an early age [103]. The risk of SCC is still significantly elevated in offspring whose parents are diagnosed with SCC at more advanced ages. Population-based data from Sweden has shown that individuals with an affected sibling or parent have a two to threefold increased incidence of SCC as compared to the general population [104]. However, a smaller population-based study conducted among like-sexed twins in Finland found no difference in SCC risk between those with a history of SCC and the general population [105]. Further studies examining the role of family history in the etiology of SCC are necessary.

Genetic Disorders

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a rare autosomal recessive inherited disorder that occurs at a frequency of about 1 in 250,000 in the United States [106]. Patients with XP have severe sun sensitivity due to mutations in several genes that are responsible for repairing UV-induced DNA damage. As a result of these mutations, XP patients experience significant degeneration of sun-exposed regions, including the eyes, and have an increased incidence of SCC and other cutaneous malignancies, regardless of their background skin pigmentation. The median age of skin cancer onset in XP patients is 8 years with over half developing either a SCC or a BCC [107, 108]. The incidence of SCC and other skin cancers in XP patients younger than 20 is approximately 2000 times greater as compared to the general population [108] and SCC is the leading cause of death, occurring in the teens or early twenties. The only way to prevent skin cancer death is total light avoidance from birth. Since early death from SCC occurs regardless of skin pigmentation, XP illustrates that melanin production plays only a partial role in natural protection from SCC formation, and that ongoing DNA repair is central for all persons, regardless of skin color, to prevent SCC.

Albinism

Albinism is a group of inherited disorders characterized by the complete or partial absence of pigmentation in the skin, hair, and eyes as a result of mutations in genes responsible for melanin synthesis. It is estimated that albinism affects between 1 in 10,000 and 1 in 20,000 newborns in North America and Europe [109, 110]. There are two main types of albinism, oculocutaneous, characterized by hypopigmentation of the eyes, skin, and hair, and ocular, characterized by

hypopigmentation of the eyes only. The incidence of oculocutaneous albinism is highest in native Africans as the mutations are more prevalent there. Several studies have shown that persons with oculocutaneous albinism are at an increased risk of developing aggressive SCC [109, 110, 112]. A study of 64 persons with oculocutaneous albinism in Tanzania found that over 75 % had been diagnosed with SCC and 30 % developed a local recurrence following surgical treatment [113]. Another study examining the natural history of albinism in 350 patients from a population-based registry in Tanzania found that of those diagnosed with cutaneous malignancies, over 90 % had SCC with 28 % of the SCCs being aggressive (over 4 cm in diameter) [114].

With early and rigorous sun protection, SCC can be largely prevented in those with albinism. However, poverty and social factors (including stigmatism due to misinformation regarding the causes of albinism, and people with albinism wanting to avoid further exclusion) can negatively impact the practice of sun protection which ideally includes wearing of wide-brimmed hats, sunglasses, full-length pants, and long-sleeved shirts from birth. Community-based educational efforts about the causes of albinism and provision of protective clothing and sunscreen to impoverished patients should help to bring down the incidence of SCC in those with albinism.

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of diseases characterized by skin fragility and blistering. There are three major types of EB: simplex, junctional, and dystrophic, and several phenotypic subtypes [112]. Dystrophic and junctional EB have been associated with an increased incidence of SCC. Dystrophic EB patients carry a mutation in a gene that is responsible for the production of collagen while junctional EB patients carry a mutation in genes that produce laminin or collagen and integrin [112]. These proteins provide structural framework for cells, tissues, and organs and allow cells to adhere to one another. Though the link to SCC formation is not precisely understood, EB patients develop SCC at a younger age as compared to the general population. Furthermore, EB patients are at an increased risk of developing multiple SCCs with a median of 2 and 3 to 3.5 per patient primarily within long-term skin wounds and scars instead of sun-exposed regions [115].

The cumulative risk of SCC in dystrophic EB patients increases significantly after age 20 from 7.5 % to 67.8 %, 80.2 %, and 90.1 % by ages 35, 45, and 55, respectively. Dystrophic EB patients have a markedly increased risk of developing poor SCC outcomes and SCC is the main cause of death for this subset of EB patients. The cumulative risk of death due to SCC is 38.7 %, 70.0 %, and 78.7 % at 34, 45, and 55 years of age, respectively [115]. Junctional EB patients also develop SCC at a greater frequency as compared to the general population. It is estimated that about 25 % develop SCCs with 21 % metastasizing and causing death within 8.9 years of initial diagnosis [116].

Epidermolysis Verruciformis

Epidermolysis verruciformis (EV) is a rare disorder that is characterized by abnormal susceptibility to human papillomavirus (HPV) infections. Patients often form chronic warty skin lesions that develop into SCC in about half the cases usually in the fourth and fifth decades of life [117, 118]. Patients with EV have mutations in genes that regulate zinc homeostasis resulting in defective cell-mediated immunity against certain types of viruses [119, 120].

Ferguson-Smith Disease

Ferguson-Smith disease is a rare disorder in which patients have mutations in genes that are involved in the regulation of several cellular processes, including division, differentiation, adhesion, and death [121–123]. Patients with Ferguson-Smith disease develop multiple locally-destructive SCCs often in sun-exposed regions. These SCCs typically grow rapidly for a few weeks before spontaneously regressing, leaving scars at the site of the tumors [112].

Rothmund-Thomson Syndrome

Rothmund-Thomson syndrome (RTS) is a rare disorder that is characterized by widespread erythema, swelling, and blistering, in the first 6 months of life gradually leading to poikiloderma (increased or decreased pigmentation and thinning of skin) [112]. RTS patients often suffer from cataracts, sparse hair, short stature, and bone defects. Patients have mutations in a gene that is responsible for regulating basic DNA processes such as replication, transcription, and repair. Several case reports documenting an increased frequency of SCC among RTS patients have been published however, the exact incidence of SCC is unknown. A review examining the prevalence of SCC and other cutaneous neoplasms in RTS patients found 8 reported cases of primary SCC among 61 patients (13 %), most of whom were <40 years old [124].

Bloom Syndrome

Bloom syndrome (BS) is characterized by severe growth retardation, recurrent infections, diabetes, and a predisposition to malignancies. Patients often have redness and scaly rashes in sun-exposed regions of the skin [112, 125]. BS is caused by mutations in genes that participate in DNA replication and repair. SCC accounts for about 14 % of the tumors diagnosed in BS patients [126].

Other Genetic Conditions

Other rare genetic conditions such as Fanconi anemia, dyskeratosis congenita, and Werner syndrome have also been associated with an increased risk of SCC.

Smoking

Tobacco smoke consists of a number of carcinogens which, have been linked to several cancers including stomach, bladder, pancreas, oral cavity, and cervix. Though there is a clear link between smoking and oropharyngeal SCC, epidemiological studies investigating the relationship between smoking and CSCC development have yielded conflicting results. Some studies have shown no relationship between smoking and SCC [127, 128] while others have shown a twofold increased risk in current smokers as compared to never smokers [129, 130]. A recent systematic review examining the relationship between smoking and the risk of NMSC found a 52 % increase in SCC risk among current smokers as compared to never smokers [131].

Diet

The relationship between diet and skin cancer risk is not clearly understood. Studies of dietary fat and SCC risk have yielded inconsistent results. Several large prospective studies have found no relationship between dietary fat intake and SCC risk [132–134] while others have shown an increased risk of SCC among those with a higher consumption of dietary fat [135]. Two large prospective studies have also demonstrated a dose-response relationship between dietary fat and SCC risk among patients with a history of SCC. The studies found a two to threefold increased risk of SCC for those in the highest tertile of dietary fat intake as compared to those in the lowest tertile of dietary fat intake after adjustment for potential confounders [132, 135]. In contrast, those with a higher consumption of fruits and vegetables, particularly green leafy vegetables, had a 52 % reduction in SCC risk [135]. The relationship between diet and SCC risk warrants further investigation.

Human Papillomavirus Infection

HPV consists of a diverse group of DNA viruses that infect mammals, birds, and reptiles. More than 100 subtypes of HPV have been characterized in human beings. HPV can be classified into three broad groups: alpha, beta, and gamma. Alpha HPV primarily infect mucosal epithelium while beta and gamma HPV infect cutaneous epithelium [136]. Cutaneous HPV infection is very common with prevalence estimated to exceed 80 % in immunocompetent individuals without SCC [137].

Several studies have reported an increased risk of SCC among immunocompetent individuals with HPV infection [138–141]. A multicenter study investigating the association between HPV infection and SCC found that the presence of betapapillomavirus was associated with a two to threefold increased risk of SCC [140]. Another study found that seropositivity for beta and gamma HPV types was associated with an increased incidence of subsequent SCCs in patients with previous NMSCs [141]. Some studies have also suggested that high-risk genital HPV types which are strongly associated with cervical cancer may also be significant risk factors for SCC formation in immunocompetent individuals [142, 143].

However, there are several studies that have found no significant relationship between HPV infection and SCC risk [136, 144–146]. A study comparing betapapillomavirus loads and viral replication (active production of viral proteins) in SCC samples found no significant difference between tumor tissue and normal tissue in immunocompetent individuals [144]. Similarly, two other studies found no difference in HPV detection between SCC and normal skin tissue, although individuals with SCC were more likely to be infected with betapapillomavirus (HPV type 2) [145, 146]. The results of these studies suggest that HPV infection may play a role early on in the pathway toward SCC formation (perhaps inducing dysplasia) but is likely not a driving factor in SCC tumor formation and maintenance.

An exception to this is anogenital and nail fold SCC. Several studies have demonstrated a high risk of HPV infection in patients diagnosed with anogenital SCCs. Between 46 and 84 % of anal and 88 and 92 % of penile SCCs among HPV-positive patients have been found to have HPV 16 DNA-the type associated with 90 % of all cervical cancers [147–153]. In addition, a number of case reports have linked HPV infection to SCC of the nail bed and these lesions are often reported to arise within a longstanding wart however; larger prospective studies are needed to corroborate these findings [154, 155].

Other Risk Factors

RAF inhibitors such as vemurafenib and dabrafenib are used in the treatment of metastatic melanoma with BRAF mutation. The most frequent side effect of RAF inhibitor treatment is SCC formation. It is estimated that SCC occurs in 15–30 % of patients treated with RAF inhibitors [156, 157]. Patients develop sporadic well-differentiated SCCs typically within 8–12 weeks of beginning therapy. Recent studies have shown that RAF inhibitors lead to the activation of the mitogen-activated protein kinase signaling pathway in patients with preexisting RAS or receptor tyrosine kinase mutations which in turn lead to accelerated proliferation of cancer cells [157, 158].

Voriconazole is a highly-effective antifungal medication that is widely used to treat serious fungal infections in immunosuppressed patients, particularly lung transplant patients [159]. One of the side effects of long-term voriconazole use is photosensitivity which can result in sunburn-like erythema on exposed areas of the

skin particularly the head and neck, hands, and forearms. In some cases, photosensitivity may be reversible after cessation of voriconazole [159–161]. An increased incidence of SCC has also been reported among immunosuppressed patients treated with voriconazole including cases of rapidly progressing, aggressive tumors leading to death. A retrospective study of lung transplant recipients showed a twofold increase in SCC incidence in those who received voriconazole compared to those who did not receive voriconazole. Importantly, all metastases and deaths from SCC occurred among patients who received voriconazole [162]. Another study among lung transplant recipients found a threefold increased risk of SCC and a 5.6 % increase in risk of SCC with each 60-day voriconazole exposure at a standard dose [163]. The risk of aggressive SCC has led many lung transplant centers to avoid voriconazole and rely on alternatives [164].

Certain blood types have been associated with a lower incidence of SCC. In a study consisting of over 90,000 white individuals derived from two large independent cohorts, blood groups A, AB, and B were associated with a 14 % decreased risk of developing SCC compared to blood group O [165]. Further studies are needed to identify the mechanism by which blood type influences SCC risk.

Exposure to radon is a well-established cause of lung cancer. However, a recent study indicates that radon may also be associated with an increased risk of SCC. The study conducted in southwest England showed that individuals living in areas with the highest mean radon levels had a twofold increased risk of SCC as compared to those living in areas with the lowest radon levels [166]. Additional studies are needed to confirm these associations.

There is conflicting evidence regarding the effect of selenium supplementation on SCC risk. A large double-blind, randomized, placebo-controlled clinical trial showed that daily oral selenium supplementation was associated with an increased risk of subsequent SCCs and total NMSCs in individuals with a history of NMSC [167]. Conversely, another study investigating the effect of serum selenium concentration found a 60 % risk reduction in subsequent SCC formation among those with high serum selenium concentration as compared to those with low serum selenium concentration [168]. Two other studies have found no association between serum selenium concentration and SCC risk [169, 170].

Anti- and pro-carcinogenic roles for vitamin D level on SCC risk have been proposed. A large prospective cohort study investigating the risk of incident SCC in white women found that those in the highest quartile of plasma 25(OH) vitamin D levels had more than a threefold increased risk of SCC as compared to women with plasma 25(OH) vitamin D levels in the lowest quartile [171]. Another prospective study found that those with serum 25(OH) vitamin D concentrations above 75 nmol/L had a lower risk of SCC incidence as compared to those with serum 25(OH) vitamin D concentrations below 75 nmol/L [172]. Several other studies have found no associations between serum vitamin D level and SCC incidence [173, 174]. Further studies are needed to decipher the role of vitamin D on cutaneous oncogenesis.

Oral contraceptives may be linked to an increased incidence of SCC in women. Two population-based studies have shown an increased risk of SCC among white

women who have used oral contraceptives compared to those who have never used oral contraceptives [175, 176]. Larger well-controlled studies are needed to investigate the etiologic basis of this association.

The use of photosensitizing diuretics has been associated with an increased incidence of SCC. Studies have shown a twofold increased risk of SCC among users of diuretics as compared to non-users [177, 178]. Additional studies replicating these results are needed to better understand the role of photosensitizing drugs in SCC formation.

Mortality Estimates

Most patients with SCC have excellent prognosis with an overall 5 year cure rate of over 90 % [87]. The annual disease-specific mortality in the United States is estimated to be about 1 % however, annual disease-specific mortality rates of 3–4 % have been reported in countries with well-established SCC surveillance [179–181]. A population-based study investigating trends in NMSC mortality as reported on death certificates in the United States found that nearly 75,000 deaths were attributed to NMSC from 1969 to 2000. The age-adjusted mortality rate for non-genital NMSC from 1969 to 2000 was 0.69 per 100,000 cases however, these data may underestimate actual values. NMSC may be underreported as a cause of death on death certificates as it is a rare and subsequently an underrecognized cause of death and most NMSC patients are elderly with comorbidites that could complicate cause of death reporting [182]. Recent studies have demonstrated mortality rates of between 1.5 and 2.1 % for primary SCCs [2, 3]. Based on this data, it has been estimated that 4000–9000 persons die from CSCC annually in the U.S. Due to the particularly high incidence of SCC in central and southern states, the estimated incidence of death from SCC in these regions is similar to many relatively common cancers including renal and oropharyngeal carcinomas and melanoma [8].

Conclusion

Cutaneous squamous cell carcinoma is a common type of skin cancer, highly prevalent in white persons over 65 years, with significant geographic variability in incidence due to fluctuations in UV intensity. Although prognosis is excellent, especially after surgical removal, a subset of tumors may recur, metastasize, and cause death.

SCC is largely preventable with sun protection. However, lifestyle changes over the past century involving increased exposure to sunlight, combined with longer life expectancy have likely led to a significant increase in SCC incidence. Primary prevention efforts should therefore focus on sun protection from an early age particularly among light-skinned white individuals and those with conditions which pre-expose them to developing SCC.

Population-based incidence and outcome data for SCC are unavailable in the United States because SCC is excluded from national cancer registries due to its commonness and subsequent high cost of surveillance. Comprehensive cost of care has not been studied. National surveillance studies focusing on select geographic areas with variable ultraviolet exposure would allow for cost effective estimation of incidence and outcome tracking. Such efforts could lead to better targeting of primary prevention efforts and better estimates of the impact of SCC on the population.

Abbreviations

CSCC	Cutaneous squamous cell carcinoma
NMSC	Non-melanoma skin cancer
BCC	Basal cell carcinoma
UV	Ultraviolet
PUVA	Psoralen + ultraviolet A
OTR	Organ transplant recipients
IBD	Inflammatory bowel disease
HIV	Human immunodeficiency virus
CLL	Chronic lymphocytic leukemia
PAH	Polycyclic aromatic hydrocarbons
XP	Xeroderma pigmentosum
EB	Epidermolysis bullosa
EV	Epidermolysis verruciformis
HPV	Human papillomavirus
FSD	Ferguson-Smith disease
RTS	Rothmund-Thomson syndrome
BS	Bloom syndrome

References

1. Johnson TM, Rowe DE, Nelson BR, Swanson NA. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). J Am Acad Dermatol. 1992;26(3 Pt 2):467–84.
2. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. JAMA Dermatol. 2013;149(5):541–7.
3. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713–20.
4. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol. 1994;30(5 Pt 1):774–8.
5. Scotto J, Fraumeni J. Incidence of non melanoma skin cancer in the United States. Bethesda, MD: National Institutes of Health; 1983.

6. Scotto J, Kopf AW, Urbach F. Non-melanoma skin cancer among Caucasians in four areas of the United States. Cancer. 1974;34(4):1333–8.
7. Glass AG, Hoover RN. The emerging epidemic of melanoma and squamous cell skin cancer. JAMA. 1989;262(15):2097–100.
8. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68(6):957–66.
9. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust. 2006;184(1):6–10.
10. Green A, Battistutta D, Hart V, Leslie D, Weedon D. Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. The Nambour Study Group. Am J Epidemiol. 1996;144(11):1034–40.
11. Buettner PG, Raasch BA. Incidence rates of skin cancer in Townsville, Australia. Int J Cancer. 1998;78(5):587–93.
12. McLean DI, Phillips N, Zhou Y, Gallagher R, Lee TK. 40-year trends in skin cancer in British Columbia, Canada, 1973 to 2003. J Cutan Med Surg. 2012;16(2):83–91.
13. Jung GW, Metelitsa AI, Dover DC, Salopek TG. Trends in incidence of nonmelanoma skin cancers in Alberta, Canada, 1988–2007. Br J Dermatol. 2010;163(1):146–54.
14. Magnus K. The Nordic profile of skin cancer incidence. A comparative epidemiological study of the three main types of skin cancer. Int J Cancer. 1991;47(1):12–9.
15. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol. 1999;135(7):781–6.
16. Katalinic A, Kunze U, Schafer T. Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumour stages and localization (epidemiology of skin cancer). Br J Dermatol. 2003;149(6):1200–6.
17. Iversen T, Tretli S. Trends for invasive squamous cell neoplasia of the skin in Norway. Br J Cancer. 1999;81(3):528–31.
18. Andersson EM, Paoli J, Wastensson G. Incidence of cutaneous squamous cell carcinoma in coastal and inland areas of Western Sweden. Cancer Epidemiol. 2011;35(6):e69–74.
19. Levi F, La Vecchia C, Te VC, Mezzanotte G. Descriptive epidemiology of skin cancer in the Swiss Canton of Vaud. Int J Cancer. 1988;42(6):811–6.
20. Roberts DL. Incidence of non-melanoma skin cancer in West Glamorgan, South Wales. Br J Dermatol. 1990;122(3):399–403.
21. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988–98. Br J Dermatol. 2000;143(6):1224–9.
22. Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992–2003. Br J Dermatol. 2007;156(6):1295–300.
23. Chuang TY, Popescu NA, Su WP, Chute CG. Squamous cell carcinoma. A population-based incidence study in Rochester, Minn. Arch Dermatol. 1990;126(2):185–8.
24. Gray DT, Suman VJ, Su WP, Clay RP, Harmsen WS, Roenigk RK. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Arch Dermatol. 1997;133(6):735–40.
25. Serrano H, Scotto J, Shornick G, Fears TR, Greenberg ER. Incidence of nonmelanoma skin cancer in New Hampshire and Vermont. J Am Acad Dermatol. 1991;24(4):574–9.
26. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer. 1999;81(4):555–9.
27. Athas WF, Hunt WC, Key CR. Changes in nonmelanoma skin cancer incidence between 1977–1978 and 1998–1999 in Northcentral New Mexico. Cancer Epidemiol Biomarkers Prev. 2003;12(10):1105–8.

28. Christenson LJ, Borrowman TA, Vachon CM, Tollefson MM, Otley CC, Weaver AL, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA. 2005;294(6):681–90.
29. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985–1996. J Am Acad Dermatol. 2001;45(4):528–36.
30. Gloster Jr HM, Neal K. Skin cancer in skin of color. J Am Acad Dermatol. 2006;55(5):741–60. quiz 61–4.
31. Singh B, Bhaya M, Shaha A, Har-El G, Lucente FE. Presentation, course, and outcome of head and neck skin cancer in African Americans: a case-control study. Laryngoscope. 1998;108(8 Pt 1):1159–63.
32. Rundel RD. Promotional effects of ultraviolet radiation on human basal and squamous cell carcinoma. Photochem Photobiol. 1983;38(5):569–75.
33. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344(13):975–83.
34. Soehnge H, Ouhtit A, Ananthaswamy ON. Mechanisms of induction of skin cancer by UV radiation. Front Biosci. 1997;2:d538–51.
35. Grossman D, Leffell DJ. The molecular basis of nonmelanoma skin cancer: new understanding. Arch Dermatol. 1997;133(10):1263–70.
36. Brash DE, Rudolph JA, Simon JA, Lin A, McKenna GJ, Baden HP, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A. 1991;88(22):10124–8.
37. Tsai KY, Tsao H. The genetics of skin cancer. Am J Med Genet C Semin Med Genet. 2004;131C(1):82–92.
38. de Gruijl FR, van Kranen HJ, Mullenders LH. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B. 2001;63(1–3):19–27.
39. Schmitt J, Seidler A, Diepgen TL, Bauer A. Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. Br J Dermatol. 2011;164(2):291–307.
40. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, et al. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer. 1990;65(12):2811–7.
41. International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. Int J Cancer. 2007;120(5):1116–22.
42. El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. A review of human carcinogens--part D: radiation. Lancet Oncol. 2009;10(8):751–2.
43. Wehner MR, Shive ML, Chren MM, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. BMJ. 2012;345:e5909.
44. Zhang M, Qureshi AA, Geller AC, Frazier L, Hunter DJ, Han J. Use of tanning beds and incidence of skin cancer. J Clin Oncol. 2012;30(14):1588–93.
45. Giles GG, Marks R, Foley P. Incidence of non-melanocytic skin cancer treated in Australia. Br Med J. 1988;296(6614):13–7.
46. Stern RS, Study PF-U. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. J Am Acad Dermatol. 2012;66(4):553–62.
47. Forman AB, Roenigk Jr HH, Caro WA, Magid ML. Long-term follow-up of skin cancer in the PUVA-48 cooperative study. Arch Dermatol. 1989;125(4):515–9.
48. Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. Int J Cancer. 1990;46(3):356–61.
49. English DR, Armstrong BK, Kricker A, Winter MG, Heenan PJ, Randell PL. Demographic characteristics, pigmentary and cutaneous risk factors for squamous cell carcinoma of the skin: a case-control study. Int J Cancer. 1998;76(5):628–34.

50. English DR, Armstrong BK, Kricker A, Winter MG, Heenan PJ, Randell PL. Case-control study of sun exposure and squamous cell carcinoma of the skin. Int J Cancer. 1998;77(3):347–53.
51. Iannacone MR, Wang W, Stockwell HG, O'Rourke K, Giuliano AR, Sondak VK, et al. Patterns and timing of sunlight exposure and risk of basal cell and squamous cell carcinomas of the skin--a case-control study. BMC Cancer. 2012;12:417.
52. Wu S, Han J, Laden F, Qureshi AA. Long-term ultraviolet flux, other potential risk factors, and skin cancer risk: a Cohort study. Cancer Epidemiol Biomarkers Prev. 2014;23(6):1080–9.
53. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet. 1999;354(9180):723–9.
54. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer Epidemiol Biomarkers Prev. 2006;15(12):2546–8.
55. Davis MM, Hanke CW, Zollinger TW, Montebello JF, Hornback NB, Norins AL. Skin cancer in patients with chronic radiation dermatitis. J Am Acad Dermatol. 1989;20(4):608–16.
56. Rowell NR. A follow-up study of superficial radiotherapy for benign dermatoses: recommendations for the use of X-rays in dermatology. Br J Dermatol. 1973;88(6):583–90.
57. Shore RE, Albert RE, Reed M, Harley N, Pasternack BS. Skin cancer incidence among children irradiated for ringworm of the scalp. Radiat Res. 1984;100(1):192–204.
58. Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice Jr JD. Radiation-induced skin carcinomas of the head and neck. Radiat Res. 1991;125(3):318–25.
59. Hildreth NG, Shore RE, Hempelmann LH, Rosenstein M. Risk of extrathyroid tumors following radiation treatment in infancy for thymic enlargement. Radiat Res. 1985;102(3):378–91.
60. Zackheim HS, Krobock E, Lang L. Cutaneous neoplasms in the rat produced by Grenz ray and 80 Kv X-ray. J Invest Dermatol. 1964;43:519–34.
61. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47(1):1–17. quiz 8–20.
62. Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, Van de Beek D, et al. Incidence of and risk factors for skin cancer after heart transplant. Arch Dermatol. 2009;145(12):1391–6.
63. Martinez JC, Otley CC, Stasko T, Euvrard S, Brown C, Schanbacher CF, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermatol. 2003;139(3):301–6.
64. Lampros TD, Cobanoglu A, Parker F, Ratkovec R, Norman DJ, Hershberger R. Squamous and basal cell carcinoma in heart transplant recipients. J Heart Lung Transplant. 1998;17(6):586–91.
65. Bouwes Bavinck JN, Hardie DR, Green A, Cutmore S, MacNaught A, O'Sullivan B, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. Transplantation. 1996;61(5):715–21.
66. Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. J Am Acad Dermatol. 1999;40(1):27–34.
67. Carroll RP, Ramsay HM, Fryer AA, Hawley CM, Nicol DL, Harden PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis. 2003;41(3):676–83.
68. Herrero JI, Espana A, Quiroga J, Sangro B, Pardo F, Alvarez-Cienfuegos J, et al. Nonmelanoma skin cancer after liver transplantation. Study of risk factors. Liver Transpl. 2005;11(9):1100–6.
69. Durando B, Reichel J. The relative effects of different systemic immunosuppressives on skin cancer development in organ transplant patients. Dermatol Ther. 2005;18(1):1–11.
70. Hofbauer GF, Bouwes Bavinck JN, Euvrard S. Organ transplantation and skin cancer: basic problems and new perspectives. Exp Dermatol. 2010;19(6):473–82.

71. Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol. 1999;40(2 Pt 1):177–86.
72. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012; 367(4):329–39.
73. Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. Am J Transplant. 2012;12(5):1146–56.
74. Gu YH, Du JX, Ma ML. Sirolimus and non-melanoma skin cancer prevention after kidney transplantation: a meta-analysis. Asian Pac J Cancer Prev. 2012;13(9):4335–9.
75. Schena FP, Pascoe MD, Alberu J, del Carmen RM, Oberbauer R, Brennan DC, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation. 2009;87(2):233–42.
76. Bjornadal L, Lofstrom B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol. 2002;31(2):66–71.
77. Singh H, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. Gastroenterology. 2011;141(5):1612–20.
78. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621–8. e1–5.
79. Silverberg MJ, Leyden W, Warton EM, Quesenberry Jr CP, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. J Natl Cancer Inst. 2013;105(5):350–60.
80. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005;53(6):1067–71.
81. Mehrany K, Byrd DR, Roenigk RK, Weenig RH, Phillips PK, Nguyen TH, et al. Lymphocytic infiltrates and subclinical epithelial tumor extension in patients with chronic leukemia and solid-organ transplantation. Dermatol Surg. 2003;29(2):129–34.
82. Mehrany K, Weenig RH, Pittelkow MR, Roenigk RK, Otley CC. High recurrence rates of squamous cell carcinoma after Mohs' surgery in patients with chronic lymphocytic leukemia. Dermatol Surg. 2005;31(1):38–42.
83. Bridges N, Steinberg JJ. Aggressive squamous cell carcinoma of the skin after chronic lymphocytic leukemia. J Surg Oncol. 1986;33(1):27–30.
84. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150(3):280–7.
85. Rowe DE, Carroll RJ, Jr Day CL. 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(6):976–90.
86. Jellouli-Elloumi A, Kochbati L, Dhraief S, Ben Romdhane K, Maalej M. Cancers arising from burn scars: 62 cases. Ann Dermatol Venereol. 2003;130(4):413–6.
87. Edwards MJ, Hirsch RM, Broadwater JR, Netscher DT, Ames FC. Squamous cell carcinoma arising in previously burned or irradiated skin. Arch Surg. 1989;124(1):115–7.
88. Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst. 1968;40(3):453–63.
89. Guo HR, Yu HS, Hu H, Monson RR. Arsenic in drinking water and skin cancers: cell-type specificity (Taiwan, ROC). Cancer Causes Control. 2001;12(10):909–16.
90. Karagas MR, Stukel TA, Morris JS, Tosteson TD, Weiss JE, Spencer SK, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. Am J Epidemiol. 2001;153(6):559–65.

91. Surdu S, Fitzgerald EF, Bloom MS, Boscoe FP, Carpenter DO, Haase RF, et al. Occupational exposure to arsenic and risk of non-melanoma skin cancer in a multinational European study. Int J Cancer. 2013;133(9):2182–91.
92. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009;10(5):453–4.
93. (ATSDR). AfTSaDR. ToxFAQs for polycyclic aromatic hydrocarbons 2011 [updated 10/18/2011; cited 2013 07/01]. http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=121&tid=25.
94. Henry SA. Occupational cutaneous cancer attributable to certain chemicals in industry. Br Med Bull. 1947;4(5–6):389–401.
95. Ross P. Occupational skin lesions due to pitch and tar. Br Med J. 1948;2(4572):369–74.
96. Miller BG, Cowie HA, Middleton WG, Seaton A. Epidemiologic studies of Scottish oil shale workers: III. Causes of death. Am J Ind Med. 1986;9(5):433–46.
97. Karlehagen S, Andersen A, Ohlson CG. Cancer incidence among creosote-exposed workers. Scand J Work Environ Health. 1992;18(1):26–9.
98. Partanen T, Boffetta P. Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. Am J Ind Med. 1994;26(6):721–40.
99. Hansen ES, Olsen JH, Tilt B. Cancer and non-cancer mortality of chimney sweeps in Copenhagen. Int J Epidemiol. 1982;11(4):356–61.
100. Voelter-Mahlknecht S, Scheriau R, Zwahr G, Koch B, Escobar Pinzon LC, Drexler H, et al. Skin tumors among employees of a tar refinery: the current data and their implications. Int Arch Occup Environ Health. 2007;80(6):485–95.
101. Kharazmi E, Fallah M, Sundquist K, Hemminki K. Familial risk of early and late onset cancer: nationwide prospective cohort study. BMJ. 2012;345:e8076.
102. Hussain SK, Sundquist J, Hemminki K. The effect of having an affected parent or sibling on invasive and in situ skin cancer risk in Sweden. J Invest Dermatol. 2009;129(9):2142–7.
103. Milan T, Verkasalo PK, Kaprio J, Koskenvuo M, Pukkala E. Malignant skin cancers in the Finnish Twin Cohort: a population-based study, 1976–97. Br J Dermatol. 2002;147(3):509–12.
104. Cleaver JE, Thompson LH, Richardson AS, States JC. A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. Hum Mutat. 1999;14(1):9–22.
105. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol. 1987;123(2):241–50.
106. Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. Arch Dermatol. 1994;130(8):1018–21.
107. Gronskov K, Ek J, Brondum-Nielsen K. Oculocutaneous albinism. Orphanet J Rare Dis. 2007;2:43.
108. Martinez-Garcia M, Montoliu L. Albinism in Europe. J Dermatol. 2013;40(5):319–24.
109. Nikolaou V, Stratigos AJ, Tsao H. Hereditary nonmelanoma skin cancer. Semin Cutan Med Surg. 2012;31(4):204–10.
110. Mabula JB, Chalya PL, McHembe MD, Jaka H, Giiti G, Rambau P, et al. Skin cancers among Albinos at a University teaching hospital in Northwestern Tanzania: a retrospective review of 64 cases. BMC Dermatol. 2012;12:5.
111. Luande J, Henschke CI, Mohammed N. The Tanzanian human albino skin. Natural history. Cancer. 1985;55(8):1823–8.
112. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986–2006. J Am Acad Dermatol. 2009;60(2):203–11.
113. Yuen WY, Jonkman MF. Risk of squamous cell carcinoma in junctional epidermolysis bullosa, non-Herlitz type: report of 7 cases and a review of the literature. J Am Acad Dermatol. 2011;65(4):780–9.

114. Majewski S, Jablonska S. Skin autografts in epidermodysplasia verruciformis: human papillomavirus-associated cutaneous changes need over 20 years for malignant conversion. Cancer Res. 1997;57(19):4214–6.
115. Dubina M, Goldenberg G. Viral-associated nonmelanoma skin cancers: a review. Am J Dermatopathol. 2009;31(6):561–73.
116. Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. Nat Genet. 2002;32(4):579–81.
117. Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. Semin Immunol. 2006;18(6):362–74.
118. Ferguson-Smith J. A case of multiple primary squamous-celled carcinomata in a young man, with spontaneous healing. Br J Dermatol. 1934;46:267–72.
119. Ferguson-Smith MA, Wallace DC, James ZH, Renwick JH. Multiple self-healing squamous epithelioma. Birth Defects Orig Artic Ser. 1971;7(8):157–63.
120. Goudie DR, D'Alessandro M, Merriman B, Lee H, Szeverenyi I, Avery S, et al. Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1. Nat Genet. 2011;43(4):365–9.
121. Stinco G, Governatori G, Mattighello P, Patrone P. Multiple cutaneous neoplasms in a patient with Rothmund-Thomson syndrome: case report and published work review. J Dermatol. 2008;35(3):154–61.
122. Karalis A, Tischkowitz M, Millington GW. Dermatological manifestations of inherited cancer syndromes in children. Br J Dermatol. 2011;164(2):245–56.
123. German J. Bloom's syndrome. XX. The first 100 cancers. Cancer Genet Cytogenet. 1997;93(1):100–6.
124. Odenbro A, Bellocco R, Boffetta P, Lindelof B, Adami J. Tobacco smoking, snuff dipping and the risk of cutaneous squamous cell carcinoma: a nationwide cohort study in Sweden. Br J Cancer. 2005;92(7):1326–8.
125. Marehbian J, Colt JS, Baris D, Stewart P, Stukel TA, Spencer SK, et al. Occupation and keratinocyte cancer risk: a population-based case-control study. Cancer Causes Control. 2007;18(8):895–908.
126. De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, et al. Relation between smoking and skin cancer. J Clin Oncol. 2001;19(1):231–8.
127. Karagas MR, Stukel TA, Greenberg ER, Baron JA, Mott LA, Stern RS. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. JAMA. 1992;267(24):3305–10.
128. Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. Arch Dermatol. 2012;148(8):939–46.
129. Ibiebele TI, van der Pols JC, Hughes MC, Marks GC, Green AC. Dietary fat intake and risk of skin cancer: a prospective study in Australian adults. Int J Cancer. 2009;125(7):1678–84.
130. Gamba CS, Stefanick M, Shikany J, Larson J, Linos E, Sims ST, et al. Low fat diet and skin cancer risk: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. Cancer Epidemiol Biomarkers Prev. 2013;22(9):1509–19.
131. Granger RH, Blizzard L, Fryer JL, Dwyer T. Association between dietary fat and skin cancer in an Australian population using case-control and cohort study designs. BMC Cancer. 2006;6:141.
132. Ibiebele TI, van der Pols JC, Hughes MC, Marks GC, Williams GM, Green AC. Dietary pattern in association with squamous cell carcinoma of the skin: a prospective study. Am J Clin Nutr. 2007;85(5):1401–8.
133. Aldabagh B, Angeles JG, Cardones AR, Arron ST. Cutaneous squamous cell carcinoma and human papillomavirus: is there an association? Dermatol Surg. 2013;39(1 Pt 1):1–23.
134. de Koning MN, Weissenborn SJ, Abeni D, Bouwes Bavinck JN, Euvrard S, Green AC, et al. Prevalence and associated factors of betapapillomavirus infections in individuals without cutaneous squamous cell carcinoma. J Gen Virol. 2009;90(Pt 7):1611–21.

135. Andersson K, Waterboer T, Kirnbauer R, Slupetzky K, Iftner T, de Villiers EM, et al. Seroreactivity to cutaneous human papillomaviruses among patients with nonmelanoma skin cancer or benign skin lesions. Cancer Epidemiol Biomarkers Prev. 2008;17(1):189–95.
136. Alotaibi L, Provost N, Gagnon S, Franco EL, Coutlee F. Diversity of cutaneous human papillomavirus types in individuals with and without skin lesion. J Clin Virol. 2006;36(2):133–40.
137. Bouwes Bavinck JN, Neale RE, Abeni D, Euvrard S, Green AC, Harwood CA, et al. Multicenter study of the association between betapapillomavirus infection and cutaneous squamous cell carcinoma. Cancer Res. 2010;70(23):9777–86.
138. Paradisi A, Waterboer T, Sampogna F, Tabolli S, Simoni S, Pawlita M, et al. Seropositivity for human papillomavirus and incidence of subsequent squamous cell and basal cell carcinomas of the skin in patients with a previous nonmelanoma skin cancer. Br J Dermatol. 2011;165(4):782–91.
139. Iftner A, Klug SJ, Garbe C, Blum A, Stancu A, Wilczynski SP, et al. The prevalence of human papillomavirus genotypes in nonmelanoma skin cancers of nonimmuno suppressed individuals identifies high-risk genital types as possible risk factors. Cancer Res. 2003;63(21):7515–9.
140. Pierceall WE, Goldberg LH, Ananthaswamy HN. Presence of human papilloma virus type 16 DNA sequences in human nonmelanoma skin cancers. J Invest Dermatol. 1991;97(5):880–4.
141. Arron ST, Ruby JG, Dybbro E, Ganem D, Derisi JL. Transcriptome sequencing demonstrates that human papillomavirus is not active in cutaneous squamous cell carcinoma. J Invest Dermatol. 2011;131(8):1745–53.
142. Asgari MM, Kiviat NB, Critchlow CW, Stern JE, Argenyi ZB, Raugi GJ, et al. Detection of human papillomavirus DNA in cutaneous squamous cell carcinoma among immunocompetent individuals. J Invest Dermatol. 2008;128(6):1409–17.
143. Forslund O, Iftner T, Andersson K, Lindelof B, Hradil E, Nordin P, et al. Cutaneous human papillomaviruses found in sun-exposed skin: beta-papillomavirus species 2 predominates in squamous cell carcinoma. J Infect Dis. 2007;196(6):876–83.
144. Crook T, Wrede D, Tidy J, Scholefield J, Crawford L, Vousden KH. Status of c-myc, p53 and retinoblastoma genes in human papillomavirus positive and negative squamous cell carcinomas of the anus. Oncogene. 1991;6(7):1251–7.
145. Holm R, Tanum G, Karlsen F, Nesland JM. Prevalence and physical state of human papillomavirus DNA in anal carcinomas. Mod Pathol. 1994;7(4):449–53.
146. Noffsinger AE, Hui YZ, Suzuk L, Yochman LK, Miller MA, Hurtubise P, et al. The relationship of human papillomavirus to proliferation and ploidy in carcinoma of the anus. Cancer. 1995;75(4):958–67.
147. Shroyer KR, Brookes CG, Markham NE, Shroyer AL. Detection of human papillomavirus in anorectal squamous cell carcinoma. Correlation with basaloid pattern of differentiation. Am J Clin Pathol. 1995;104(3):299–305.
148. Frisch M, Glimelius B, van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med. 1997;337(19):1350–8.
149. Madsen BS, van den Brule AJ, Jensen HL, Wohlfahrt J, Frisch M. Risk factors for squamous cell carcinoma of the penis--population-based case-control study in Denmark. Cancer Epidemiol Biomarkers Prev. 2008;17(10):2683–91.
150. Gregoire L, Cubilla AL, Reuter VE, Haas GP, Lancaster WD. Preferential association of human papillomavirus with high-grade histologic variants of penile-invasive squamous cell carcinoma. J Natl Cancer Inst. 1995;87(22):1705–9.
151. Ashinoff R, Li JJ, Jacobson M, Friedman-Kien AE, Geronemus RG. Detection of human papillomavirus DNA in squamous cell carcinoma of the nail bed and finger determined by polymerase chain reaction. Arch Dermatol. 1991;127(12):1813–8.
152. Zabawski Jr EJ, Washak RV, Cohen JB, Cockerell CJ, Brown SM. Squamous cell carcinoma of the nail bed: is finger predominance another clue to etiology? A report of 5 cases. Cutis. 2001;67(1):59–64.

153. Anforth R, Fernandez-Penas P, Long GV. Cutaneous toxicities of RAF inhibitors. Lancet Oncol. 2013;14(1):e11–8.
154. Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med. 2012;366(3):207–15.
155. Oberholzer PA, Kee D, Dziunycz P, Sucker A, Kamsukom N, Jones R, et al. RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. J Clin Oncol. 2012;30(3):316–21.
156. Winston DJ, Chandrasekar PH, Lazarus HM, Goodman JL, Silber JL, Horowitz H, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. Ann Intern Med. 1993;118(7):495–503.
157. Patel AR, Turner ML, Baird K, Gea-Banacloche J, Mitchell S, Pavletic SZ, et al. Voriconazole-induced phototoxicity masquerading as chronic graft-versus-host disease of the skin in allogeneic hematopoietic cell transplant recipients. Biol Blood Marrow Transplant. 2009;15(3):370–6.
158. Frick MA, Soler-Palacin P, Martin Nalda A, Guarner ME, Nadal CF. Photosensitivity in immunocompromised patients receiving long-term therapy with oral voriconazole. Pediatr Infect Dis J. 2010;29(5):480–1.
159. Feist A, Lee R, Osborne S, Lane J, Yung G. Increased incidence of cutaneous squamous cell carcinoma in lung transplant recipients taking long-term voriconazole. J Heart Lung Transplant. 2012;31(11):1177–81.
160. Singer JP, Boker A, Metchnikoff C, Binstock M, Boettger R, Golden JA, et al. High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. J Heart Lung Transplant. 2012;31(7):694–9.
161. Williams K, Mansh M, Chin-Hong P, Singer J, Arron ST. Voriconazole-associated cutaneous malignancy: a literature review on photocarcinogenesis in organ transplant recipients. Clin Infect Dis. 2014;58(7):997–1002.
162. Xie J, Qureshi AA, Li Y, Han J. ABO blood group and incidence of skin cancer. PLoS One. 2010;5(8):e11972.
163. Wheeler BW, Allen J, Depledge MH, Curnow A. Radon and skin cancer in southwest England: an ecologic study. Epidemiology. 2012;23(1):44–52.
164. Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs Jr GF, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. J Natl Cancer Inst. 2003;95(19):1477–81.
165. van der Pols JC, Heinen MM, Hughes MC, Ibiebele TI, Marks GC, Green AC. Serum antioxidants and skin cancer risk: an 8-year community-based follow-up study. Cancer Epidemiol Biomarkers Prev. 2009;18(4):1167–73.
166. Karagas MR, Greenberg ER, Nierenberg D, Stukel TA, Morris JS, Stevens MM, et al. Risk of squamous cell carcinoma of the skin in relation to plasma selenium, alpha-tocopherol, beta-carotene, and retinol: a nested case-control study. Cancer Epidemiol Biomarkers Prev. 1997;6(1):25–9.
167. Breslow RA, Alberg AJ, Helzlsouer KJ, Bush TL, Norkus EP, Morris JS, et al. Serological precursors of cancer: malignant melanoma, basal and squamous cell skin cancer, and prediagnostic levels of retinol, beta- carotene, lycopene, alpha-tocopherol, and selenium. Cancer Epidemiol Biomarkers Prev. 1995;4(8):837–42.
168. Liang G, Nan H, Qureshi AA, Han J. Pre-diagnostic plasma 25-hydroxyvitamin D levels and risk of non-melanoma skin cancer in women. PLoS One. 2012;7(4):e35211.
169. van der Pols JC, Russell A, Bauer U, Neale RE, Kimlin MG, Green AC. Vitamin D status and skin cancer risk independent of time outdoors: 11-year prospective study in an Australian community. J Invest Dermatol. 2013;133(3):637–41.

170. Eide MJ, Johnson DA, Jacobsen GR, Krajenta RJ, Rao DS, Lim HW, et al. Vitamin D and nonmelanoma skin cancer in a health maintenance organization cohort. Arch Dermatol. 2011;147(12):1379–84.
171. Tang JY, Fu T, Leblanc E, Manson JE, Feldman D, Linos E, et al. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. J Clin Oncol. 2011;29(22):3078–84.
172. Applebaum KM, Nelson HH, Zens MS, Stukel TA, Spencer SK, Karagas MR. Oral contraceptives: a risk factor for squamous cell carcinoma? J Invest Dermatol. 2009;129(12):2760–5.
173. Asgari MM, Efird JT, Warton EM, Friedman GD. Potential risk factors for cutaneous squamous cell carcinoma include oral contraceptives: results of a nested case-control study. Int J Environ Res Public Health. 2010;7(2):427–42.
174. de Vries E, Trakatelli M, Kalabalikis D, Ferrandiz L, Ruiz-de-Casas A, Moreno-Ramirez D, et al. Known and potential new risk factors for skin cancer in European populations: a multicentre case-control study. Br J Dermatol. 2012;167 Suppl 2:1–13.
175. Jensen AO, Thomsen HF, Engebjerg MC, Olesen AB, Sorensen HT, Karagas MR. Use of photosensitising diuretics and risk of skin cancer: a population-based case-control study. Br J Cancer. 2008;99(9):1522–8.
176. Osterlind A, Hjalgrim H, Kulinsky B, Frentz G. Skin cancer as a cause of death in Denmark. Br J Dermatol. 1991;125(6):580–2.
177. Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. Aust N Z J Surg. 1992;62(9):697–701.
178. Weinstock MA. Epidemiologic investigation of nonmelanoma skin cancer mortality: the Rhode Island Follow-Back Study. J Invest Dermatol. 1994;102(6):6S–9.
179. Lewis KG, Weinstock MA. Trends in nonmelanoma skin cancer mortality rates in the United States, 1969 through 2000. J Invest Dermatol. 2007;127(10):2323–7.

Chapter 2
Tumor Staging Systems and Prognostic Stratification

Anokhi Jambusaria-Pahlajani

Introduction

Squamous cell carcinoma (SCC) is the 2nd most common cancer diagnosed worldwide with an estimated 186,000–420,000 cases diagnosed per year [1]. While the overall prognosis is excellent, a small subset of tumors recur, metastasize, and cause death. A reported 3.6–4 % of patients develop nodal metastasis and 1.5–2 % die from CSCC according to academic medical center cohort studies [2, 3]. Accurate identification of a high-risk subgroup at risk for these poor outcomes is important for both patients and clinicians. Providing appropriate counseling to low-risk patients can provide them with peace of mind and avoid unnecessary aggressive treatment. Conversely, if a patient's tumor is high-risk, clinicians can be alerted to follow this patient more closely and/or consider adjuvant staging or treatment. This chapter will review the available data on high-risk CSCC, summarize the current staging and prognostic stratification systems, and discuss areas of research that may improve future prognostic stratification systems.

Risk Factors Associated with Poor SCC Outcomes

Risk factors associated with recurrence and metastasis from CSCC in case series studies include size > 2 cm, depth beyond Clark's Level IV or V (reticular dermis or subcutaneous fat), poorly differentiated histology, location on the vermillion lip or ear, perineural invasion (PNI), growth within a chronic scar, recurrent tumors, and

A. Jambusaria-Pahlajani, MD, MSCE (✉)
Department of Dermatology, Mayo Medical School, Mayo Clinic Florida,
4500 San Pablo Road, Jacksonville, FL 32224, USA
e-mail: Jambusaria.anokhi@mayo.edu

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_2

patient immunosuppression. There have been several cohort studies that have attempted to identify which of these risk factors are independently associated with poor outcomes and these are summarized in Table 2.1 [2, 4–10, 12]. The number of tumors evaluated in these studies ranged from 149 to 8997. The majority of these studies examined common variables previously associated with poor outcomes including tissue depth, PNI, diameter, location, and histologic differentiation. Five out of nine papers examined the role of immunosuppression [2, 3, 8–10]. Risk factors for regional (nodal) metastasis was reported in six out of nine studies and was the most common outcome studied. In the remaining three studies, recurrence free survival or metastasis free survival was reported. Local recurrence was an endpoint in four of the studies. Risk factors found to be significant predictors of poor outcomes in these studies are explored further below.

Perineural Invasion

The perineurium is a thin membrane that covers nerve fascicles. CSCC tumor cells can invade the space between the nerves and perineurium and track along the nerves in this plane into the central nervous system. Tumors with PNI may exhibit "skip" areas along the nerve track and therefore histologic margins may be imprecise and not be possible in all cases, even with complete circumferential and deep histopathologic margin evaluation [13]. This may explain the higher rate of recurrence and metastasis, even when negative surgical margins are obtained.

Less than 5 % of CSCC tumors exhibit PNI [11, 14]. As the majority of PNI cases occur on the head and neck, the most common nerves involved are the V2 (mandibular) and V3 (maxillary) branches of the trigeminal nerve or branches of the facial nerve [13, 15, 16]. PNI is more common in tumors with other high risk factors, such as recurrent tumors, large tumors, or poorly differentiated tumors [17]. PNI can be divided into incidental PNI, where PNI is noted on histopathology in an asymptomatic patient, or clinical PNI, where the patient has signs or symptoms of PNI.

Tumors with PNI demonstrate a more aggressive biological behavior and have a higher risk of local recurrence, nodal metastasis, and disease specific death according to the studies in Table 2.1. Multivariable analysis in these studies demonstrated that PNI was a significant predictor for at least one outcome of interest in seven out of eight (88 %) studies [2–4, 6, 7, 9, 10]. Of note, in one study, desmoplasia was reported as a significant predictor which was always associated with PNI [2]. Presence of PNI and the associated imprecision of histologic margins is one of the main reasons that clinicians recommend adjuvant radiotherapy or radiologic imaging. However, various levels of PNI appear to have different prognostic implications. For example, clinical PNI (symptomatic PNI with features such as formication, dysesthesias, numbness, etc), PNI of named nerves, or extensive PNI of multiple smaller unnamed nerves has been associated with poor outcomes [18, 19]. More recently, nerve diameter has been identified as a reliable prognostic indicator.

Table 2.1 Published studies reporting adjusted risks of recurrence of cutaneous squamous cell carcinoma

Author, Year	Type of study	Number of tumors	Variables examined	High-risk factors for local recurrence on multivariable analysis	High-risk factors for nodal metastasis on multivariable analysis	High-risk factors for disease specific death on multivariable analysis	High-risk factors for overall survival on multivariable analysis	High-risk factors for recurrence free survival on multivariable analysis
Clayman et al. [4] (2005)	Retrospective Cohort Study of all SCC, single institution	277	Recurrent tumors, tissue depth beyond subcutaneous tissue, PNI, diameter	NR	NR	NR	NR	*Diameter ≥4 cm*- HR 4.5; 95 % CI 1.9–11.1[a] *Perineural invasion*- HR 2.8; 95 % CI 1.2–6.6[a]
Mullen et al. [5] (2006)	Prospective Cohort Study of all SCC, single institution	149	Presence of nodal disease at presentation, tumor diameter >2 cm, presence of scar carcinoma, histologic differentiation	NR	NR	NR	NR	*Regional nodal disease at presentation*- HR 7.6; 95 % CI 3.1–18.6
Brantsch et al. (2008)	Prospective Cohort Study of all SCC, single institution	615	Gender, tumor thickness, diameter, histologic differentiation, desmoplastic growth, location on the ear or vermilion lip, immunosuppression	*Tumor thickness >6 mm*- HR 6.0; 95 % CI 2.7–13.4 *Desmoplasia*- HR 16.11; 95 % CI 6.6–39.5[b]	*Tumor thickness >6 mm*- HR 4.8; 95 % CI 2.2–10.4 *Diameter ≥2 cm*- HR 2.2; 95 % CI 1.2–4.2 *Location on the ear*- HR 3.6; 95 % CI 1.5–8.7 *Immunosuppression*- HR 4.3; 95 % CI 1.6–11.5	NR	NR	NR

(continued)

Table 2.1 (continued)

Author, Year	Type of study	Number of tumors	Variables examined	High-risk factors for local recurrence on multivariable analysis	High-risk factors for nodal metastasis on multivariable analysis	High-risk factors for disease specific death on multivariable analysis	High-risk factors for overall survival on multivariable analysis	High-risk factors for recurrence free survival on multivariable analysis
Kyrgidis et al. [6] (2010)	Prospective Cohort Study of Head and Neck CSCC, single institution	315	AJCC stage (6th Ed), location (excluded lip), PNI, tissue depth, inflammation around tumor, treatment, age of pt at diagnosis, gender, histologic differentiation	NR	*Depth beyond subcutaneous fat*- OR 16.6; 95 % CI 4.7–59	NR	*Histologic differentiation*- good-moderate vs, good (HR 3.9; 95 % CI 1.8–8.3); moderate differentiation vs. good (HR 1.9; 95 % CI 1.2–3.4)	*Increasing T stage*- T2 vs. T1 not significant; T3 vs T1 (HR 11.3, 95 % CI 2.0–62.8); T4 vs T1 (HR 9.7; 95 % CI 2.8–34.2)
					Inflammation- OR 4.0; 95 % CI 1.5–10.6			*N stage*- HR 2.3; 95 % CI 1.2–4.5
							Perineural invasion- HR 2.0; 95 % CI 1.1–3.8	*Inflammation*- HR 2.3; 95 % CI 1.3–4.5
							Inflammation- HR 2.6; 95 % CI 1.5–4.4	*Perineural invasion*- HR 3.3; 95 % CI 1.5–7.4

Brougham et al. [7] (2012)	Prospective Cohort Study of all SCC, central New Zealand	8997	Patient age, gender, diameter (analyzed as continuous variable), histologic differentiation, location, PNI, lymphovascular invasion	NR	NR	NR	NR	*PNI*- HR 5.3; 95 % CI 2.5–11.21[c]
								Location- cheek (HR 3.2; 95 % CI 1.2–8.8), auricular area (HR 3.3; 95 % CI 1.2–9.3), lip (HR 4.8; 95 % CI 1.5–16)[c]
								Poorly differentiated histology- HR 4.3; 95 % CI 2.3–7.9[c]
								Diameter- HR 1.4; 95 % CI 1.3–1.6[c]
Roozeboom et al. [8] (2012)	Retrospective Cohort study of all SCC	224	Location, immunosuppression, tumor diameter (analyzed as a continous variable), tumor thickness (mm), invasion of deeper structures (beyond subcutaneous fat), histologic differentiation, PNI	*Tumor diameter in mm*- HR 1.1; 95 % CI 1.0–1.1	*Location on ear*- HR 21.3; 95 % CI 2.5–182.2[d]	NR	NR	NR
				Tumor thickness in mm- HR 1.3; 95 % CI 1.1–1.5	*Tumor diameter in mm*- HR 1.1; 95 % CI 1.0–1.1[d]			
					Tumor thickness in mm- HR 1.2; 95 % CI 1.1–1.4[d]			
					Invasion of deeper structures- HR 20.8; 95 % CI 4.6–93.7[d]			
					Poorly differentiated histology- HR 15.7; 95 % CI 3.5–70.3[d]			

(continued)

Table 2.1 (continued)

Author, Year	Type of study	Number of tumors	Variables examined	High-risk factors for local recurrence on multivariable analysis	High-risk factors for nodal metastasis on multivariable analysis	High-risk factors for disease specific death on multivariable analysis	High-risk factors for overall survival on multivariable analysis	High-risk factors for recurrence free survival on multivariable analysis
Peat et al. [9] (2012)	Retrospective Case–control Study	170 (92 metastatic, 78 non-metastatic)	Immunosuppression, ulceration, tissue depth, diameter, histologic differentiation, PNI, lymphovascular invasion, incomplete excision	NR	*Poorly differentiated histology:* HR 5.63[d]	NR	NR	NR
					PNI/lymphovascular invasion: HR 4.53[d]			
					Diameter ≥2 cm: HR 3.1[d]			
					Tumor recurrence: HR 2.81[d]			
					Clark level V: HR 2.33[d]			
Jambusaria-Pahlajani et al. [10] (2013)	Retrospective Cohort Study of a subset of high risk SCC, single institution	256	Diameter, location on ear or vermilion lip, tissue depth, immunosuppression, histologic differentiation, PNI, infiltrative histology, age of pt at diagnosis, gender	*Poorly differentiated histology*- SHR 2.5; 95 % CI 0.8–7.5	*Depth beyond subcutaneous fat*- SHR 7.2; 95 % CI 3.1–17.1	*Poorly differentiated histology*- SHR 4.1; 95 % CI 1.1–14.9	*Poorly differentiated histology*- SHR 1.9; 95 % CI 1.1–3.3	NR
				Diameter ≥2 cm- SHR 4.2; 95 % CI 1.4–13.3	*Poorly differentiated histology*- SHR 3.3; 95 % CI 1.4–7.8	*Diameter ≥2 cm*- SHR 3.7; 95 % CI 0.9–15.1	*Diameter ≥2 cm*- SHR 2.6; 95 % CI 1.5–4.3	
				Immunosuppression- SHR 3.5; 95 % CI 1.2–10.7	*Perineural invasion*- SHR 2.2; 95 % CI 0.9–5.1	*PNI*- SHR 3.4; 95 % CI 0.9–13.3		
						Depth beyond subcutaneous fat- SHR 4.1; 95 % CI 1.3–13.4		

Schmults et al. [11] (2013)	Retrospective Cohort Study of all SCC, single institution	1818	Diameter, location on ear or lip, diameter, tissue depth, immunosuppression status, histologic differentiation, PNI, infiltrative histology, age of pt at diagnosis, gender	*Diameter ≥2 cm*- SHR 5.8; 95 % CI 3.1–11.2	*Diameter ≥2 cm*- SHR 9.9; 95 % CI 3.5–27.7	*Diameter ≥2 cm*- SHR 17.2; 95 % CI 5.2–57.4	No significant variables found	NR
				Poorly differentiated histology- SHR 4.1; 95 % CI 2.3–7.4	*Poorly differentiated histology*- SHR 7.3; 95 % CI 2.9–18.3	*Poorly differentiated histology*- SHR 8.6; 95 % CI 3.0–24.2		
				Depth beyond subcutaneous fat- SHR 7.0; 95 % CI 3.3–14.8	*Depth beyond fat*- SHR 7.4; 95 % CI 2.2–25.1	*Depth beyond subcutaneous fat*- SHR 10.7; 95 % CI 3.3–34.8		
				PNI- SHR 3.8; 95 % CI 1.8–8.0		*PNI*- SHR 4.7; 95 % CI 1.5–15.0		
				Ear/temple location- SHR 3.3; 95 % CI 1.5–7.3		*Ear/temple location*- SHR 5.4; 95 % CI 1.3–23.2		

NR not reported
[a]Disease specific survival
[b]Always associated with PNI in this dataset
[c]Metastasis free survival
[d]Outcome reported in manuscript as metastasis

PNI of small caliber nerves (<0.1 mm diameter) have a very low rate of local recurrence, nodal metastasis, and disease specific death, particularly if no other high risk factors are present (moderate or poor differentiation, diameter ≥2 cm, or deep invasion beyond the subcutaneous fat). Conversely, if there is PNI of large caliber nerves ≥ 0.1 mm diameter, there is an elevated risk of poor outcomes and this risk increases further if other risk factors are present [20, 21].

Desmoplastic or Sclerosing Growth Pattern

Desmoplasia is defined as the induction of activated fibroblasts and subsequent production of a densely collagenous stroma in the tissue surrounding the tumor. Typically, the periphery of desmoplastic SCC consists of fine branches of atypical tumor cells and a prominent trabecular/infiltrative growth pattern. Unfortunately, the role of desmoplasia has not been well studied, as it is not reported routinely on pathology reports at many institutions. In a study of 44 CSCCs where at least 1/3 of the tumor mass met criteria for desmoplasia, the rate of local recurrence, nodal metastasis and both local recurrence and nodal metastasis was 27.3 % (n = 12), 22.7 % (n = 10), and 15.9 % (n = 7) respectively. This was in stark contrast to rates of local recurrence and/or nodal metastasis in the comparison group with no evidence of desmoplasia (1.1–3.8 %). Only one study has evaluated the role of desmoplasia in tumor recurrence when adjusting for other known risk factors and found that tumors with desmoplasia were 16 times more likely to develop a local recurrence (95 % CI 6.6–39.5). In this study, desmoplastic growth was always associated with PNI, suggesting these two variables may be colinear making it difficult to know the contribution of each to poor outcomes [2]. In a similar study of 73 desmoplastic CSCCs, where at least 50 % of the tumor met criteria for desmoplasia, PNI was present in 53 (73 %) cases. During a median follow-up of 36 months, 100 % of tumors treated with cryotherapy or electrodessication and curettage (n = 7) locally recurred, 80 % of tumors treated with wide local excision (n = 15) locally recurred, and 9 % of tumors treated with Mohs micrographic surgery (n = 34) locally recurred. The rate of local recurrence after Mohs micrographic surgery dropped to 3 % when postoperative adjuvant radiotherapy was added after clear surgical margins were obtained. No patients developed regional nodal metastasis [22].

Tumor Diameter

Tumor clinical diameter most often is measured at the initial office visit based on the pre-biopsy clinical examination. As a general rule, tumors with a larger diameter have a greater risk of recurrence. The relationship is likely linear and continuous. However, investigators have often used defined but somewhat artificial prognostic cut-points to facilitate care recommendations. Tumor diameter was a significant

predictor of recurrence in seven out of eight studies in Table 2.1 [3–5, 7–10]. Five papers reported diameter dichotomously [2–4, 9, 10], while the remaining two studies examined tumor diameter as a continuous variable [7, 8]. When diameter was examined as a dichotomous variable, the majority of studies found an increase in rates of recurrence in tumors ≥ 2 cm [2, 3, 9, 10]. Therefore, clinical tumor diameter ≥2 cm is the keystone risk factor in prior AJCC and UICC tumor staging systems. In Clayman, et al. a 4 cm diameter cutoff was significant, with tumors ≥4 cm in diameter being 4.5 times more likely to recur than those <4 cm [4]. Jambusaria-Pahlajani et al. found that when other size cutoffs were tested, 2 cm remained the optimal cut-point to differentiate low vs. high risk tumors. Roozeboom et al. and Brougham et al. evaluated tumor diameter as a continuous variable and found that there was a significantly higher risk for recurrence and metastasis in larger tumors (Table 2.1) [7, 8].

Location

For over 30 years, the "mask areas" of the face, which include the periorbital area, nose, periauricular area, lateral face and temples have been considered high-risk locations [23]. More recent studies using multivariate modeling indicate location may have a lesser impact than previously thought [3, 6–8, 10]. Locations associated with worse outcomes include the ear [3, 7, 8], cheek [7], lip [7], and temple [3]. However, it is important to note that four of nine studies did not find location to be an independent risk factor (Table 2.1).

Current prognostic stratification systems include location on the lip or ear as a high-risk site (Table 2.2). The inclusion of the lip is a result of several reports demonstrating an above-average risk of poor outcomes in this subgroup [24–27]. In the largest study of 1252 lip tumors, of which 96 % were squamous cell carcinomas, there were 118 (9.4 %) local recurrences, 95 (7.6 %) cervical metastasis, and 75 (7.2 %) disease specific deaths [24]. However, this study may have had an over-representation of tumors with other risk factors which led to poor outcomes overall. For example, tumors that were >3 cm diameter, had nodal metastasis at the time of presentation, or were poorly/undifferentiated had lower survival rates. In a similar retrospective study of 38 lower lip SCCs without metastasis and 16 SCCs that metastasized to the lymph nodes, those that developed metastasis were more likely to be >2 cm diameter, poorly differentiated or undifferentiated, and >6 mm in thickness. In five studies from Table 2.1 that included lip as a potential predictive variable [2, 3, 7, 8, 10], only one found location on the lip as an independent risk factor (for recurrence free survival).

The precise anatomic area(s) of the lip that portend a higher risk of recurrence warrants further discussion, as this has been an area of confusion in the literature and staging systems. The lip is divided into three distinct zones (Fig. 2.1). (1) The *mucosal lip* (also referred to as the wet lip) extends from the junction of the wet and dry mucosa of the lip posteriorly into the oral cavity. (2) The *vermilion lip*

Table 2.2 Definition of risk factors

	AJCC 7th Edition	UICC 7th Edition	NCCN 2014
Diameter	>2 cm diameter	>2 cm diameter	≥2 cm on the trunk and extremities (excluding the hands/feet/pretibia), ≥ 1 cm on the cheeks, forehead, scalp, neck and pretibia, or ≥0.6 cm on the mask areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, ears, temple, pre-auricular and postauricular skin/sulci), genitalia, hands and feet
Depth	>2 mm thickness	>4 mm thickness	≥2 mm thickness
	Clark Level ≥ IV	Clark Level ≥ IV	Clark level ≥ IV
Invasion of nerves/vessels	Perineural invasion	Perineural invasion	Perineural invasion
		Lymphovascular invasion	Vascular invasion
Anatomic location	Ear	Ear	As above in NCCN size criteria
	Cutaneous lip	Vermilion lip	
Histology	Poorly differentiated	Poorly differentiated	Poorly differentiated
	Undifferentiated	Undifferentiated	Adenoid (acantholytic), adenosquamous, or desmoplastic subtype
Historical/clinical factors	Not applicable[a]	Not applicable[a]	History of XRT
			Development of tumor in chronic inflammatory process
			Patient immunosuppression
			Recurrent tumors
			Clinically ill-defined borders
			Neurologic symptoms

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com; and permission from Sobin, LH, Gospodarowicz MK, Wittekind, C. TNM Classification of Malignant Tumours, 7th ed. New York: Wiley; 2009; and with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Basal Cell and Squamous Cell Skin Cancers V.2.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [2/6/14]. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

[a]AJCC and UICC do not include clinical factors as risk factors (with the exception of clinical tumor diameter)

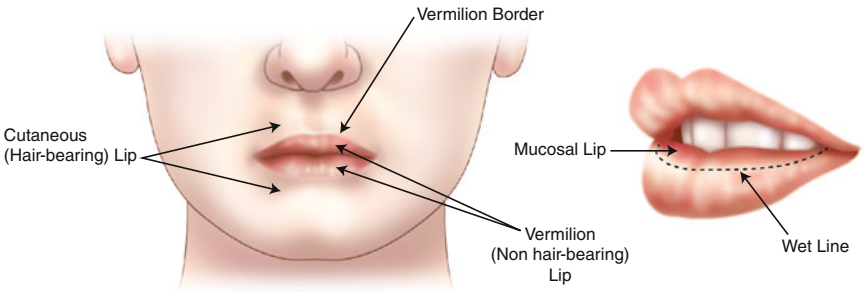


Fig. 2.1 The lip is divided into three distinct zones: mucosal lip, vermilion lip, and cutaneous lip. The wet line divides the mucosal and vermilion lip while the vermilion border divides the vermilion lip and cutaneous lip

(also referred to as non-hair bearing lip) begins at the exterior edge of the intraoral labial mucosa and extends outwards, terminating at the extraoral labial-cutaneous junction (also known as the vermilion border). (3) The *cutaneous lip* (also referred to as hair bearing lip) begins at the vermillion border and extends outwards onto hair bearing skin and approximates the area of skin overlying the orbicularis oris muscle. The high-risk zones of the lip are not consistent between published studies. In the five studies examining the role of lip location on CSCC outcomes, two defined it as tumor arising on the vermilion lip, whereas the remaining three did not specify the lip boundaries.

In AJCC staging, different zones of the lip are staged using different staging systems. According to the AJCC, tumors arising on the mucosal lip should be staged using the Lip and Oral Cavity Staging System, rather than the CSCC staging system. However, the boundaries of the mucosal lip defined in the AJCC manual differ from the standard definition of mucosal lip stated above. In the 7th Edition AJCC Lip and Oral Cavity Staging Manual, the mucosal lip "begins at the junction of the vermilion border with the skin and includes only the vermilion surface or that portion of the lip that comes into contact with the opposing lip". This definition is problematic since the vermillion lip does not come into contact with the opposing lip. The portion of the lip that comes into contact with the opposing lip describes the wet-dry line which is the junction between the vermillion and mucosal lip. Based on the biological behavior of SCC arising on different zones of the lip, it makes more sense to include SCC on the vermilion lip with the CSCC staging system as tumors arising on the vermilion lip are sun induced tumors, similar to SCC elsewhere on the skin. In contrast, SCC arising on the mucosal lip is a non-sun induced SCC that is often virally induced and therefore more akin to SCC arising elsewhere in the oral mucosa.

Tumors arising on the cutaneous lip are clearly staged using the SCC Staging System and this location is considered a high-risk feature for T staging. However, it is likely that most of the increased risk of poor outcomes associated with lip location

is due to vermillion lip involvement. There is no zone of adipose tissue between skin and muscle on the vermillion lip so tumors arising on the vermillion lip more quickly have access to the increased lymphovascular space of muscle and thus higher potential for metastasis.

The UICC defines location on the vermilion lip as a high-risk location [28] (Table 2.2), while the National Comprehensive Cancer Network® (NCCN®) includes both the vermilion and cutaneous lip as a high-risk location as long as the tumor is ≥0.6 cm[1] (Table 2.2).

Thickness/Depth

The vertical growth of a tumor can be measured either by tissue level (Clark's level) or millimeter depth (Breslow's depth). When Breslow's depth is used, the tumor should be measured from the stratum granulosum down to the deepest portion of the tumor. However, since the stratum granulosum is lost in SCC, it must be measured from the adjacent normal skin and this is not always provided on biopsy. It is important that the exophytic component of the tumor not be included in the final measurement. Another difficulty in using Breslow depth is that most CSCCs are diagnosed with a shave biopsy and therefore are often transected or only partially sampled. In these cases, millimeter depth is either not possible to assess or may be inaccurate. Millimeter depth is not routinely reported by most dermatopathologists [29] and may not be feasible in clinical practice given the high number of CSCC diagnoses rendered by pathologists. Tissue level depth is easier to evaluate and pathologists tend to report when tumors penetrate beyond the dermis. However, it is unknown whether tissue level (Clark's level) or millimeter depth (Breslow's depth) is of greater prognostic significance.

In studies examining independent risk factors for poor outcomes (Table 2.1), tumor depth (either mm or tissue level) is an independent significant predictor of any recurrence in six out of seven studies [2, 3, 6, 8–10]. Four studies measured depth by Clark's level; three of these studies found invasion beyond the subcutaneous fat to be an important predictor of poor outcomes [3, 6, 10] whereas one study found invasion of the subcutaneous fat as well as deeper structures to be a prognostic factor. Despite this evidence that invasion into the subcutaneous fat or deeper structures (Clark's level V or greater) is a high-risk factor, the AJCC and UICC continue to identify more superficial invasion (Clark's level IV/papillary dermis or greater) as a high-risk feature.

[1] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Basal Cell and Squamous Cell Skin Cancers V.2.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [July 7, 2014]. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Two of six studies examined the prognostic significance of millimeter depth. One study measured millimeter depth for each CSCC and found a 0 % risk of metastasis in tumors <2 mm [2]. The metastatic risk increased with increasing depth from 4.0 to 4.5 % for tumors between 2.1–6.0 mm, and 15–16 % for tumors ≥6.0 mm [2, 30]. On multivariable analysis, thickness ≥6 mm remained significant with a HR of 5.98 (95 % CI 2.06–17.37) for local recurrence and 5.88 (95 % CI 2.36–14.69) for nodal metastasis. Roozeboom et al. found that increased millimeter depth carries a significantly higher hazard of local recurrence and metastasis with a 30 % increased risk of local recurrence and 10 % increased risk of nodal metastasis for each 1 mm increase in tumor depth [8]. In an analysis of 81 patients with metastatic CSCC with a reported tumor millimeter depth, 65 % of these cases had a tumor depth >4 mm [31]. Therefore, the available data point towards a prognostic threshold somewhere between 2 and 6 mm. Additional prognostic studies of CSCC will help to clarify the prognostic contributions of tissue level vs. millimeter depth and establish the most useful prognostic cut-points. The methods for measuring millimeter depth have not been clearly reported in prior studies. A standardized methodology needs to be developed for SCC since the granular layer used in melanoma is often lost in SCC and large exophytic components such as those seen in keratoacanthoma may not have prognostic significance and should likely be discounted. Measuring from the basal cell layer immediately adjacent to the tumor to the tumor base may be the most practical way of measuring millimeter depth in SCC.

Histologic Differentiation

SCC is categorized based on the degree of differentiation into well-differentiated, moderately differentiated, poorly differentiated/undifferentiated subtypes. Histopathologically, well-differentiated tumors have abundant squamous epithelium demonstrating keratinization. Intercellular bridges between epithelial cells are readily apparent. Tumor cells are not pleomorphic and if mitotic figures are present, they are typically at the base of the tumor only. Moderately differentiated tumors possess greater structural disorganization when compared to well-differentiated SCC. The squamous derivation of cells is less obvious with keratinization being limited to presence of keratin 'pearls', horn cysts, or scattered individually keratinized cells. At the cellular level, there is significant cellular pleomorphism and atypical mitotic figures are common. Poorly differentiated or undifferentiated tumors are often difficult to characterize as being epithelial in origin and may thus require additional immunohistochemical stains to establish the diagnosis. Keratinization is not a prominent feature. Typically, significant pleomorphism and numerous mitotic figures are present. Desmoplasia (a stroma with increased numbers of activated fibroblasts) is also often seen in association with poor differentiation. If features of more than one category of differentiation are present within the tumor, tumors should be characterized based on the least differentiated area, even if it constitutes a minority of the tumor. Classification of the

differentiation of tumors may be somewhat subjective (e.g. number of mitoses upstages tumors from well to moderately differentiated and from moderately to poorly differentiated but standard mitotic count thresholds for upgrading do not exist). Therefore differentiation classifications can vary amongst pathologists [32].

Several studies have identified an increased risk of local recurrence, nodal metastasis, and disease specific death in tumors with poorly differentiated or undifferentiated histology (Table 2.1). Poorly differentiated histology was identified as an independent predictor of recurrence in six of eight studies [3, 6–10]. The largest of these studies found that patients with poorly differentiated tumors had a significantly elevated risk of nodal metastasis (HR 4.3; 95 % CI 2.3–7.9) [7]. The impact of moderately differentiated histology on prognosis has yet to be fully elucidated. In one study, moderately differentiated tumors had a lower survival than well differentiated tumors (HR 1.9; 95 % CI 1.2–3.4), but the risk was lower than for poorly differentiated tumors [6].

Immunosuppression

This topic is covered more fully in Chap. 10.

Patients with conditions that result in defective CD4 T cell immunity, such as that seen in solid organ transplantation, HIV, and chronic lymphocytic leukemia (CLL), have a higher morbidity and mortality from CSCC than nonimmunosuppressed patients. The majority of the data regarding the relationship of immunosuppression and CSCC development are in the solid organ transplant population. Transplant patients are at higher risk of developing aggressive cutaneous malignancies (defined as tumors with extensive local infiltration, regional metastasis at diagnosis, poor differentiation, and locoregional/systemic relapse following treatment). The risk of developing an aggressive cutaneous malignancy is approximately 4.4–10 % during the post-transplant period [33, 34]. CLL patients have an elevated risk of developing high-risk SCC's as well. In a case control study of 28 CLL patients with SCC, the CLL group was more likely to develop metastasis or die from their SCC than the non-CLL group (11 % in the CLL group and 0 % in the control group) [35]. In fact, patients with advanced CLL (Rai stage III/IV) have as high a risk of dying from CSCC as they do from CLL (12 %), regardless of whether the CLL is in remission. Thus CSCC is a major cause of morbidity and mortality in CLL patients [36]. HIV patients also have defective T cell immunity and may therefore be at higher risk of recurrence from SCC. In a cohort study of 1202 patients, of which 34 were HIV positive, CSCC arising in the HIV positive patients were 9.6 times more likely to recur ($p<0.01$) than CSCC occurring in healthy patients over a 5 year period [37].

In the majority of studies examining overall prognostic factors for CSCC (Table 2.1), the number of tumors arising in immunosuppressed patients is low [2, 3, 10], which limits study of the relative contribution of immunosuppression towards risk

of poor outcomes compared to other well-known prognostic factors. Two cohort studies have identified immunosuppression as an independent risk factor for recurrence. Jambusaria-Pahlajani et al. found immunosuppression increased the risk of local recurrence (SHR 2.5; 95 % CI 1.2–10.7) [10] and Brantsch et al. found immunosuppression was associated with a 4.3-fold higher risk of nodal metastasis (95 % CI 1.6–11.5) [2].

Published Consensus Statements on High-Risk Criteria

The American Joint Committee on Cancer (AJCC) [38], Union for International Cancer Control (UICC) [28], and NCCN® (see footenote 1) have all published consensus statements on the criteria for high-risk CSCC. All three groups have developed these criteria based on consensus opinion and review of available data summarized above. While the AJCC and UICC have developed staging systems based on these high-risk criteria, the NCCN recommends differential treatment options for low-risk vs. high-risk tumors. The definitions of high-risk for each of the three groups are detailed in Table 2.2 and include tumor diameter, depth, invasion of nerves/vessels, tumor location, histopathologic differentiation and other historical or clinical factors.

Important discrepancies in the definition of high-risk between the groups are:

1. While the AJCC and NCCN have a diameter cutoff of 2 cm for high-risk regardless of location, the NCCN uses smaller diameter cutoffs for tumors on the head and neck, hands, feet, and genitalia. In the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®), tumors that are ≥0.6 cm on the "mask areas" of the face (central face, eyelids, eyebrows, periorbital area, nose, vermillion lip, cutaneous lip, chin, mandible, ear, pre-auricular and post-auricular skin), genitalia, hands, and feet are considered high-risk. Tumors on the cheeks, forehead, scalp, neck and pretibia that are ≥1 cm and tumors ≥2 cm elsewhere on the trunk and extremities are defined as high-risk.
2. The AJCC and NCCN identify tumors >2 mm thick as high risk while the UICC categorizes tumors >4 mm thick as high risk.
3. There is no mention of lymphovascular invasion as a high-risk feature in AJCC, but it is noted in UICC and NCCN.
4. Location on the vermilion lip is considered high-risk in AJCC and UICC, whereas NCCN defines location on either the cutaneous or vermillion lip as high risk (as long as the tumor is ≥0.6 cm).
5. Certain histologic SCC subtypes (e.g. adenoid, adenosquamous, desmoplastic) are considered high-risk in NCCN, but not AJCC or UICC criteria.

Despite the discrepancies, these variables likely identify tumors with a high risk of poor outcomes. NCCN Guidelines® state that any SCC having one of its high-risk criteria can be excised with either Mohs surgery (or another form of complete circumferential peripheral and deep margin assessment with frozen or permanent sections)

or wide local excision with a surgical margin greater than 6 mm and linear or delayed repair (no flap or graft closures until clear margins are histologically verified). If margins are positive after wide local excision, Mohs surgery or resection with complete circumferential peripheral and deep margin assessment is recommended. As most high-risk CSCC occurs on the head and neck, there are relatively few high risk SCCs where excision can be done with wide margins and closed in a linear fashion; thus Mohs surgery or another form of complete circumferential peripheral and deep margin assessment is routinely employed. See Chap. 6 for a full discussion of the surgical management of high-risk SCC.

Tumor Staging Systems

Cancer staging is important for both patients and clinicians. Staging aids the clinician in the planning of cancer treatment and can help to standardize treatment across patients. For patients, it provides some indication of prognosis and for those diagnosed with early stage cancer, it provides them with the peace of mind that their cancer is unlikely to recur. Finally, unified cancer staging allows for clear communication amongst health care providers and promotes advances in treatment of cancer by providing rationales for inclusion criteria in clinical trials and providing structure for treatment recommendations and evaluation of their impact.

A clinically useful staging system possesses several important qualities. First, it must be distinctive in that it groups tumor characteristics such that survival differs between tumor stages. Second, it must be monotonous in that survival decreases with increasing stage, ideally with equal differences in survival between consecutive stages. Finally, it must be homogenous with similar survival rates within an individual stage [39]. From a practical standpoint, staging systems should be easy to interpret and incorporate into daily practice. In tumors where the risk of poor outcomes is low overall as with CSCC, staging systems should be able to concentrate those who are at highest risk of developing poor outcomes into the highest stage group [40].

History of Cancer Staging Systems

The concept of developing unified cancer staging began in the early 1930s, when cancer researchers recognized the need to standardize classification of cancer in order to share knowledge and expertise globally. To achieve this, the International Union for Cancer Control (UICC) was formed. In the 1940s that the Tumor-Lymph Node-Distant Metastasis (TNM) Classification System which is still used today was developed by Pierre Denoix [41]. Dr. Denoix astutely observed that patients with localized cancer tended to have better outcomes than those with cancer that had already spread beyond the primary site. He developed a system that took into account

not only the extent of the tumor in the primary site (T Stage) but also extent of tumor in distant organs (regional lymph nodes and distant organs, N and M Stage, respectively). This TNM classification was adopted by the UICC in the 1950s and served as the basis for cancer staging across all body sites. In 1958, the Committee on Clinical Stage Classification published the first cancer staging book for breast and laryngeal cancer. One year later, the American Joint Committee on Cancer (AJCC) was developed to complement the work of the UICC and published its own cancer staging manual. Since the 1980s, the AJCC and UICC have been coordinated and publish revisions of their cancer staging manuals simultaneously. Revisions of staging systems occur every 6–8 years, allowing ample time for advances in cancer care to be incorporated into the newer versions [28, 38].

Refinements to the UICC and AJCC staging systems are typically based on expert consensus evaluation of high-quality data from large population-based registries. For example, addition of mitotic rate to the melanoma staging system was due to analysis of the AJCC Melanoma Staging Database, which included outcome data for greater than 60,000 melanoma patients across the world. Unfortunately, there are no active population-based registries for CSCC, and therefore limited outcome data, which has hindered development of accurate prognostic stratification systems for CSCC.

Rules of the TNM Classification System and Staging

As the TNM classification system is the foundation of any tumor staging system, the AJCC and UICC have provided clinicians with general guidelines on how to classify tumors:

1. Pathologic documentation of a malignancy must be confirmed before TNM categories are assigned to an individual tumor.
2. The TNM system is primarily a dual system where classification is done based on clinical data and then once again when pathological data is obtained. In general, clinical TNM helps to choose the appropriate treatment whereas pathologic TNM is important for prognosis and decision to perform adjuvant treatments. Clinical staging occurs prior to treatment of primary tumor or within 4 months of diagnosis (whichever is shorter), as long as the cancer has not clearly progressed. It may take into account factors acquired prior to treatment, such as physical examination, results of imaging studies, histopathologic findings, and surgical exploratory procedures. A lowercase “c” prior to the T, N, and/or M designates a clinical stage. Pathologic staging occurs post-surgically or within 4 months after the date of diagnosis (whichever is longer), as long as the cancer has not clearly progressed. It is based on the factors taken into clinical staging as well as evidence acquired during treatment of the primary tumor and subsequent histopathologic review. A lowercase “p” prior to the T, N, and/or M identifies a pathologic confirmation was made. A designation of “X” after the T and/or N indicates

that the stage could not be adequately assessed. MX is not considered a valid category as if there is no evidence of metastasis, cM0 should be assigned.

3. In cases where there is documented progression of cancer prior to the initiation of therapy or surgery, TNM classification should be based on information obtained prior to disease progression.
4. If there is doubt regarding the T, N, or M category to which a tumor should be assigned, the lower category should be chosen. For example, if a CT scan shows a small lymph node in the draining basin of a high-risk SCC that is not amenable to biopsy, the tumor should be staged as N0 despite the concern for metastatic disease.
5. For patients that develop two or more synchronous primary tumors in a single organ (e.g. three synchronous CSCCs in a transplant recipient), the tumor with the highest T stage should be classified and a designation of multiplicity (m) or number of multiple tumors should be reported in parentheses (e.g. T2(m) or T2(3)). If metachronous primary tumors occur in a single organ (patient develops two independent cancers at different time points), each tumor should be staged separately.
6. If there is direct extension of the primary tumor into the lymph node, it is defined as a lymph node metastasis. Metastasis in a lymph node other than the draining nodal basin is considered a distant metastasis. Table 2.3 lists regional lymph node basins by primary tumor site. In cases where the N classification is based on the size of metastasis, the critical discrimination points are based on the measurements of the metastatic foci within lymph nodes, not measurements of the lymph nodes themselves (unless specified otherwise in disease-specific rules).

Table 2.3 Draining lymph node basin by primary tumor location [42]

Location	Draining nodal basin
Head, neck	Ipsilateral preauricular, submandibular, cervical, and supraclavicular lymph nodes
Thorax	Ipsilateral axillary lymph nodes
Upper limb	Ipsilateral epitrochlear and axillary lymph nodes
Abdomen, loins, buttocks	Ipsilateral inguinal lymph nodes
Lower limb	Ipsilateral popliteal and inguinal lymph nodes
Anal margin and perianal skin	Ipsilateral inguinal lymph nodes
Boundary zones[a]	
Right/left	Midline
Head,neck/thorax	Clavicular-acromion-upper shoulder blade edge
Thorax/upper limbs	Shoulder-axilla-shoulder
Thorax/abdomen,loins,buttocks	Front: middle abdomen between navel and costal arch
	Back: lower border of thoracic vertebrae (mid-transverse axis)
Abdomen,loins,buttock/lower limb	Groin-trochanter-gluteal sulcus

[a]4 cm wide bands along these anatomic zones are considered boundary zones and may drain to either side lymph nodes

Reprinted with permission from Wittekind Ch, Compton CC, Brierley J, and Sobin LH. *TNM Supplement: A Commentary on Uniform Use*. 4th Ed, Wiley-Blackwell 2012

The final cTNM classification and tumor stage should be established just prior to initiating treatment or before making the decision to not treat. Once the final pTNM and stage has been assigned, it must remain unchanged. Once cTNM or pTNM classifications have been made, they are grouped into stages (Stages 0–IV) based on permutations and combinations of T, N, and M categories that place patients in clearly defined risk groups. Traditionally, Stage 0 is reserved for non-invasive cancer and Stage IV is reserved for cancer that has spread to distant sites. Stages I, II, and III are intermediate categories, with increased tumor burden and decreased survival with increasing stage.

In addition to the clinical and pathologic TNM classifications, three additional sub-classifications may be described for each site:

1. ycTNM or ypTNM- Post-therapy classification to assess extent of cancer after neoadjuvant or primary systemic and/or radiation therapy. These patients should also have a clinical TNM classification documented prior to starting treatment.
2. rTNM- Retreatment or recurrence classification. This is utilized when the tumor has recurred after a disease free interval or progressed.
3. aTNM- Autopsy classification. This is typically done when the first classification is performed during autopsy.

There are optional patient and tumor parameters that may be documented in addition to the TNM classification. Tumor histopathologic grade or presence of perineural/lymphovascular invasion are features that may be recorded. As the current system tries to group tumors into prognostic categories independent of treatment and it is well known that residual tumor after treatment often impacts further management and prognosis, the Residual Classification can also be recorded to document the margin status after surgery. These classification systems are described in Table 2.4. Finally, a designation of "i" can be included after the TNM stage to designate the tumor arose in an immunosuppressed individual (e.g. T2N0M0i). Based on the 2010 AJCC recommendation, only centers that are studying CSCC are encouraged to document immunosuppression status. Currently, the TNM classification system does not provide designations for other clinical risk factors, such as history of XRT or tumor formation in a chronic ulcer.

Current Staging Systems

The AJCC and UICC have both published staging systems for CSCC. Up until very recently, these two systems grouped cutaneous squamous cell carcinoma (CSCC) with other nonmelanoma skin cancers, including basal cell carcinoma (BCC). Due to the varied biological behavior between these tumors, the recent 7th edition of the AJCC created a staging system for CSCC separate from BCC [38]. The UICC staging system continues to group CSCC with BCC [28].

Table 2.4 AJCC and UICC optional descriptors [28, 38]

Grading classification		Lymphatic classification		Perineural classification		Venous invasion		Residual tumor classification	
Gx	Grade or differentiation cannot be assessed	LX	Lymphatic invasion cannot be assessed	PnX	Perineural invasion cannot be assessed	VX	Venous invasion cannot be assessed	R0	No residual tumor
G1	Well differentiated	L0	No lymphatic invasion	Pn0	No perineural invasion	V0	No venous invasion	R1	Microscopic residual tumor (Tumor identified microscopically at margin)
G2	Moderately differentiated	L1	Lymphatic invasion	Pn1	Perineural invasion	V1	Microscopic venous invasion	R2	Macroscopic residual tumor (Tumor identified grossly at margin)
G3	Poorly differentiated[a]					V2	Macroscopic venous invasion	RX	Presence of residual tumor cannot be assessed
G4	Undifferentiated[a]								

[a]In some circumstances, G3 and G4 can be combined

7th Edition AJCC Staging System

The development of a new CSCC staging system was part of a multidisciplinary effort which included dermatologists, otolaryngology head and neck surgeons (ENT surgeons), surgical oncologists, dermatopathologists, medical oncologists, plastic surgeons and oral and maxillofacial surgeons. This task force reviewed the available outcome data on CSCC. Given most studies analyzing early stage CSCC are retrospective in nature or do not conduct multivariable analysis, the Stage I and II revision was primarily based on consensus opinion of the AJCC task force. CSCC on any part of the body can be staged using this system, with the exception of eyelid SCC which is staged with the Carcinoma of the Eyelid staging system. Because the majority of CSCC tumors occur on the head and neck, the 7th edition AJCC staging system for SCC was developed to parallel the AJCC Head and Neck Cancer staging system.

For accurate staging, the AJCC recommends the following factors be collected on a routine basis: Tumor thickness (in mm), Clark's level, presence vs. absence of perineural invasion, primary site location on the ear or cutaneous lip, histologic grade based on the recommended grading system, and size of largest lymph node metastasis.

T Classification

The current Tumor (T) classification system (Tables 2.5 and 2.6) incorporates several clinical and pathologic risk factors including diameter >2 cm, >2 mm thickness, Clark level ≥IV (reticular dermis), perineural invasion, location on the ear or hair-bearing lip, or poorly differentiated or undifferentiated histology.

Clinical diameter size >2 cm was identified as the sentinel high-risk feature to differentiate T1 vs. T2 tumors for two main reasons. First, it has been shown in multiple studies to be independently associated with tumor recurrence. Second, this breakpoint allowed for congruence between cutaneous and head and neck SCC staging systems. In the 6th edition AJCC staging, size ≥5 cm was a significant breakpoint. The task force argued that prognostically important cutoffs other than 2 cm were difficult to establish based on available data, and therefore the 5 cm threshold was removed.

Other risk factors of importance include depth (>2 mm or Clark level ≥ IV), location on the cutaneous lip or ear, poorly differentiated or undifferentiated histology, and perineural invasion. As there is evidence that tumors ≤2 cm have the potential to metastasize, particularly when one or more of the other risk factors are present, those factors were incorporated into T classification. The task force felt that there was insufficient evidence to accurately categorize each remaining factor into stage specific locations. Therefore, these risk factors were treated with equal weight and grouped as "high-risk" with presence of ≥2 features upstaging to T2 classification.

Table 2.5 AJCC 7th edition TNM staging system definitions

T classification		N classification		M classification	
Tx	Primary tumor cannot be assessed	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in-situ	N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
T1	Tumor 2 cm or less in greatest dimension with less than two high-risk features[a]	N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
T2	Tumor greater than 2 cm in greatest dimension or tumor of any size with to or more high-risk features[a]	N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone	N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base	N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		

[a]High-risk features: depth >2 mm thickness, Clark level >=IV, perineural invasion, primary site ear, primary site cutaneous lip, poorly differentiated or undifferentiated histology

Table 2.6 AJCC 7th edition TNM staging

Stage	**T**	**N**	**M**
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
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

N Classification

The lymph node classification system was adopted to mirror the staging system for head and neck mucosal SCC (e.g. larynx, oral cavity). While adopting an established staging system has advantages such as familiarity, it was not developed based on primary outcome data from CSCC. In this system, N0 indicates there is no evidence of regional metastatic disease. If regional lymph node disease is present, the N classification divided into three main groups (N1, N2, and N3) based on the size of the metastatic focus and number of lymph nodes involved. N2 is further divided into three groups (N2a, N2b, and N2c) based on the laterality (ipsilateral vs. contralateral) of the lymph node and size of the metastatic focus (<3 cm, ≥3 cm but less than 6 cm, or ≥6 cm) (Tables 2.5 and 2.6).

Lymph node involvement in a non-regional draining basin is classified as distant metastasis. Table 2.3 lists the regional lymph node basins based on anatomic site of primary tumor. Lymph node drainage from head and neck CSCC can be ambiguous due to disparate drainage between patients as well as potential for contralateral drainage if the tumor is near the midline. Therefore classification of positive lymph node involvement as regional or metastatic can be subjective, particularly if the tumor is midline.

M Classification

The current Metastases (M) classification system is dichotomous, where M0 designates no metastatic disease and M1 designates presence of distant metastasis. A classification of M0 is inferred unless M1 status is known.

Stratification of TNM Classifications into Stages

The Task Force then combined the various permutations of the TNM classification into specific stages. (See Tables 2.5 and 2.6) In the 7th edition AJCC staging system, the task force did not discuss the rationale for these stage groupings. Stages 0–II are relatively straightforward with Stage 0 reserved for intraepidermal squamous cell carcinoma, Stage I indicative of a T1N0M0 tumor, and Stage II used for a T2N0M0 tumor. There are several TNM classifications that categorize Stage III or Stage IV tumors. Stage III tumors include T3 tumors with no evidence of nodal or distant metastasis or T1–T3 tumors with metastatic focus in a single ipsilateral lymph node <3 cm in diameter. Stage IV tumors are for the remainder of the TNM classifications.

7th Edition UICC Staging System

The UICC organizes CSCC staging based on tumor diameter and depth of invasion. All nonmelanoma skin cancers other than Merkel cell carcinoma are staged by this system (Tables 2.7 and 2.8).

Table 2.7 UICC 7th edition TNM staging system definitions

T classification		N classification		M classification	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant Metastasis
Tis	Carcinoma in situ	N1	Metastasis in a single lymph node, 3 cm or less in greatest dimension		
T1	Tumor 2 cm or less in greatest dimension	N2	Metastasis in a single lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple lymph nodes, none more than 6 cm in greatest dimension		
T2	Tumor more than 2 cm in greatest dimension	N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		
T3	Tumor with invasion of deep structures (e.g. cartilage, muscle, bone, jaws, and orbit)				
T4	Tumor with direct or perineural invasion of skull base or axial skeleton				

Table 2.8 UICC 7th edition TNM staging

Stage	**T**	**N**	**M**
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 or N3	M0
	T2	N2 or N3	M0
	T3	N2 or N4	M0
	T4	Any N	M0
	Any T	Any N	M1

Reprinted from LH Sobin, MK Gospodarowicz, C Wittekind. Union for International Cancer Control: TNM Classification of Malignant Tumors, 7th Ed (2009), with permission from Wiley-Blackwell

T Classification

The UICC Tumor (T) classification is based primarily on the diameter of the primary tumor, tissue level depth of invasion, whether there is perineural invasion into the skull base or invasion of the skeleton. Other high-risk features defined by the UICC in Table 2.2 are not incorporated into current staging.

N Classification

The UICC Nodal (N) classification system is a 3 tiered system based on the number of lymph nodes involved (single vs. multiple) and size of the metastatic focus (<3 cm, ≥3 cm but less than 6 cm, or ≥6 cm). The laterality of lymph nodes is not taken into account in the UICC N classification system.

M Classification

The UICC Metastasis (M) classification is the same as the AJCC where M0 indicates no evidence of metastatic disease and M1 is used when there is presence of metastatic disease.

Stratification of TNM Classifications into Stages

Based on the above UICC TNM classification criteria, tumors are assigned to a specific stage. Stage 0 is limited to SCC in situ. Stage I tumors are invasive CSCC that are ≤2 cm in diameter. Stage II is assigned to invasive tumors that are >2 cm in diameter. Stage III is reserved for T3N0M0 tumors (tumors that are infiltrating into deeper structures such as the muscle, bone, cartilage, jaws, and orbit) or tumors of any T classification with nodal metastasis to a single lymph node ≤ 3 cm in greatest dimension. Stage IV is assigned for tumors that have more advanced nodal disease or distant metastasis, regardless of T classification.

Factors Excluded from Current AJCC and UICC Staging Systems

There are several factors that are currently not incorporated into current AJCC and/or UICC staging, although there is evidence of the importance of these factors regarding prognosis. These factors include recurrent tumors and immunosuppressed status of the patient. In addition, there is evidence PNI of large caliber nerves is prognostically more significant than PNI of small caliber nerves [20, 21]. Histopathologic grading is an area that has yet to be explored further. The metastatic

risk of moderately differentiated tumors is not well known, although there is some evidence demonstrating it may be prognostically significant [6]. For poorly differentiated tumors, it is likely that a tumor with a small focus of poor differentiation may behave more aggressively than a tumor that is completely poorly differentiated, but there is little evidence to support this hypothesis. Whether tissue level depth (Clark Level) or millimeter depth (Breslow's depth) better predicts recurrence also has yet to be studied. Other than lip and ear, there are other high-risk locations, such as the temple or the scalp. These factors that are not currently incorporated into the staging systems may be important, but play a less significant role towards risk of poor outcomes. Unfortunately, studies conducted thus far have been underpowered to detect these small differences and therefore these factors have been excluded from current staging.

Important Differences between 7th Edition AJCC and UICC Staging Systems

There are several important differences to note between the two current staging systems:

1. The AJCC staging system is applicable to only CSCC whereas the UICC staging system continues to group CSCC with other nonmelanoma skin cancers (excluding Merkel cell carcinoma).
2. The AJCC staging system takes into account high risk factors other than diameter and depth such as histopathologic grade, perineural and/or lymphovascular invasion, and location on the cutaneous lip or ear. UICC continues to stratify tumor classification based on diameter and depth alone. Tumors that are <2 cm and do not invade deep structures but have two or more other high risk factors would be upstaged to T2 in AJCC but remain T1 in UICC (and therefore would be Stage 2 in the AJCC system but only Stage 1 in the UICC system).
3. It is easier for a tumor to be upgraded to T3 in the UICC system as a tumor is UICC T3 if it invades muscle or cartilage whereas AJCC T3 requires invasion of bone.
4. There is lack of congruence regarding tumor depth between the staging systems. The AJCC identifies a high-risk tumor if it is >2 mm deep or Clark's level IV or greater (reticular dermis or deeper structures). The UICC identifies >4 mm depth as a high-risk feature, but this breakpoint is not incorporated into the system. Instead, the T system depth is broadly defined as tumor invasion into deeper structures, such as muscle, bone or fascia.
5. The AJCC Nodal classification is based on the number of involved lymph nodes, greatest dimension of a tumor focus within a node, and location of the involved nodes in relation to the primary tumor (ipsilateral or contralateral). While the diameter of the lymph node metastatic foci and number of lymph nodes with metastases are included in UICC, the lateralization of involved nodes is not incorporated in UICC N classification.

Validation of Current Staging Systems

Since the AJCC and UICC were developed largely on expert opinion of limited data, a few studies have attempted to validate these systems with cohort data. The majority of studies have been performed on the 7th Edition AJCC staging system, as this separated out CSCC from other NMSC's.

Validation of Tumor Classification

There are four published studies that have validated the AJCC tumor (T) classification system. One of these studies was limited to CSCC occurring in immunosuppressed individuals [43]. It included data on 41 organ transplant recipients who developed 225 CSCCs during the study period. During followup, there were 19 local recurrences. The authors found that T2 tumors had nearly 10 times increased risk of local recurrence than T1 tumors (HR 9.9; 95 % CI 3.0–32.7) when they also adjusted for duration of immunosuppression, treatment modality, and patient gender.

The remaining three studies [10, 12, 44] were retrospective cohort studies of CSCC. In each of these studies, tumors were classified according to the AJCC T classification system. The risk of local recurrence, nodal metastasis, and disease specific death by T classification is detailed in Table 2.9. Two studies examined the risk of local recurrence by T classification. Of the 2074 tumors amongst two studies, there were a total of 63 local recurrences. The rate of local recurrences for T1, T2, T3 and T4 tumors were 0.8 % (95 % CI 0.4–1.4 %), 8.4 % (95 % CI 6–11 %), 60 % (95 % CI 23–88 %), and 60 % (95 % CI 23–88 %) respectively. Three studies examined the risk of nodal metastasis by T classification. These studies included 2689 primary CSCC's and there were a total of 83 nodal metastases. The rate of nodal metastasis for T1, T2, T3 and T4 tumors were 0.2 % (95 % CI 0.1–0.7 %), 6.9 % (95 % CI 5.5–8.6 %), 22 % (95 % CI 9–45 %), and 36.4 % (95 % CI 15–65 %) respectively. Two studies examined the risk of disease specific death by T classification. Of the 2074 included tumors, there were 31 disease specific deaths. The rate of disease specific death for T1, T2, T3 and T4 tumors were 0 % (95 % CI 0–0.2 %), 4.3 % (95 % CI 3–7 %), 60 % (95 % CI 23–88 %), and 80 % (95 % CI 38–96 %) respectively.

Based on this data, the AJCC fulfilled a basic requirement of distinctiveness, with rates of recurrence increase with increasing T stage. However, when looking at the data closely, it did not appear monotonous or homogenous. T3 and T4 tumors accounted for only a small minority of the cohort in the three datasets (29/2689 or approximately 1 % of the cohort). The majority of the local recurrences (45/63; 71 %), nodal metastases (71/83; 85.6 %), and disease specific deaths (23/31; 74.2 %) subsequently occurred in T2 classification. With relatively few tumors meeting T3/T4 criteria as well as the vast majority of poor outcomes being clustered in AJCC T2, the authors of all three studies concluded that the current AJCC staging system offered little prognostic discrimination.

Table 2.9 Published validation studies of 7th edition AJCC CSCC tumor (T) classification

Validation for local recurrence							
Study	# Tumors	Total number of local recurrences	AJCC T1 local recurrences	AJCC T2 local recurrences	AJCC T3 local recurrences	AJCC T4 local recurrences	Percentage of local recurrences in T1 or T2
Jambusaria-Pahlajani et al. [10]	256	16	3/112 (2.7 %)	11/91 (12.1 %)	1/2 (50 %)	1/2 (50 %)	87.50 %
Karia et al. [12]	1818	47	9/1361 (0.6 %)	34/447 (7.6 %)	2/3 (66 %)	2/3 (66 %)	91.50 %
Total	2074	63	12/1473 (0.8 %)	45/538 (8.4 %)	3/5 (60 %)	3/5 (60 %)	91 %
Validation for lymph node metastasis							
Study	# Tumors	Total number of LN metastasis	AJCC T1 LN metastasis	AJCC T2 LN metastasis	AJCC T3 LN metastasis	AJCC T4 LN metastasis	Percentage of nodal metastases in T1 or T2
Breunninger et al. [44]	615	26	0/107 (0%)	24/490 (4.9 %)	1/13 (7.7 %)	1/6 (16.7 %)	92 %
Jambusaria-Pahlajani et al. [10]	256	24	2/112 (1.7 %)	20/91 (22 %)	1/2 (50 %)	1/2 (50 %)	91.70 %
Karia et al. [12]	1818	33	2/1361 (0.2 %)	27/447 (6 %)	2/3 (66 %)	2/3 (66 %)	87.90 %
Total	2689	83	4/1580 (0.2 %)	71/1028 (6.9 %)	4/18 (33.3 %)	4/11 (36.4 %)	90.40 %
Validation for disease specific death							
Study	# Tumors	Total number of disease specific deaths	AJCC T1 disease specific deaths	AJCC T2 disease specific deaths	AJCC T3 disease specific deaths	AJCC T4 disease specific deaths	Percentage of disease specific deaths in T1 or T2
Jambusaria-Pahlajani et al. [10]	256	12	0/112 (0 %)	11/91 (12.1 %)	0/2 (0 %)	1/2 (50 %)	91.20 %
Karia et al.[12]	1818	19	0/1361 (0 %)	12/447 (2.7 %)	3/3 (100 %)	3/3 (100 %)	63.20 %
Total	2074	31	0/1473 (0 %)	23/538 (4.3 %)	3/5 (60 %)	4/5 (80 %)	74.20 %

The discriminative properties of the UICC 7th Edition CSCC staging system have been evaluated in only one study of 1818 CSCC tumors [12]. As with AJCC stage, the rates of LR, NM and DSD increased with increasing T classification. However, the majority of poor outcomes occurred in early UICC T stages, with 80.1 % LR, 66 % NM, and 44 % DSD occurring in UICC T1 and T2 tumors. Conversely, only 19 % LR, 33 % NM, and 56 % DSD occurred in UICC T3 and UICC T4 stages. In addition, when 10 year cumulative incidence rates for LR, NM, and DSD were tabulated for each UICC T stage, there was significant overlap between the 95 % confidence intervals, indicating each stage was not distinct from the next. Thus, the authors concluded the UICC system offered limited prognostic discrimination as well.

Validation of Nodal Classification

Only one study has validated the AJCC nodal (N) classification system based on 603 patients with nodal metastasis from CSCC located on the head and neck [45]. In this dataset, <10 % of tumors fell in the N2 category with 12/603 (2 %) tumors classified as N2c (requirement of contralateral lymph nodes involved). The Kaplan Meier curves demonstrated that several of the survival curves overlapped between two N categories. On multivariable analysis, the adjusted hazards ratios for recurrence for N2a, N2b, N2c, an N3 compared to N1 was 1.1, 1.5, 1.4, and 2.1, respectively, and had widely overlapping confidence intervals. These analyses indicate these categories were neither distinctive nor monotonous. The authors suggested the AJCC Nodal system was suboptimal and questioned the clinical utility of incorporating the laterality of lymph nodes (N2c category), given the paucity of tumors that fell into this category.

Alternative Staging Systems

As discussed earlier, the 7th Edition AJCC staging system for CSCC was developed to parallel the staging system for mucosal SCC from the head and neck. The major advantage of using an established system is its familiarity in clinical practice and relative ease of use. However, the clinical presentation and biological behavior of CSCC is not the same as mucosal SCC and therefore it may be flawed to base a CSCC staging system on that of mucosal SCC. The above validation studies have demonstrated that this approach is suboptimal. Several groups have published reports that have proposed alternative stratification systems that may offer improved prognostic discrimination over current AJCC and UICC T and N staging (Table 2.10).

Table 2.10 Alternative staging systems

Tumor	
BWH system, Jambusaria-Pahlajani et al. system[a]	
T1	0 High-risk factors
T2a	1 High-risk factor
T2b	2-3 High-risk factors
T3	All 4 high-risk factors or bone invasion
Peat, et al System[b]	
Low-Risk	1 Relative risk factor
Intermediate Risk	2 or 3 Relative risk factors
High-risk	At least 1 absolute risk factor or all 3 relative high risk factors
Nodal	
N1S3 system	
N1	Single lymph node metastasis <3 cm
N2	Multiple lymph node metastasis ≤3 cm or a single lymph node metastasis >3 cm
N3	Multiple lymph node metastasis with at least one metastatic focus being >3 cm

[a]HR factors include size >2 cm, depth beyond subcutaneous fat, poorly differentiated histology, and perineural invasion. PNI of any nerve diameter is a risk factor in Jambusaria-Pahlajani, Schmults et al. Only PNI of nerves ≥0.1 mm is a risk factor in the BWH System

[b]Relative risk factors include size >=2 cm, moderately differentiated histology, Clark's Level V or greater. Absolute risk factors include poorly differentiated histology or PNI/Lymphovascular invasion

Reprinted with permission from references #: [9, 10, 12, 46]

Alternative Tumor (T) Classification Systems

In 2012, Peat et al. [9] performed a case control study of 92 metastatic and 78 non-metastatic head and neck CSCCs. Based on multivariable analysis, they categorized risk factors independently associated with metastasis into two groups based on the magnitude of their hazard ratios. Absolute risk factors had the greatest predictive value for metastasis, and included tumors with poorly differentiated histology and neural, lymphatic or vascular invasion. Relative risk factors had a lower predictive value for metastasis and included tumors with a diameter ≥2 cm, moderate differentiation, and Clark's level V (depth into subcutaneous fat). The authors recommended a stratification system based on the number of absolute and relative risk factors (Table 2.10) with three categories (low, intermediate, and high risk). In their dataset, 78 % of metastatic tumors were high risk, 18 % were intermediate risk, and 4 % were low-risk. Conversely, 72 % of nonmetastatic tumors were low risk, 20 % were intermediate risk, and 8 % were high-risk.

Jambusaria-Pahlajani et al. [10] performed a retrospective cohort study of 257 CSCCs having at least one histologic or clinical risk factor. Based on multivariable analysis for LR, NM, and DSD, an alternative staging system was developed based on four risk factors of interest: PNI (regardless of the diameter of the nerve involved),

Table 2.11 10-Year cumulative incidence of outcomes by T stage in alternative T classification systems

		Local recurrence		Nodal metastasis		Disease specific death		All cause death	
	No. of tumors	10 year CIN (%)	95 % CI	10 year CIN (%)	95 % CI	10 year CIN (%)	95 % CI	10 year CIN (%)	95 % CI
Jambusaria-Pahlajani et al. [10]									
T1	134	2	1–6	0.8	0.1–4	No events		27	20–35
T2a	67	9	4–18	4	2–12	No events		30	20–41
T2b	49	18	10–31	37	25–51	20	11–34	53	39–66
T3	6	50	19–81	50	19–81	33 %	10–70	50	19–81
BWH system [12]									
T1	1393	0.6	0–1	0.1	0–0.4	No events		32	30–35
T2a	332	5	3–8	3	1–5	1	0–3	32	28–37
T2b	86	21	13–27	21	13–27	10	6–19	51	41–58
T3	6	67	30–90	67	30–90	1000	61–100	100	60–100

CIN cumulative incidence, *CI* confidence interval
Reprinted with permissions from: [10, 12]

poorly differentiated histology, size >2 cm, and depth beyond the subcutaneous fat. One point was given for the presence of each of these risk factors, and four tumor stage categories were developed based on statistical analysis. The final tumor (T) staging system is outlined in Table 2.10. Cumulative Incidence Function curves for LR, NM, and DSD demonstrated an interval increased incidence of LR, NM, and DSD with increased alternative T classification, suggesting a Tumor classification system which gives equal weight to risk factors including tumor diameter may be of greater utility. In addition, the clustering of poor outcomes previously seen in AJCC T2 was now largely shifted to a T2b category with T2a having a relatively low risk of poor outcomes.

A similar study was conducted at Brigham and Women's Hospital in 1818 CSCC tumors histologically diagnosed over a 10-year period at a single institution [12]. The alternative T staging system above was validated with the modification that PNI was only considered a risk factor if the diameter of the nerve involved was ≥ 0.1 mm. This system, termed the Brigham and Women's Hospital (BWH) tumor staging system demonstrated greater homogeneity, monotonicity, and distinctiveness over the AJCC and UICC T classifications. The cumulative incidence function curves demonstrated an increased risk of LR, NM, and DSD with increasing BWH T stage. In addition, the 10-year cumulative incidence rates of LR, NM, and DSD increased with increasing BWH T stage, with minimal overlap in 95 % confidence intervals, indicating that these were statistically different categories.

The incidence and 95 % confidence intervals of LR, NM or DSD for T1 vs. T2a vs. T2b vs. T3 for both the Jambusaria-Pahlajani et al. and BWH systems is tabulated in Table 2.11. In the BWH system, there was a sequentially higher risk of recurrence or death with each alternative T stage and very little overlap in the 95 % confidence interval, suggesting these are indeed distinct categories.

While the Peat system and the BWH system both appear to offer improved prognostic discrimination over current staging, the BWH system aligns well with the AJCC and UICC systems, which both use a 4-tiered T classification system. More importantly, the BWH system was developed by analyzing risk factors for all endpoints of interest (LR, NM, and DSD) whereas the Peat system was developed based on risk factors for metastasis only. Thus, the BWH system may be more easily used to refine the current staging systems already in use.

Alternative Nodal (N) Classification Systems

The discrepancy between mucosal head and neck SCC nodal staging and CSCC nodal staging has prompted several groups to develop alternative nodal classification systems. Initially, the alternative systems were developed for cutaneous SSC arising on the head and neck and were based on separating regional parotid involvement from cervical lymph node involvement, as separating parotid and cervical involvement was thought to improve prognostic discrimination [47]. However, this system did not perform well when validated in external datasets [48, 49]. When compared to prior staging systems, it was rather complex and difficult to incorporate into daily practice and therefore fell out of favor.

Recently, an alternative nodal system called the "N1S3" staging system [46] (Table 2.10) has been proposed. This system takes into account the number of lymph nodes involved (single vs. multiple) and the size of metastatic foci within the nodes (≤3 cm vs. >3 cm). In a validation study of 603 patients with nodal metastasis, the Kaplan Meier curves using the N1S3 system had a statistically significant difference in survivor functions between the groups with decreased survival with increasing N1S3 stage. On multivariable analysis, adjusted hazards ratios showed a HR of 1.4 (95 % CI 1.2–1.5) for N1S3 Stage II vs. N1S3 Stage I and HR of 2.6 (95 % CI 2.06–2.18) for N1S3 Stage III vs. N1S3 Stage II [45]. Based on this analysis, the N1S3 Nodal Staging system for CSCC appears to offer improved prognostic discrimination over the AJCC Nodal Staging system. Another advantage of this 3-tiered system is that it is much easier to incorporate into daily clinical practice than the current AJCC 5-tiered system.

Conclusion

While there are approximately 186,000–420,000 new cases of CSCC each year, a subset of tumors are considered high-risk based on certain histopathologic or clinical characteristics. Generally accepted high-risk factors include tumor diameter>2 cm, deep tumors, poorly differentiated histology, perineural invasion, location on certain anatomic sites, and immunosuppression. The relative contributions of each of these factors towards prognosis have only recently begun to

be quantified. The AJCC and UICC staging systems for CSCC were developed based on consensus opinion and review of very limited available data. When recently validated using new datasets, the current systems offered limited prognostic utility. Alternative staging systems, which appear to offer improved prognostic discrimination, have been developed and validated and are currently undergoing further validation and refinement. Improved staging in CSCC will aid clinicians and patients, offering accurate prognostic estimates which will promote further study to determine optimal treatment strategies.

References

1. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68(6):957–66.
2. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, Breuninger H. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713–20.
3. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. JAMA Dermatol. 2013;149(5):541–7.
4. Clayman GL, Lee JJ, Holsinger FC, Zhou X, Duvic M, El-Naggar AK, Prieto VG, Altamirano E, Tucker SL, Strom SS, Kripke ML, Lippman SM. Mortality risk from squamous cell skin cancer. J Clin Oncol. 2005;23(4):759–65.
5. Mullen JT, Feng L, Xing Y, Mansfield PF, Gershenwald JE, Lee JE, Ross MI, Cormier JN. Invasive squamous cell carcinoma of the skin: defining a high-risk group. Ann Surg Oncol. 2006;13(7):902–9.
6. Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K, Bourlidou E, Vahtsevanos K, Antoniades K. Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival. Eur J Cancer. 2010;46(9): 1563–72.
7. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J Surg Oncol. 2012;106(7):811–5.
8. Roozeboom MH, Lohman BG, Westers-Attema A, Nelemans PJ, Botterweck AA, van Marion AM, Kelleners-Smeets NW. Clinical and histological prognostic factors for local recurrence and metastasis of cutaneous squamous cell carcinoma: analysis of a defined population. Acta Derm Venereol. 2013; 93(4): 417–21.
9. Peat B, Insull P, Ayers R. Risk stratification for metastasis from cutaneous squamous cell carcinoma of the head and neck. ANZ J Surg. 2012;82(4):230–3.
10. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang WT, Gelfand JM, Whalen FM, Elenitsas R, Xu X, Schmults CD. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. JAMA Dermatol. 2013;149(4):402–10.
11. Ballantyne AJ, McCarten AB, Ibanez ML. The extension of cancer of the head and neck through peripheral nerves. Am J Surg. 1963;106:651–67.
12. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy G, Qureshi AA, Schmults CD. Evaluation of AJCC, UICC, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. J Clin Oncol. 2014; 32(4): 327–34.
13. Matorin PA, Wagner Jr RF. Mohs micrographic surgery: technical difficulties posed by perineural invasion. Int J Dermatol. 1992;31(2):83–6.

14. Mohs FE, Lathrop TG. Modes of spread of cancer of skin. AMA Arch Derm Syphilol. 1952;66(4):427–39.
15. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. Am J Surg. 1984;148(4):542–7.
16. Dodd GD, Dolan PA, Ballantyne AJ, Ibanez ML, Chau P. The dissemination of tumors of the head and neck via the cranial nerves. Radiol Clin North Am. 1970;8(3):445–61.
17. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia II. Perineural invasion. J Am Acad Dermatol. 2005;53(2):261–6.
18. McNab AA, Francis IC, Benger R, Crompton JL. Perineural spread of cutaneous squamous cell carcinoma via the orbit. Clinical features and outcome in 21 cases. Ophthalmology. 1997;104(9):1457–62.
19. Mendenhall WM, Ferlito A, Takes RP, Bradford CR, Corry J, Fagan JJ, Rinaldo A, Strojan P, Rodrigo JP. Cutaneous head and neck basal and squamous cell carcinomas with perineural invasion. Oral Oncol. 2012;48(10):918–22.
20. Ross AS, Whalen FM, Elenitsas R, Xu X, Troxel AB, Schmults CD. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. Dermatol Surg. 2009;35(12):1859–66.
21. Carter JB, Johnson MM, Chua TL, Karia PS, Schmults CD. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: an 11-year cohort study. JAMA Dermatol. 2013;149(1):35–41.
22. Salmon PJ, Hussain W, Geisse JK, Grekin RC, Mortimer NJ. Sclerosing squamous cell carcinoma of the skin, an underemphasized locally aggressive variant: a 20-year experience. Dermatol Surg. 2011;37(5):664–70.
23. Swanson NA, Grekin RC, Baker SR. Mohs surgery: techniques, indications, and applications in head and neck surgery. Head Neck Surg. 1983;6(2):683–92.
24. Zitsch 3rd RP, Park CW, Renner GJ, Rea JL. Outcome analysis for lip carcinoma. Otolaryngol Head Neck Surg. 1995;113(5):589–96.
25. Babington S, Veness MJ, Cakir B, Gebski VJ, Morgan GJ. Squamous cell carcinoma of the lip: is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision? ANZ J Surg. 2003;73(8):621–5.
26. Vukadinovic M, Jezdic Z, Petrovic M, Medenica LM, Lens M. Surgical management of squamous cell carcinoma of the lip: analysis of a 10-year experience in 223 patients. Journal Oral Maxillofac Surg. 2007;65(4):675–9.
27. Daniele E, Rodolico V, Leonardi V, Tralongo V. Prognosis in lower lip squamous cell carcinoma: assessment of tumor factors. Pathol Res Pract. 1998;194(5):319–24.
28. Sobin L, Gospodarowicz M, Wittekind C, editors. Union for International Cancer Control. Chichester: UICC and Wiley; 2010
29. Khanna M, Fortier-Riberdy G, Dinehart SM, Smoller B. Histopathologic evaluation of cutaneous squamous cell carcinoma: results of a survey among dermatopathologists. J Am Acad Dermatol. 2003;48(5):721–6.
30. Breuninger H, Schaumburg-Lever G, Holzschuh J, Horny HP. Desmoplastic squamous cell carcinoma of skin and vermilion surface: a highly malignant subtype of skin cancer. Cancer. 1997;79(5):915–9.
31. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. Cancer. 2006;106(11):2389–96.
32. Calonje E, Brenn T, Azar AL, McKee PH. McKee's pathology of the skin. 4th edn. Tumors of the surface epithelium, vol 2. Elsevier; 2012; Philadelphia, PA
33. Euvrard S, Kanitakis J, Pouteil-Noble C, Disant F, Dureau G, Finaz de Villaine J, Claudy A, Thivolet J. Aggressive squamous cell carcinomas in organ transplant recipients. Transplant Proc. 1995;27(2):1767–8.
34. Veness MJ, Quinn DI, Ong CS, Keogh AM, Macdonald PS, Cooper SG, Morgan GW. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. Cancer. 1999;85(8):1758–64.

35. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005;53(6):1067–71.
36. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150(3):280–7.
37. Hausauer AK, Maurer T, Leslie KS, Parvataneni R, Stuart SE, Chren MM. Recurrence after treatment of cutaneous basal cell and squamous cell carcinomas in patients infected with human immunodeficiency virus. JAMA Dermatol. 2013;149(2):239–41.
38. Edge SB. American Joint Committee on Cancer (AJCC): cancer staging manual. 7th ed. New York: Springer; 2010.
39. Ishwaran H, Blackstone EH, Apperson-Hansen C, Rice TW. A novel approach to cancer staging: application to esophageal cancer. Biostatistics. 2009;10(4):603–20.
40. Miller SJ. Staging cutaneous squamous cell carcinoma. JAMA Dermatol. 2013;149(4): 472–4.
41. Denoix P. Enquete permanent dans les centres anticanceraux. Bulletin Institut national d'hygiene. 1946;1:12–7.
42. Wittekind C, Compton CC, Brierley J, Sobin LH. TNM supplement: a commentary on uniform use. 4th ed. Oxford: Wiley-Blackwell; 2012.
43. Metchnikoff C, Mully T, Singer JP, Golden JA, Arron ST. The 7th edition AJCC staging system for cutaneous squamous cell carcinoma accurately predicts risk of recurrence for heart and lung transplant recipients. J Am Acad Dermatol. 2012;67(5):829–35.
44. Breuninger H, Brantsch K, Eigentler T, Hafner HM. Comparison and evaluation of the current staging of cutaneous carcinomas. J Dtsch Dermatol Ges. 2012;10(8):579–86.
45. Clark JR, Rumcheva P, Veness MJ. Analysis and comparison of the 7th edition American Joint Committee on Cancer (AJCC) nodal staging system for metastatic cutaneous squamous cell carcinoma of the head and neck. Ann Surg Oncol. 2012;19(13):4252–8.
46. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases results of 2 Australian Cancer Centers. Cancer. 2010;116(5):1298–304.
47. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. Head Neck. 2002;24(5):417–22.
48. Andruchow JL, Veness MJ, Morgan GJ, Gao K, Clifford A, Shannon KF, Poulsen M, Kenny L, Palme CE, Gullane P, Morris C, Mendenhall WM, Patel KN, Shah JP, O'Brien CJ. Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicenter study of treatment outcomes. Cancer. 2006;106(5):1078–83.
49. Palme CE, O'Brien CJ, Veness MJ, McNeil EB, Bron LP, Morgan GJ. Extent of parotid disease influences outcome in patients with metastatic cutaneous squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2003;129(7):750–3.

Part II
The Science of SCC

Chapter 3
Genomics of SCC: Tumor Formation, Progression, and Future Therapeutic Implications for High-Risk Cutaneous Squamous Cell Carcinoma

Catherine Anne Harwood, Charlotte Mary Proby, and Sarah Tuttleton Arron

Introduction

The progressive transformation of a normal keratinocyte into a pre-malignant actinic keratosis (AK), carcinoma-in situ (CIS, Bowen's disease), invasive cutaneous squamous cell carcinoma (CSCC) and finally into metastasis is regarded, as with other epithelial cancers, to be a multistep process reflecting the accumulation of genetic and epigenetic alterations. However, there remain many fundamental uncertainties: the exact sequence of events in this apparent clinicopathological continuum is unclear; AK and CIS stages may not always be evident or necessary; the position of keratoacanthoma (KA) is uncertain; and the clinical and molecular factors which govern transition though each of these stages are poorly understood.

Ultraviolet radiation (UVR) is the principle carcinogen responsible for cutaneous squamous carcinogenesis and causes DNA damage that leads to aberrations in oncogenes and tumor suppressor genes and induction of immunological tolerance. Other risk factors include immunosuppression (iatrogenic or innate), chronic inflammation, ionizing radiation, drugs, viruses, genodermatoses (Table 3.1) and host-specific genetic polymorphisms in genes of pigmentation and DNA repair.

C.A. Harwood, BA, MA, PhD, FRCP (✉)
Centre for Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Royal London Hospital, 4 Newark Street, London E1 2AT, UK
e-mail: caharwood@doctors.org.uk

C.M. Proby, BA, MBBS, FRCP
Ninewells Hospital and Medical School, Jacqui Wood Cancer Center, Medical Research Institute, University of Dundee, James Arrott Drive, Dundee PH2 7PQ, UK

S.T. Arron, MD, PhD
Department of Dermatology, University of California, San Francisco, 2340 Sutter Street N425, San Francisco, CA 94115, USA

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_3

Table 3.1 Genetic disorders associated with an increased risk of CSCC

Disease	Transmission	Gene	Locus	Function	CSCC features, risk and metastatic potential
Epidermolysis bullosa					
Junctional (JEB)					
Herlitz (lethal) JEB	AR	LAMA3, LAMC2, LAMB3	18q11.2, 1q25-q31, 1q32	Laminin 5 (laminin 322)	
Non-Herlitz JEB		COL17A1	10q25.1, 17q25.1	Type XVII collagen, a6b4 integrin, laminin 5	Lifetime risk of aggressive SCC 25% in non-Herlitz JEB. Average age of onset 50 years. Usually multiple. Lower extremities. Areas of chronic blistering and scarring (rather than UV exposed areas).
Dystrophic (DEB)					
Dominant DEB	AD	COL7A1	3p21.3	Type VII collagen in anchoring fibrils: Dysfunctional basement membrane-dermal collagen anchorage	SCC cumulative risk of 6% by age 20 years and 85% by age 45 years in RDEB; Areas of chronic blistering and scarring (rather than UV exposed areas). Usually multiple and aggressive. >80% die from metastatic SCC.
Recessive DEB	AR				
Kindler syndrome	AR	FERMT1 (KIND1)	20p12.3	Kindlin links actin cytoseleton to extracellular matrix	Some cases of aggressive and metastatic SCC reported

Epidermodysplasia verruciformis	AR/AD	EVER1, EVER2	17q25	Regulate zinc homeotstasis forming complexes with zinc transporter 1 which is blocked by beta HPV proteins.	SCC in 50–60 %; onset in third to fifth decade; Multiple SCC in UV exposed areas: 90 % of SCC harbour beta-HPV (especially HPV 5,8). SCC usually localised, but aggressive and metastatic SCC reported.
Xeroderma pigmentosum	AR	XPA-G	9q34.1, 2q21, 3p25.1, 19q13.2,11q12-13 and 11p11-12,16p13.3,13q32-33	Nucleotide excision repair of UV-induced DNA damage	SCC in up to 50 %. Early onset (average aged 8 years). Multiple SCC in UV exposed sites. Metastases are uncommon. However, patients succumb to uncontrollable loco-regional SCC in teens without total UV avoidance.
		XPV	6p21	Defects in the translesion-synthesis DNA polymerase Polη coded by the POLH gene	
Ferguson-Smith syndrome (multiple self-healing squamous epitheliomas)	AD	TGFBR1	9q22.3	TGFbeta-mediated growth factor signalling	Multiple spontaneously resolving KA-like SCC; no aggressive/metastatic SCC reported but may be locally destructive.
Oculocutaneous albinism	AR	TYR (OCA1, tyrosinase)	11q14.3	Synthesis of melanin	Multiple, aggressive SCC from childhood in OCA 1 and OCA2
		OCA2 (P-protein)	15q11.2-q12		
		TYRP1 (OCA3, tyrosinase related gene)	9p23		
		MATP/OCA4	5p13.3		

(continued)

Table 3.1 (continued)

Disease	Transmission	Gene	Locus	Function	CSCC features, risk and metastatic potential
Muir-Torre syndrome	AD	hMSH2	2p22-p21	DNA mismatch repair	KA-like SCC (+/− sebaceous differentiation); other sebaceous neoplasms including sebaceous adenomas and carcinomas.
		hMLH1	3p21.3		
Rothmund–Thomson syndrome	AR	RECQL4	8q24.3	DNA helicase (DNA repair and chromosomal segregation).	5–10 % predisposed to skin cancer—SCC most common type (prevalence 5 %). Multiple SCC from early age
Werner syndrome	AR	WRN/RECQL2	8p12-p11.2	RecQDNA helicase required for DNA repair, replication, recombination and chromosomal stability	May develop aggressive SCC (5 %), but acral lentiginous melanoma more common.
Bloom syndrome	AR	BLM/RECQL3	15q26.1	DNA helicase required for maintaining DNA stability during replication	SCC occurs in 14 % of all individuals at mean age of 31 years.
Dyskeratosis congenita	XLR, AD, AR	DKC1, TERC, TINF2, NHP2/NOLA2, NOP10/NOLA3, TERT, WRAP53	Xq28	Telomere homeostasis and function	CSCC in 1.5 % at young ages; mucosal SCC more common.
			3q21-q28		
			14q12		
			5q35.3		
			15q14-q15		
			5q15.33		

Fanconi anemia	AR, XLR	FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG/XRCC9, FANCI, FANCJ/BRIP1, FANCL	16q24.3, Xp22.31, 9q22.3, 13q12.3, 3p25.3, 6p21.3, 11p15, 9p13, 15q25-26, 17q22.3, 2p16.1, 14q21.3, 16p12.1	DNA repair	SCC common but majority of malignancies are leukaemias and Wilm's tumours.
Li-Fraumeni syndrome	AR	TP53	17p13.1	DNA repair, apoptosis	SCC uncommon and no associated mortality reported (brain tumours, breast cancer, soft tissue sarcomas more common)
Keratitis-ichthyosis-deafness syndrome	AD	GJB2 (connexin 26)	13q11-q12	Gap junction protein involved in proliferation growth and differentiation	29% develop SCC at mean age 25 years; no reports of aggressive/metastatic SCC
Huriez syndrome (sclerotylosis)	AD	–	Maps to 4q23	–	SCC in 15% and may be aggressive and metastatic. Often arise in scleroatrophic areas (100-fold increased risk).
Palmar Plantar keratoderma and XX sex reversal	AR	RSPO1	1q34-35	Enhanced Wnt signalling	Males with 46XX genotype and PPK may develop metastatic SCC.
Cowden syndrome	AD	PTEN	10q23.31	Regulation of AKT signalling pathway	SCC less frequent than trichilemmomas

Based upon Somoano et al. [163]; Winship and Dudding [185]; Gerstenblith et al. [58]; Nikolaou et al. [129]; Knoch et al. [93]; Ng et al. [119]

These risk factors may have oncogenic potential through direct or indirect genetic and epigenetic alterations in keratinocytes and/or the tumor microenvironment.

Understanding of the molecular pathogenesis underpinning cutaneous squamous carcinogenesis is in its infancy compared with many less common malignancies. Although there has been significant progress in recent years, much remains obscure. However, as has been demonstrated in tumors such as breast and colorectal cancer and, more recently, melanoma and basal cell carcinoma, characterization of the genes and pathways involved in CSCC has the potential to identify therapeutic targets, facilitate development of diagnostic and prognostic biomarkers, and, ultimately, translate into more rational and effective management strategies.

In the first section of this chapter we review the published literature on genetic and epigenetic changes in the tumor and tumor microenvironment in addition to known host-specific changes predisposing to CSCC. In the second section, we summarize how this information is currently being exploited clinically and speculate on future therapeutic directions.

Section I: Tumor Formation and Progression

Genetic Changes in Cutaneous Squamous Carcinogenesis

Dissecting Relevant Genetic Changes in Tumor and Tumor Microenvironment

In recent years whole genome and exome sequencing has provided extensive information about the tumor-specific genetic changes in many common human cancers: on average, a cancer is estimated to contain 2–8 'driver' gene mutations that confer a selective growth advantage, with the great majority of other mutations being 'passengers' that confer no growth advantage [181]. It is proposed that the majority of driver genes—around 140—have already been identified and that these can be classified into 12 signaling pathways regulating cell fate, cell survival and genome maintenance [181]. As described below, the extensive genomic aberrations and vast number of mutations found in CSCC have hampered identification of critical drivers and it is becoming increasingly apparent that multiple genes and pathways are likely to be involved (Figs. 3.1 and 3.2). In addition, a crucial determinant of tumor behavior is the tumor microenvironment [8] and there is increasing evidence for significant 'cross-talk' between stroma and tumor [113].

Cell of Origin of CSCC; Do Tumor Initiating Cells (TICs) Exist?

The cell of origin of human CSCC is not known. The existence of cancer stem cells or tumor initiating cells (TICs) is controversial, yet full understanding of the cellular and molecular basis of squamous carcinogenesis and its successful treatment is likely to require identification and therapeutic targeting of TICs if they do indeed exist [36].

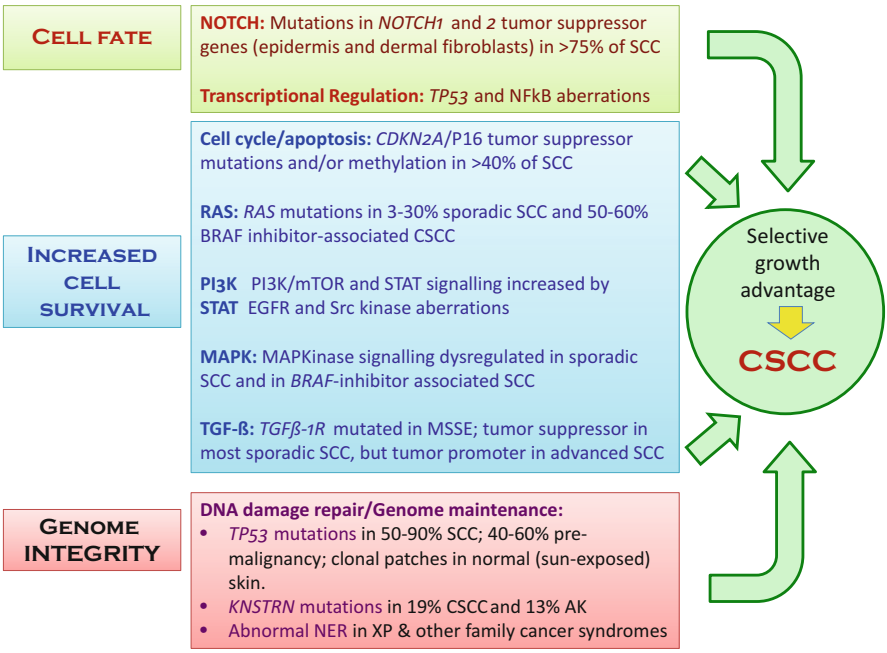


Fig. 3.1 Schematic of cancer cell signaling pathways relevant to CSCC. Cancer 'driver' genes can be classified into a number of key pathways (*Bold typeface*) that confer a selective growth advantage [181]. These signaling pathways may be further organized into three core cellular processes governing cell fate, cell survival and genome integrity. Those pathways known to be dysregulated in CSCC are illustrated in this schematic. *CSCC* cutaneous squamous cell carcinoma, *AK* actinic keratosis, *MSSE* multiple self-healing squamous epithelioma, *NER* nucleotide excision repair, *XP* xeroderma pigmentosum

CSCCs show impaired differentiation, but possess both proliferating and differentiated keratinocytes, recapitulating the organizational hierarchy of normal epidermis. This cellular hierarchy derives from keratinocyte stem cells so it has been proposed that CSCC arises from TICs with long-term proliferative and self-renewal capacity [36]. Epidermal stem cells in the basal layer of the interfollicular epidermis and hair follicle bulge have been proposed as putative TICs based upon experimental data in mice [7, 23, 26, 101, 121], but mice do not necessarily reflect the situation in humans [36]. In xenograft assays, a subset of human CSCC cells expressing CD133 recapitulate the original CSCC histology and are capable of self-renewal in serial transplantation studies [134]. However, it is possible that these cell surface markers are an epiphenomenon and that cancer sub-populations selected with putative stem cell markers do not show differences in transplantation models. Furthermore, putative TICs may not always arise in epidermis: in separate experiments, it is evident that bone marrow derived cells may migrate to the bulge region, differentiate into keratinocyte stem cells [23] and undergo malignant transformation [85] and that donor-derived cells from grafted kidneys are present in CSCC from organ transplant recipients and may contribute to skin carcinogenesis [3, 180].

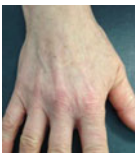
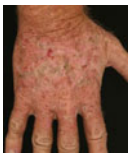
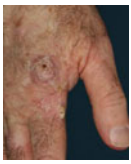
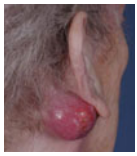
	 Normal sun exposed skin	 Actinic keratosis/ Field cancerization	 CSCC	 Metastasis
Genomic changes	**LOH:** ***NOTCH1***	**LOH:** genetic aberrations 3p, 9p, 13q, 17p and 17q **SNP**: no differences between immunosuppressed and immunocompetent	**LOH:** more extensive than AK (9p loss 75% and 3p loss 65%; recurrent losses 2q, 8p, 13; allelic gain on 3q, 8q and 11q) **CGH:** loss of 3p, 9; gain of 11q; isochromosomes 3q, 8q and 9q **M-FISH:** loss of 3p, 5q, 8p and 17p with gain of 3q, 5p 7p, 8q and 11q. **SNP:** fewer changes in WD compared with MD and PD	Deletion at 9p23
Activating mutation Increased gene expression / signaling	***RAS*** ***FGFR3***	***RAS-*** mostly mutations in *HRAS* ***EGFR*** **SFKs** including *Src, Fyn, FAK* **NFkB**	***RAS-*** activating mutation 20% sporadic SCC; 60% BRAF inhibitor SCC; epigenetic ***C-MYC*** amplifications ***MAPK-PI3K-AKT-mTOR*** **EGFR** overexpression (but amplifications and mutations rare) **SFKs** including Src, Fyn, FAK **NFkB** **TNF** **Mir21, 365** **MMPs**	***EGFR*** **MiRNA9** **RAS-RAF-MEK-ERK** **PI3K-AKT** **HRAS** **AJUBA** **CASP8** **FAT1** **KMT2C (MLL3)** **PARD3** **RASA1**
Loss of function mutation Decreased gene expression / signaling	***TP53*** ***NOTCH1-3*** ***FAT1*** ***RBM10***	***TP53*** ***NOTCH1&2*** mutations ***NOTCH*** methylation in dermal fibroblasts ***KNSTRN*** mutation ***CDKN2A*** p16/p14ARF **Srcasm**	***TP53*** (mutation 40-90%) ***NOTCH*** mutations in 75% (1 or 2>3 or 4) ***CDKN2A*** p16INK4a/p14ARF mutation and methylation **Srcasm** **TGFbeta:** TS early stages then pro-proliferative later stages ***KNSTRN*** mutation **Mir203, 214, 124, 125b, 361-5-b** **TINCR** **E-cadherin**	***PTPRD*** ***FRZB*** **methylation** **E-cadherin**

Fig. 3.2 A comparison of reported molecular features of sun-exposed skin, AKs, invasive CSCC and metastatic SCC. The 'Holy Grail' in cancer genetics is to identify critical molecular signatures associated with each stage of the tumorigenic progression from non-malignant to premalignancy, primary invasive malignancy and ultimately metastasis. The reported molecular features of these stages of human squamous carcinogenesis discussed in the text are summarized here. Those changes primarily associated with the tumor microenvironment are discussed in Chap. 4. *LOH* loss of heterozygosity, *SNP* single nucleotide polymorphism, *CGH* comparative genomic hybridization, *M-FISH* multiplex fluorescence in situ hybridization, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated

Chromosomal Changes in CSCC

Many studies have shown that CSCC display complex karyotypes with large numbers of allelic imbalances ([4, 145, 146]; Fig. 2). Chromosomal changes are well recognized in cancer and many solid tumors display widespread changes in chromosome number, as well as deletions, inversions and translocations [136]. Karyotyping, comparative genomic hybridization (CGH), multiplex fluorescence in situ hybridization (M-FISH), microsatellite PCR and, more recently, single nucleotide polymorphism (SNP) arrays allow genome-wide profiling of gains and losses in genetic material. These studies confirm considerable karyotypic complexity and cytogenetic heterogeneity in CSCC. Many recurrent changes have been documented, but the

functional consequences of most are unknown: even when the loss or duplication of a large part of a chromosome confers a clear growth advantage, it is often difficult to identify the target gene, although this may be easier with homozygous deletions which often involve a smaller number of potential target genes.

CGH and M-FISH Studies Show Differences Between KA and CSCC

CGH studies report loss of 3p, 9p and gain of 11q in CSCC and, although these changes are also present in KA, the latter are karyotypically simpler, consistent with KA being a modified form of CSCC [19]. Clausen and colleagues similarly found significantly less chromosomal instability in KA versus CSCC but reported differences in recurrent aberrations between the two tumor types, which may point to different genetic mechanisms [35, 112]. Jin and colleagues also found fewer chromosomal alterations in AK and KA compared to CSCC, with structural aberrations affecting centromeric regions in CSCC, but not AK, leading to whole-arm translocations and duplication of chromosome arms causing formation of isochromosomes or copy number-neutral LOH [84]. Isochromosome formation is tissue-specific and in CSCC most commonly involves chromosomes 3q, 8q and 9q [19, 84], [19]. Additionally, genetically unrelated clones occurring within the same tumor suggest that tumor heterogeneity is frequent in CSCC [84]. In a progression model of primary, recurrent and metastatic CSCC-derived cell lines, most gains and losses identified by CGH were common to both tumors and derived cell lines and included loss of 3p, 5q, 8p and 17p with gain of 3q, 5p 7p, 8q and 11q; M-FISH identified complex translocations and confirmed their common origin [141].

Loss-of-Heterozygosity (LOH) Studies Confirm Recurrent Regions of Loss and Gain, Which Correlate with Differentiation Status and Identify a Common Microdeletion in PTPRD

LOH is an established mechanism of tumor suppressor gene inactivation in which loss of a normal allele at a specific locus occurs within a genome already harbouring a deleterious mutation on the corresponding allele. LOH arises through deletion, gene conversion, mitotic recombination and chromosome loss (which may be followed by duplication of the remaining chromosome) and leaves a cell either hemizygous (one deleterious allele and one deleted allele) or homozygous for the deleterious allele. In the earliest studies, LOH was assessed by microsatellite PCR techniques [149–151]. More recently, single nucleotide polymorphism (SNP) arrays have been employed [19, 145, 146]. These LOH approaches to examining chromosomal change have indicated that substantial genomic instability is already present at the pre-malignant AK stage, with genetic aberrations identified at 3p, 9p, 13q, 17p and 17q [149, 151]. More extensive LOH is observed in CSCC, with frequent 9p loss (75 %) and 3p loss (65 %) [19, 145, 146]. Recurrent losses at 2q, 8p, chromosome 13 and allelic

gain on 3q, 8q and 11q are also consistently recognized [19, 145, 146]. SNP array analysis in a series of 60 CSCC found significantly fewer aberrations in well-differentiated (WD) versus moderately- (MD) or poorly-differentiated (PD) SCC ($p < 0.001$; [145]) and this has now been confirmed by another group [68]. Although specific aberrations,—notably 3p loss, 3q gain and 9q gain—were equally frequent in all groups, WD-SCC clustered separately suggesting a characteristic genotype that is different from MD/PD tumors [145]. This study did not confirm an earlier report that the rate of LOH in CSCC from immunosuppressed organ transplant recipients (OTR) was less than half that observed in CSCC from immunocompetent (IC) patients as assessed by microsatellite analysis [150], although this may be at least partly explained by the higher proportion of WD-CSCC in the OTR group (60 vs 35 %).

Purdie and colleagues [145] also reported a deletion at 9p23 present in 15 % of all tumors overall and 40 % of PD-SCC compared with 7 % of WD-SCC ($p = 0.01$). This microdeletion is within the locus of the protein tyrosine phosphatase receptor delta (PTPRD) gene and deletion or LOH at the PTPRD locus was significantly associated with metastatic potential in a further series of 74 CSCC ($p = 0.007$) and missense mutations were present in 37 % of tumors without homozygous PTPRD deletion [99]. Although these data suggest a possible tumor suppressor role, it is noteworthy that PTPRD partially overlaps a chromosomal location identified as a fragile site [15] and a 'driver' role for PTPRD in CSCC is currently unproven.

Telomere Dysfunction Is Associated with Chromosomal Instability in CSCC

Telomeres are hexanucleotide TTAGGG repeats at chromosome ends and are essential in preserving chromosome integrity; telomere loss and aberrant spatial telomere distribution may be an early event in CSCC formation [19, 108]. Telomere length analysis in AK and CSCC has revealed two distinct CSCC subtypes—short/intermediate homogenous and long/heterogeneous telomere phenotypes [108]. The authors propose that aberrant telomere loss is an early event in a subgroup of AK/CSCC originating in epidermal stem cells which also display the short telomere phenotype and that these subgroups correlate with p53 expression and karyotypic complexity but not telomerase levels [108]. A similar dichotomy was evident in both immunosuppressed and immunocompetent individuals, in contrast to previous data suggesting that telomeres were significantly longer and telomerase levels increased in CSCC from OTRs [137]. Aberrant telomere distribution is also associated with genomic instability: transient clustering of telomeres as telomere aggregates (TAs) contributes to exchange of chromosomal material and the multi-chromosomal translocations seen in CSCC [19]. It may be induced by c-MYC overexpression, which is common in CSCC as a result of 8q isochromosome formation amplifying the *cMYC* oncogene on 8q24 [135, 174]. UV also induces TA formation though reactive oxygen species generation [108].

Gene-Specific Mutations in CSCC

CSCC Harbor Significantly More Mutations than All Other Tumors with the Exception of BCC

UVR is a complete carcinogen sufficient to initiate, promote and progress all stages of squamous carcinogenesis [21]. High rates of C>T transitions and CC to TT double base changes confirm UV-exposure as the primary cause of most mutations in CSCC [21] and the prevalence of these mutations demonstrates both the efficiency of UVR as a mutagen and the remarkable tolerance of human keratinocytes to mutations traditionally regarded as hazardous [166]. Many specific genetic abnormalities have been described in CSCC but, for most, the evidence that they are drivers of CSCC tumorigenesis is lacking. Recent whole exome sequencing studies in CSCC [48, 165] report a burden of approximately 1300 mutations per tumor (equivalent to 1 mutation per 30,000 base pairs of coding sequence). With the exception of BCC [83], this is a significantly greater level of mutation than in any other common human cancer (e.g. fivefold greater than lung cancer) and higher even than tumors with microsatellite instability, which are specifically characterized by hypermutation [181]. This vast mutational burden, together with the karyotypic complexity described above, questions the integrity of DNA repair in contributing to CSCC. However, whole exome sequencing has not found evidence for mutations in DNA excision repair pathway genes or in the DNA polymerase subunit, POLE [165], both of which are prevalent in highly mutated colorectal and endometrial carcinomas [30, 87]. The extensive genomic aberrations and vast number of mutations found in CSCC and, most recently, even in normal sun-exposed skin, have hampered identification of critical drivers and multiple genes and pathways are likely to be involved [116, 165]. Published research has particularly focused on *TP53, NOTCH*, *RAS*, *CDKN2A*, *EGFR*, *TGFß*, *NF-κB*, *src* family kinases and *KNSTRN*. Mitochondrial DNA mutations have also been described and genetic changes relevant to the tumor microenvironment will be discussed briefly.

Sun-Exposed Normal Skin Is a 'Polyclonal Quilt' of Genetic Mutations

Whole exome studies have pointed to a high level of mutations in clinically normal skin [165]. Recent ultra-deep genome sequencing of normal, sun-exposed eyelid skin has confirmed a remarkably high level of somatic mutations, with an average of 2–6 mutations per megabase per cell, a rate similar to that seen in many cancers, with most exhibiting characteristic UV signatures. Many of the key drivers of CSCC have been identified at a density of ~140 driver mutations per square centimeter and include *TP53*, *NOTCH*1–3, *FGFR3*, *FAT1* and *RBM10*, demonstrating tolerance of cancer-causing mutations (most frequently biallelic loss of *NOTCH1*) in more than a quarter of all keratinocytes in sun-exposed skin [116]. This 'polyclonal quilt' of

driver mutations subject to positive selection renders sun-exposed skin a potential field of 'preprocancers' and has important implications for understanding of squamous carcinogenesis and targeted therapy [20].

TP53 Tumor Suppressor Is Mutated Early in Cutaneous Squamous Carcinogenesis

An early and central role in CSCC for the tumor suppressor p53 has been long established, with *TP53* mutations present in 50–90 % [60]. p53 exerts its tumor suppressive functions through induction of apoptosis, cell cycle arrest or senescence. UV-specific mutations in *TP53* are found in normal sun-damaged skin; the size and frequency of such clonal 'patches' of keratinocytes carrying mutant or aberrant p53 protein are related to age and lifetime cumulative UV-exposure [103] and 70 % of p53 patches identified by immunohistochemistry have an underlying *TP53* mutation [86]. Deep sequencing of small epidermal units in sun-exposed normal skin each finds p53 mutations in 14 % of all epidermal cells, with an estimated annual accrual of 35,000 new protein-altering, persistent p53 mutations, suggesting extensive tolerance of keratinocytes to UV-induced genetic damage [166]. Clonal expansion of *TP53* mutant patches in otherwise normal skin appears to be driven by chronic UVB exposure, with preferential sparing of apoptosis-resistant *TP53* mutant cells [22, 192]. *TP53* mutation is also highly prevalent in AK and this is likely to allow accumulation of further genetic damage that would otherwise trigger cell cycle arrest leading to DNA repair or apoptosis. Loss of the second *TP53* allele is a critical event in progression to CSCC [48]. Exome sequencing of 8 primary CSCC found *TP53* mutations in 7 of 8 CSCC and, based on the assumption that the ratio of heterozygous to homozygous mutations in a region of copy neutral LOH directly measures the age of the duplication in evolutionary time, these authors argue that *TP53* mutations occurred and were duplicated before most other mutations arose. They argue that both the expanded mutagenesis and the majority of chromosomal aberrations follow loss of the second TP53 allele because complete loss of p53 function prevents apoptosis allowing the mutagenic insults of ongoing DNA damage to rapidly accumulate [48]. In summary, *TP53* mutations occur in normal sun-exposed skin and are frequent in the earliest stages of UV-squamous carcinogenesis, with biallelic loss or inactivation of *TP53* preceding additional acquisition of mutations and chromosomal aberrations.

NOTCH Genes Are Critical Tumor Suppressors in CSCC

Among its many targets in keratinocytes, p53 induces expression of *NOTCH* genes [107], which increasingly appear to be important tumor suppressors in CSCC [37, 165, 183]. Notch signaling is a highly conserved pathway and regulates many

important cellular processes, including stem cell maintenance, cell fate decisions, growth and survival in a context-dependent manner. In many tissue lineages, Notch signaling enhances stem cell potential and suppresses differentiation, whilst in keratinocytes it exerts an opposite effect and induces keratinocyte differentiation [46]. The mammalian *NOTCH* gene family encodes four transmembrane receptors that are activated by ligand binding and proteolytic cleavage, with release and translocation of the intracellular domain of NOTCH (ICN) to the nucleus where it forms a short-lived transcription activation complex with the DNA-binding factor RBPJ and co-activators of the MAML family [94]. Most Notch signaling is via this canonical pathway but is significantly influenced by gene dose and cellular context [46, 164]. NOTCH1 is expressed in all layers of the epidermis and is a direct transcriptional target of p53 [107]. NOTCH2 is expressed in the basal layer and its contribution to tumor suppression is less clear [46].

It is well established that in T- and B-cell hematological malignancies, including acute T-cell lymphoblastic leukemia/lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma, Notch1 functions as an oncoprotein [54] and oncogenic NOTCH1 signaling targets *MYC* and the PI3K-AKT pathway [96]. In skin, however, Notch acts as a tumor suppressor [42, 107] and multiple mechanisms underlie this function [46, 164]. For example, p21 is an important mediator of NOTCH1-induced cell cycle withdrawal and interferon regulatory factor 6 [153] and p63 [128] modulate Notch pro-differentiation function in keratinocytes. Exome sequencing has identified a high prevalence of biallelic inactivation in *NOTCH1* and *2* genes (and, less frequently 3 and 4), with 75–80 % of CSCC harboring loss-of-function mutations [48, 165, 183]. These studies found inactivation of multiple Notch receptors within the same tumor and this was more frequent in PD- versus WD-SCC suggesting a possible dose effect [165]. This fits with studies in transgenic mice in which conditional deletion of multiple Notch genes yields more profound differentiation and barrier function defects than deletion of any single gene [42] and suggests that multiple mutations may act in concert to progressively disable downstream signaling targets. The timing of these Notch gene mutations is not known, but clonal patches of notch-mutated cells have been identified in normal, sun-exposed skin [116]. Epigenetic dysregulation of the Notch pathway and its role in development of pre-malignancy is discussed below.

RAS Genes Are Key Oncogenes in Mouse Chemical Skin Carcinogenesis, but Their Role in Human CSCC Is Less Clear

TP53 and *NOTCH* genes are important tumor suppressors, but the relevant oncogene(s) driving CSCC is unclear. Three *RAS* proto-oncogenes, *HRAS*, *NRAS* and *KRAS*, are among the most frequently mutated genes in human cancers, with oncogenic activating mutations found characteristically in codons 12, 13 and 61.

Ras molecules are GTP-binding proteins that transduce signals from a number of transmembrane growth factor and extracellular matrix receptors to the nucleus, with downstream signaling through the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways and Ral guanine nucleotide exchange factors. Ras functions in adult murine epidermis to support proliferative capacity and oppose differentiation [172]. Activating mutation in *HRAS* is the initiating event in the mouse chemical carcinogenesis model [90]. However, primary human cells are more resistant to malignant transformation and constitutive signaling from oncogenic *RAS* causes irreversible growth inhibition and /or keratinocyte senescence mediated at least in part by downregulation of the G1 kinase, CD4K [102]. In human models, additional genetic manipulation is necessary to induce invasive CSCC [90, 155, 156]. By either combining Ras activation with CDK4 expression [102] or with IκBα-inhibition of NF-κB [39], Khavari and colleagues have shown efficient transformation of human keratinocytes into invasive CSCC with protein expression changes characteristic of SCC, including decreased E-cadherin and increased VEGF and MMPs [90]; they hypothesize that NF-κB blockade by IκBα overcomes Ras-driven suppression of CDK4 and thus overcomes CDK4-mediated, Ras-induced cell cycle arrest [156].

Although *RAS* clearly has the potential to be an important oncogenic influence in CSCC, the majority of human CSCC and AK do not harbor activating mutations in *H-*, *N-* or *KRAS* genes. The frequency varied in older reports, but more recent studies find *RAS* mutations in 20–21 % of CSCC, most frequently in *HRAS* [9, 165]. Despite this, MAPK pathway induction is frequently found in CSCC at both mRNA and protein level [39, 52, 68, 100, 193]. This disparity suggests that *RAS* may be activated due to upstream events from over-expression of receptor tyrosine kinases or that there may be cross talk from PI3K-AKT-mTOR signaling [24]. This has become particularly relevant with the introduction of small-molecule kinase inhibitors targeting the MAPK pathway for treatment of metastatic melanoma: approximately 50 % of melanomas carry an activating mutation in the *BRAF* gene, usually a *BRAFV600E* mutation and selective *BRAF* inhibitors (vemurafenib, dabrafenib) have yielded impressive, albeit transient, response rates [55]. A striking clinical finding has been the development of multiple squamoproliferative lesions (KA CSCC and warty papillomas) in about 25 % of patients soon after initiation of BRAF inhibition [32]. Experimental evidence suggests that BRAF-blockade, in the presence of an upstream activating mutation in *RAS*, results in paradoxical increased MAPK signaling [75, 168]. Sequencing of candidate genes in vemurafenib-induced KA/CSCC has found an increased frequency of activating *RAS* mutation (35–60 %), especially *HRASQ61L* mutations, compared with sporadic CSCC [130, 165, 168]. This is consistent with the hypothesis that there is paradoxical MAPK signaling from an activated *RAS* in the context of BRAF inhibition in *BRAF* wild-type keratinocytes. These data suggest that *RAS* mutations may be common in UV-exposed skin, but that the majority of RAS-mutated keratinocytes will not clonally expand or progress to invasive

malignancy without additional factors, such as BRAF inhibition or NOTCH1 inactivation [107, 165], to facilitate such progression.

CDKN2A Tumor Suppressor Gene Inactivation Is Common in CSCC

Another common genetic change found in CSCC is inactivation of the *CDKN2A* tumor suppressor gene on 9p21. The frequency of 9p loss identified in CSCC [19, 145, 146] suggests selection for deletion of the *CDKN2A* locus encoding p16INK4a and p14ARF tumor suppressor genes. CDKN2A mutations and progression of AK to CSCC has been hypothesized to correlate with deletion of p16INK4a [122]. CDKN2A mutation frequencies of up to 50 % have been identified in CSCC [25, 161, 165], but are uncommon in normal skin [116, 165]. Although *CDKN2A* may be inactivated via mutation and/or chromosomal loss, epigenetic events such as methylation seem to be at least as frequent as genetic mechanisms for inactivation, as discussed further below [25, 123].

TGF Beta May Have Both Tumor Suppressor and Tumor Promoter Roles in CSCC and Is Closely Involved in Tumor Microenvironment Interactions

There are few genes with more influence on the tumor microenvironment than transforming growth factor beta (TGFβ). TGFβ is a pleiotropic cytokine acting as a potent tumor suppressor in the majority of CSCC, but switching in advanced CSCC to become a potent tumor promoter. Loss-of-function mutations in TGFβ-type 1 receptor (TGFβR1) cause the multiple self-healing epitheliomata of Ferguson-Smith ([63]; Table 1). These are spontaneously resolving malignancies that clinically resemble KA-like CSCC. This may fit with an inhibitory role for TGFβ in proliferative, spontaneously-resolving tumors such as KA, but whether mutations in TGFβR1 are relevant in sporadic KA has not yet been established. The switch to a pro-proliferative TGFβ response may be controlled epigenetically and may be a biomarker for high-risk head and neck SCC [72], but the prognostic implications have not been studied in CSCC. Tumor-promoting activities of TGFβ noted in other cancers include tumor cell proliferation, survival, motility, invasion and maintenance of cancer stem cells [81]. The process of epithelial-mesenchymal transition (EMT) is central to the healing response following wounding and is equally central to tumor invasiveness and aggressive behavior. If TGFβ is the conductor, then EMT is orchestrated in significant part by stromal cells of the tumor microenvironment with important contributions from myofibroblasts, fibroblasts and even adipocytes and involves secreted mediators, particularly the matrix metalloproteinases (MMPs), the tissue inhibitors of MMPs (TIMPs) and disintegrin and metalloproteinase (ADAM) family members [16, 103, 168].

NK-Kappa B May Have Also Have Both Pro- and Anti-Tumorigenic Actions in CSCC

Many studies have suggested a role for the NF-κB family of inducible transcription factors in the development of CSCC, but this remains controversial [39, 90, 156]. NF-κB proteins are important in skin homeostasis, with a complex pathway involving 5 mammalian NF-κB subunits, which form homo- and heterodimers (RelA [p65], p50, p52, RelB and c-Rel), together with upstream regulators including IKBα proteins [45]. The overall effects of NF-κB signaling are highly cell context-dependent and, whilst some in vitro and mouse models support a pro-tumorigenic role in skin [92, 152], there is also evidence for a role in tumor prevention in other models [47, 187]. Although there are contradictory experimental data regarding a role in hyperproliferation of keratinocytes, it is notable that both inhibition and activation of NF-κB in keratinocytes can drive epidermal inflammation. A recent mouse model which exhibits enhanced NF-κB-induced transcriptional responses but remains subject to inhibition by IkB has shown that enhanced NF-κB activity in the absence of additional oncogenic events increases keratinocyte susceptibility to chemical carcinogenesis and AK-like dysplasia (which is TNF-dependent) and KA development (which is TNF-independent) but was not sufficient for CSCC development [140]. The authors speculate that the tumor suppressor activities of NF-κB may be protective against developing invasive CSCC, but that formation of KA through a non-oncogenic proliferative pathway is promoted. In human genome-wide expression studies, genes controlled by NF-κB are upregulated in CSCC and AK, suggesting that activation of the pathway is an early event [68, 100].

Epidermal Growth Factor Receptor (EGFR) Is Overexpressed but Rarely Mutated in CSCC

EGFR signaling is one of the most intensely studied determinants of epithelial cell proliferation and is persistently activated in CSCC [177]. EGFR (HER-1), a member of the ErbB or HER family of receptor tyrosine kinases (RTKs), is aberrantly expressed in many human tumors and in some such as lung, colon and head and neck SCC, targeted molecular therapies to EGFR have proved successful [177, 191]. The extracellular domain binds multiple ligands including EGF and TGFα, producing a conformational change that allows homodimerization or heterodimerization with other HER family members, leading to autophosphorylation, receptor trafficking and signaling to downstream pathways including PI3K-AKT, PI3K-JAK-STAT, RAS-ERK-MAPK, PLCγ-PKC and NF-κB. EGFR activation can occur through gene amplification, activating gene mutations or upregulation of constitutive signaling, for example due to aberrant receptor trafficking or autocrine stimulatory loops [191].

In keratinocytes, EGFR signaling maintains keratinocyte self-renewal and suppresses differentiation in the proliferative compartment of the epidermis, whereas in the upper layers it is downregulated [177]. EGFR activation by ligand binding or UV radiation induces increased cellular proliferation, migration, survival and resistance to apoptosis and is a strong contender as a driver for CSCC. However, reported rates of *EGFR* mutations and amplifications in CSCC are generally low [50, 119, 154, 177]. Ridd reported *EGFR* mutation in 1/40 (2.5 %) CSCC and amplifications in 3/268 (1.1 %) CSCC and *EGFR* overexpression in 19/275 (6.9 %) [154] and Uribe and colleagues found no mutations in 62 CSCC [177]. Cytoplasmic EGFR localization may be evidence of constitutive overexpression due to receptor mutation or dysregulated receptor trafficking/down-regulation [177] and most immunohistochemistry studies find both membranous and cytoplasmic EGFR localization in transformed cells [56]. Toll and colleagues found EGFR amplification in 20 % and overexpression in 78 % of CSCC with evidence of amplification also present in AK [175]. Most recently, Jacobs et al. reported *EGFR* gene amplifications in 14/19 (74 %) of CSCC, a significantly higher level than in KA [82].

Thus, there is evidence of EGFR overexpression in the majority of CSCC, but only low levels of *EGFR* mutation and variable levels of gene amplification and the mechanism(s) driving this EGFR activation are not clear. Several studies have addressed the clinical relevance of EGFR overexpression. In one study a high proportion of primary CSCC that metastasized showed increased levels and/or cytoplasmic localization of EGFR [118]. Sweeney retrospectively reviewed patients with advanced head and neck CSCC and identified EGFR overexpression in 56 % (28/50) of primary CSCC and 58 % (7/12) of lymph node metastases, but EGFR overexpression did not correlate with recurrence or overall survival, [170]. Targeted therapy to EGFR for CSCC is discussed further in Sect. II.

Src Family Kinase (SFK) Signaling Is Upregulated in CSCC

SFKs including Src, Focal Adhesion Kinase (FAK) and Fyn are non-receptor tyrosine kinases that integrate signals from integrins and growth factor receptors and are regulators of cell proliferation, invasion, metastasis and angiogenesis; increased SFK activity is common in human cancers [29]. Fyn transgenic mice spontaneously develop precancerous lesions resembling AKs and CSCC in which three pro-oncogenic signaling pathways are activated: PDK-1/Akt/mTOR, MEK/ERK, and STAT3 and Fyn-induced downregulation of p53 and NOTCH1 represents a strong oncogenic signal that can induce spontaneous skin tumor formation [196]. Src-activating and signaling molecule (Srcasm) is a negative regulator of SFKs, reducing proliferation and promoting differentiation in primary human keratinocytes [111] and increasing Srcasm levels inhibits Fyn-induced skin neoplasia [196]. In humans, elevated Fyn, activated SFK levels [6, 105] and decreased Srcasm levels are found in human AK and CSCC, consistent with a tumor

suppressor role for Srcasm in human CSCC [196]. Finally, in a 3D human CSCC model, E-cadherin suppression, a common event in CSCC development, was linked to upregulated FAK and Src [2].

Kinestrin Mutations Are Found in a Small Proportion of CSCC

Recent evidence has identified *KNSTRN* as a previously unrecognized oncogene [104]. WES of 12 CSCC-normal pairs, validated in 100 CSCC and 5 CSCC cell lines, revealed UV-related *KNSTRN* gene mutations in 19 % CSCC. *KNSTRN* encodes a kinetochore protein and mutations disrupt chromatid cohesion in normal cells, correlate with aneuploidy in clinical samples and enhance tumorigenesis in a mouse model of human Ras-driven SCC. Mutations were not present in normal skin but were detected in 13 % AK and therefore, with *TP53* and *NOTCH*, they appear to be a relatively early event in squamous carcinogenesis [104].

Mitochondrial DNA (mtDNA) Mutations in CSCC

A number of studies have investigated the association between mitochondrial DNA deletions or mutations and CSCC; several regions including displacement or D-loop appear to be involved [47, 73, 144]. Although mitochondrial DNA mutations may be a sensitive biomarker of cumulative UV exposure and oxidative stress [17] and are also reported in arsenic-associated squamous carcinogenesis [106], their correlation with the phenotypic behavior of CSCC has not been investigated.

Genetic Changes Driving AK-CSCC Transition and Metastatic Progression

The molecular factors governing the transition though premalignancy to invasive CSCC are poorly understood [68, 133, 146], yet may potentially provide important targets for developing preventative interventions. Most evidence points to significant similarities between AK and CSCC across the spectrum of molecular changes outlined in previous sections: for example, LOH studies indicate that substantial genomic instability is already present in AK [149, 151] and chromosomal alterations in AK are similar to CSCC, but display less karyotypic complexity [84]; similarly, EGFR protein expression is seen in AK, but levels are higher in CSCC [175]; genes controlled by NF-κB are upregulated in both AK and CSCC, suggesting that activation of the pathway is an early event [68, 100]; the presence of *TP53* and *KNSTRN* mutations at comparable frequencies in AK and SCCs suggest these mutations are also early events [104].

Even fewer data are available for progression to metastatic CSCC, yet this is an area of considerable unmet clinical need. Recent studies of aggressive CSCC [138] and a study of lymph node metastases [110] identified a wide range of potential

oncogenic drivers, including activating mutations in RAS-RAF-MEK-ERK and PI3K/AKT pathways and chromatin remodeling genes [110], for example, *TP53*, *CDKN2A*, *NOTCH1*, *AJUBA*, *HRAS*, *CASP8*, *FAT1*, *and KMT2C* (*MLL3*), *NOTCH2*, *PARD3*, and *RASA1* [138], Although no dominant and clinically targetable oncogenes were clearly identified, given the diversity of oncogenic targets, it is proposed that treatments currently available for other cancer types might also be considered in advanced CSCC [110].

Epigenetic Changes in CSCC

Epigenetic changes are those molecular mechanisms that regulate gene expression without changes in DNA sequence; these heritable modifications to DNA include methylation, histone variants and modifications, chromatin remodeling, nucleosome positioning and microRNA deregulation and they play an important role in early cancer development, progression and metastasis [11, 14, 142, 176]. Unlike genes that are inactivated by nucleotide sequence variation, genes silenced by epigenetic mechanisms remain intact and retain the potential to be reactivated by environmental stimuli or medical intervention.

Progression to invasive and metastatic CSCC is likely to involve epigenetic changes and their characterization has the potential to identify relevant skin cancer biomarkers as well as therapeutic targets [14, 64]. However, until recently, this has been a relatively under-researched area in CSCC.

DNA Methylation and Histone Modifications

DNA methylation and histone modifications play a significant role in the organization of nuclear structure and ultimately influence gene expression. Tumor progression is associated with changes in genomic DNA methylation including global DNA hypomethylation, gene-specific hyper- or hypomethylation and histone modifications. In contrast to other cancers, including head and neck SCC, these epigenetic alterations and their prognostic significance have yet to be systematically studied in CSCC [139, 173, 186].

In many cancers, global hypomethylation occurs together with hypermethylation of CpG-rich sequences associated with gene promoters resulting in the inappropriate transcriptional silencing of critical genes including a variety of tumor suppressor genes. These DNA methylation events represent an important tumor-specific marker occurring early in tumor progression. Because promoter hypermethylation is potentially reversible, the molecules that regulate methylation status of DNA are considered promising targets for new cancer therapies. There is preliminary evidence that global hypomethylation is a feature of CSCC in transplant recipients [98] and there have been studies of individual gene methylation changes in CSCC. For example, promoter hypermethylation of

p16INK4a and *p14ARF* is detected in almost 40 % of tumors, representing the commonest mechanism of *CDKN2A* tumor suppressor gene inactivation known [25]. A higher frequency of *FOXE1* promoter hypermethylation was also found in CSCC compared to normal skin, indicating that *FOXE1* may be a target for aberrant methylation in CSCC [179].

In a recent study using a genome-wide approach, methylation profiles of metastatic CSCC were compared with non-metastatic primary CSCC using a CpG site promoter methylation array [40]. There were no widespread differences in methylation patterns, but differential methylation was identified in the promoter region of *FRZB*, the protein product of which is an antagonist of Wnt signaling. Overexpression is associated with a more differentiated and less invasive tumor phenotypes in gastric, prostate cancer and bladder cancer and it was proposed that *FRZB* methylation is a potential biomarker of tumor aggressiveness or metastatic potential CSCC [40].

The role of *NOTCH1/2* UV-induced mutations in keratinocytes in squamous carcinogenesis has been described earlier in this chapter. Hu and colleagues recently proposed a model in which UVA epigenetically inactivates the Notch pathway in dermal fibroblasts through DNA methylation [78]. They report that these cells develop a cancer-activated fibroblast-like phenotype and secrete fibroblast growth factors, extracellular matrix proteins, and proteases that increase proliferation of overlying epidermal keratinocytes. The latter become enriched with CD45-positive inflammatory cells, which in turn promote keratinocyte proliferation and the emergence of actinic keratosis. These data highlight the central importance of dysregulated Notch in squamous carcinogenesis and also the importance of stroma-tumor interactions in CSCC and suggest that in some cases epigenetic changes in dermal fibroblasts may actually precede the development of CSCC.

In addition to CpG methylation, histone modification plays an active role in regulating gene expression. Histones are dynamic molecules that physically determine whether transcription occurs by either allowing or blocking transcription factor access to promoter regions. Histone post-translational modifications include methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. To date, there is increasing evidence for their significance in head and neck SCC [34, 115], and preliminary data supporting a role in UV-induced skin carcinogenesis [126].

MicroRNA and Long Non Coding RNA Changes in CSCC

Protein coding genes account for approximately 2 % of the human genome, whereas the great majority of transcripts are non-coding RNAs including both microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are emerging as key regulators of mammalian mRNA transcription and/or translation with an important role in cancer.

To date, most studies of the role of noncoding RNAs have focused on microRNAs, a family of short (~22 to 24 nucleotide) regulatory non-protein coding RNA

molecules that act as a class of RNA-interference agents and negatively regulate target proteins at the post-transcriptional level, mainly by annealing with their 3′ untranslated region and causing translational repression or cleavage. Mutation or abnormal expression of miRNAs, which can function as either tumor suppressors or oncogenes, is implicated in various cancers and about 40 % of confirmed miRNAs are proposed regulators of cancer-associated pathways.

Evidence for miRNA dysregulation in CSCC is now emerging [91, 160]. The miRNA profile is altered in CSCC with increased miR21 levels [51, 160], a miR known to play an oncogenic role in other epithelial cancers through suppression of critical tumor suppressors [120]. miR203, an antagonist of p63, was down-regulated in CSCC [51], consistent with upregulated p63 in CSCC and its role in the proliferation and maintenance of epidermal stem cells. miR124 and 214 are also downregulated in CSCC and may be responsible for over expression of ERK1/2 and abnormal cellular proliferation in CSCC [189]. miR-365 is overexpressed and may act as an onco-miR in CSCC; levels correlate inversely with differentiation status and vascular invasion [197]. miR-361-5p is one of the most sensitive miRNAs to UVB irradiation and levels are inversely correlated with VEGFA expression in CSCC in which it has been proposed to play a pathogenic role [88]. miR-125b may act as a tumor suppressor in CSCC in which it is downregulated in the early stages; it suppresses growth and motility of tumor cells through its effects of a network of pro-tumorigenic genes including matrix metalloproteinase (MMP) 13, MMP7 and MAP2K7 [187]. In a more recent publication, 88 cancer-related miRNAs were analyzed in 43 patients with CSCC. miR-135b was the most upregulated (13.3-fold, 21.5-fold; $p=0.0001$). Inhibition or overexpression of miR-135b in functional studies resulted in alterations of its target gene *LZTS1* mRNA and protein levels with decreased or increased cell motility and invasion of both primary and metastatic CSCC cell lines respectively, indicating that miR-135b may function as an oncogene in CSCC [131]. However, results vary considerably between studies as different studies have investigated different miRNAs. For example, in one study, microarray analysis of CSCC compared with normal skin reported significant differential upregulation of miR-135b, 424 and 766 and downregulation of miRs 30a, 378, 145, 140-3p, 30a and 26a [160], whereas in another study, miR-21, 31 and 205 were upregulated and miR 184, 203, 205-5p, let-7a-5p and let-7b-5p downregulated [28]. Much of the discrepant data may be methodological and, despite the apparently low consensus between studies, this is an important area of current research given the potential of microRNA therapies.

LncRNAs are a type of non-coding RNA ranging from 200 to 100,000 nucleotides in length. They have critical roles in development and differentiation as well as in disease, including cancer [31, 80]. They are also known to play an important part normal skin homeostasis [76]. Although there are no systematic data as yet for their regulation and function in CSCC, there is evidence that the lncRNA TINCR, which is highly induced during keratinocyte differentiation, is repressed in SCC compared to normal epidermis, suggesting that TINCR may play a role in repressing neoplastic progression in otherwise predisposed keratinocytes [95].

Immune Surveillance and the Tumor Microenvironment

Although genetic aberrations in keratinocytes are critically important, many aspects of CSCC development and maintenance depend upon immune surveillance by resident and circulating immune cells and also upon interactions between malignant keratinocytes, basement membrane zone components (e.g. collagen VII and adhesion molecules such as cadherins and integrins) and the tumor microenvironment (TME)—the tumour-associated stroma consisting of interstitial extracellular matrix and its cellular components [8, 113, 117, 132]. Cells of diverse lineages are found in the CSCC TME and include infiltrating immune cells, cancer associated fibroblasts, myofibroblasts and vasculature. Substantial data demonstrate extensive 'cross-talk' between these elements involving multiple signaling pathways including TGF-beta, Notch, Wnt/beta-catenin, Shh/Gli3, PDGFC, PI3/AKT-mTOR and p63-FGFR2 [78, 113, 127]. These cellular components together with other TME components such as proteases (including matrix metalloproteinases (MMPs), inhibitors of MMPs (TIMPs) and a disintegrin and metalloproteinase (ADAM) family members), contribute to inhibiting progression of cancer: shifts in the balance of these interactions appear to provide a 'permissive' environment for tumor cells to proliferate, escape host defenses and metastasize and possible opportunities for therapeutic intervention [8, 113, 158]. These topics will be covered in detail in Chap. 4.

Host-Specific Genetic Changes Predisposing to CSCC

Human genome sequencing has raised interest in germ line single nucleotide polymorphisms (SNPs) associated with increased risk of disease. Much research on SNPs and CSCC risk has focused on genes of pigmentation. A recent systematic review has highlighted correlations between SNPs and SCC risk in pigment genes, some of which are retained even after controlling for clinical skin phenotype traits [16]. The melanocortin 1 receptor (MC1R) has been the most extensively studied as it is associated with the phenotype of red hair and freckling, which are clinical risk factors for CSCC. Multiple SNPs in this gene have been associated with CSCC [10, 49, 70, 71]. Agouti signaling peptide (ASIP) is an inverse regulator of MC1R, and SNPs in ASIP also confer risk of CSCC [27, 66, 114, 124, 125].

Polymorphisms in DNA repair genes are also under investigation, given the increased risk for CSCC in patients with xeroderma pigmentosum and other DNA repair deficiencies. There is a trend towards association, but larger studies will be needed to substantiate these findings [62, 159, 184].

MdM2 is a negative regulator of p53; the SNP309 G allele of MdM2 is associated with an increased risk of CSCC [1]. Other polymorphisms under investigation include those in the vitamin D receptor and methylenetetrahydrofolate reductase (MTFHR) pathways [43, 69]. Interferon regulatory factor 4 has also emerged as a potential locus for CSCC risk [71, 194].

It is not currently clear whether SNP genotyping will improve screening recommendations for CSCC. Currently, dermatologists stratify patient risk by skin coloring and propensity to burn and tan with UV exposure [61]. Some genes of pigmentation appear to confer CSCC risk independent of pigmentary phenotype, but additional research is needed. This field is rapidly evolving; future studies may allow improved patient-based risk prediction.

Section II: Therapeutic Implications

Chapter 10 provides a discussion of current chemotherapeutic options for advanced or unresectable CSCC. This section gives a brief overview in the context of the discussion of CSCC genetics above and a summary of ongoing clinical investigation.

Understanding the genetic and molecular pathogenesis of CSCC will have immediate clinical relevance. Specific mutations or aberrantly expressed proteins can serve as diagnostic markers, and may some day serve as prognostic biomarkers. The progression from AK to CSCC is of particular interest, as a targeted therapy for AK may prevent or reverse progression to invasive cancer since 65 % of CSCC have been shown to arise from AK precursors [38].

Targeting the molecular aberrations in invasive SCC will enable systemic therapy for those tumors not amenable to surgical excision or curative radiation therapy. Traditional chemotherapeutic approaches, primarily platinum-based regimens, are highly toxic and non-specific, and there are no predictive biomarkers of response to treatment. The advent of molecular targeted therapy has changed the therapeutic landscape for cancer. Although no molecular therapies have yet been approved to specifically target CSCC, the pathways described above can inform trials with existing agents or development of novel drugs. These may include antibodies or small molecule tyrosine kinase inhibitors (TKI). Given the large mutational burden of CSCC and the lack of knowledge regarding clear driving mutations at this time, targeted therapeutic agents may need to be combined with radiation and/or traditional chemotherapy to achieve optimal control. Clinical trials have been notably lacking for advanced, unresectable CSCC. Studies to date are summarized below. Several new trials are ongoing which may provide more clinical options for patients in the near future.

Epidermal Growth Factor Receptor Inhibitors

As described above, the majority of CSCC show evidence of EGFR overexpression with low levels of EGFR mutation or gene amplification. Inhibition of EGFR inhibits activation of the Ras signaling cascade. Activating Ras mutation can overcome EGFR inhibition, but activating Ras mutation is rare in primary human CSCC [165]. Thus EGFR inhibition is an attractive therapeutic option, and indeed, the majority

of research in targeted therapy for CSCC has focused on this class of inhibitors. There are two types of EGFR inhibitors, monoclonal antibodies and tyrosine kinase inhibitors (TKIs).

Monoclonal Antibody Inhibitors of EGFR

Cetuximab (Erbitux, Bristol-Meyers Squibb, Eli Lilly) is a chimeric human-mouse monoclonal IgG1 anti-EGFR antibody approved by the US Food and Drug Administration (FDA) for mucosal (oronasopharyngeal) SCC of the head and neck as well as colorectal cancer. Cetuximab binds the extracellular domain of EGFR, preventing ligand binding, EGFR dimerization, and downstream signaling. Cetuximab has been reported to be effective in case reports and small, uncontrolled series for locally advanced or metastatic CSCC. In addition, a phase II trial of 36 patients with unresectable CSCC utilizing cetuximab monotherapy demonstrated a 69 % disease control rate at 6 weeks [118], but further studies are needed to demonstrate duration of response. Cetuximab is a known radiosensitizing agent [79], and use has been reported with concurrent radiation for CSCC [59]. No clinical trials have been performed with concurrent cetuximab and radiation, but radiation enhancement may potentially be extrapolated from the head and neck SCC literature.

In colorectal cancer, predictive biomarkers for success with cetuximab include presence of EGFR in the tumor and wild-type K-ras [12] and BRAF [44]. The rationale is that these mutations constitutively activate the downstream MAPK pathway independent of EGFR activity. While EGFR mutation has not been definitively associated with response to EGFR inhibitors in head and neck mucosal SCC, increased tumor EGFR expression does predict response to treatment [162]. Exploratory analyses have yet to identify biomarkers for CSCC response to cetuximab, though there is a single report of a patient with activating *HRAS* mutation who did not respond to therapy [118].

Panitumumab (Vectibix, Amgen) is a human IgG2 monoclonal anti-EGFR antibody approved for colorectal cancer. In a phase II study of 16 patients receiving panitumumab monotherapy for unresectable disease, there was a 31 % overall response rate and 38 % stable disease rate. The median progression free survival was 8 months and overall survival was 11 months [57].

Tyrosine Kinase Inhibitors of EGFR

Gefitinib (Iressa, AstraZeneca) is an EGFR inhibitor approved for non-small cell lung cancer. A phase II trial of neoadjuvent gefitinib prior to surgery or radiation in 23 patients with unresectable CSCC demonstrated an 18 % complete response rate and 27 % partial response rate [109]. A single case has been reported in which gefitinib offered 30-month progression-free survival (PFS), at which point addition of the mTOR inhibitor sirolimus (Rapamune, Pfizer) provided an additional 12 month

PFS [18]. This multi-pathway approach is under examination in other tumor types and deserves future study in CSCC.

Erlotinib (Tarceva, Genentech) is another EGFR inhibitor approved for non-small cell lung and pancreatic cancer. A phase I toxicity study of erlotinib with radiation in 15 patients with stage III CSCC demonstrated an acceptable toxicity profile and 2-year disease-free survival of 60 % [74] representing the best control rates to date. Both gefitinib and erlotinib bind the ATP-binding site of EGFR, inhibiting activation of the Ras signaling cascade. A single center phase II study is currently in progress for recurrent or metastatic CSCC (NCT01198028) and as neo-adjuvent treatment before surgery or radiation (NCT01059305).

Lapatinib (Tykerb/Tyverb, GlaxoSmithKline) is a third EGFR inhibitor approved for breast cancer in combination with capecitabine (Xeloda, Roche). There are no published data on lapatinib for CSCC.

Future Therapeutic Directions

Beyond EGFR inhibition, targeted therapy for CSCC is still largely investigational. Dasatinib (Sprycel, Bristol-Myers Squibb) is a multi-kinase inhibitor that targets BCR/Abl and Src family tyrosine kinases and is approved for chronic myelogenous leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia. In a single-center phase II study for dasatinib in unresectable or metastatic CSCC, none of the seven patients enrolled survived long enough to achieve response (NCT00563290; T. Olencki, personal communication).

TP53 and *NOTCH* have been implicated as major tumor suppressors in CSCC, but they are less attractive targets for therapy as these mutations result in loss of function, which is difficult to restore, although research is ongoing in this area [67, 171]. Future research will need to identify downstream targets that are aberrantly upregulated in *TP53*- or *NOTCH*-mutant tumors, as these may be targets for inhibition.

MAPK pathway induction in CSCC provides another avenue for targeted therapy. Activating Ras mutation is rare in sporadic CSCC but appears to be more common in vemurafenib-associated CSCC. There are currently no specific Ras inhibitors available, but these may be developed in the future. Meanwhile, there are experimental data to suggest that the drug metformin, a biguanide commonly used in diabetes, may prevent squamous carcinogenesis by inhibiting MAPK in addition to NFKB and mTOR signaling pathways [33]. Any targeting downstream of Ras should probably be given in combination with PI3K inhibitors, EGFR inhibitors, or mTOR inhibitors to prevent compensatory increase in PI3K-AKT signaling.

The mTOR pathway is also activated in CSCC and is targeted by mTOR inhibitors such as rapamycin (sirolimus) and everolimus. These drugs are associated with a reduced CSCC burden in organ transplant recipients in whom they are used in place of calcineurin inhibitors as immunosuppressive agents to prevent allograft rejection [5, 53, 77] although the mechanisms responsible have yet to be fully characterized [41, 65, 169, 182].

Epigenetic mechanisms of squamous carcinogenesis may be amenable to therapeutic intervention particularly given that, in contrast to DNA mutations, they are potentially reversible. Demethylating agents have been successfully used in a range of cancers and may theoretically be beneficial in the treatment or prevention of CSCC, although this remains to be investigated. Vorinostat, a potent histone deacetylase inhibitor has already shown anti-cancer activity in a xenograft model of CSCC and its action may also be through inhibition of the mTOR and MAPK signaling pathways [97]. miRNAs regulate multiple target genes simultaneously potentially making miRNA-based treatments for CSCC more promising targets for future development than traditional single target therapy. However, the side-effect profile of drugs with more broad-based effects may also be potentially limiting.

Conclusions

Despite significant progress in recent years in understanding the genomic basis of cutaneous squamous carcinogenesis, much remains uncertain. The emerging molecular landscape of CSCC underscores the high mutational burden, dysregulation of multiple signaling pathways and tumor heterogeneity and this, together with recent evidence of high levels of mutation in potential oncogenic drivers in UV-exposed normal skin, has presented significant challenges in terms of identifying druggable cancer drivers and predictive biomarkers for targeted therapies. Nonetheless, the prospect of 'precision medicine' for CSCC treatment and prevention may be drawing closer.

References

1. Almquist LM, Karagas MR, Christensen BC, et al. The role of TP53 and MDM2 polymorphisms in TP53 mutagenesis and risk of non-melanoma skin cancer. Carcinogenesis. 2011;32(3):327–30.
2. Alt-Holland A, Sowalsky AG, et al. Suppression of E-cadherin function drives the early stages of Ras-induced squamous cell carcinoma through upregulation of FAK and Src. J Invest Dermatol. 2011;131(11):2306–15.
3. Aractingi S, Kanitakis J, et al. Skin carcinoma arising from donor cells in a kidney transplant recipient. Cancer Res. 2005;65(5):1755–60.
4. Ashton KJ, Weinstein SR, et al. Chromosomal aberrations in squamous cell carcinoma and solar keratoses revealed by comparative genomic hybridization. Arch Dermatol. 2003;139(7):876–82.
5. Athar M, Kopelovich L. Rapamycin and mTORC1 inhibition in the mouse: skin cancer prevention. Cancer Prev Res (Phila). 2011;4(7):957–61.
6. Ayli EE, Li W, Brown TT, Witkiewicz A, Elenitsas R, Seykora JT. Activation of Src-family tyrosine kinases in hyperproliferative epidermal disorders. J Cutan Pathol. 2008;35(3):273–7. doi:10.1111/j.1600-0560.2007.00807.x.

7. Bailleul B et al. Skin hyperkeratosis and papilloma formation in transgenic mice expressing a ras oncogene from a suprabasal keratin promoter. Cell. 1990;62(4):697–708.
8. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. J Cell Sci. 2012;125:5591–6.
9. Bamford S, Dawson E, et al. The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. Br J Cancer. 2004;91(2):355–8.
10. Bastiaens MT, ter Huurne JA, et al. Melanocortin-1 receptor gene variants determine the risk of nonmelanoma skin cancer independently of fair skin and red hair. Am J Hum Genet. 2001;68(4):884–94.
11. Baylin SB, Jones PA. A decade of exploring the cancer epigenome—biological and translational implications. Nat Rev Cancer. 2011;11:726–34.
12. Benvenuti S, Sartore-Bianchi A, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res. 2007;67(6):2643–8.
13. Bergers G, Brekken R, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol. 2000;2(10):737–44.
14. Besaratinia A, Tommasi S. Epigenetics of human melanoma: promises and challenges. J Mol Cell Biol. 2014;6(5):356–67.
15. Bignell GR, Greenman CD, et al. Signatures of mutation and selection in the cancer genome. Nature. 2010;463(7283):893–8.
16. Binstock M, Hafeez F, Metchnikoff C, Arron ST. Singlenucleotide polymorphisms in pigment genes and non melanoma skin cancer predisposition: a systematic review. Br J Dermatol. 2014;171:713–21.
17. Birch-Machin MA, Russell EV, Latimer JA. Mitochondrial DNA damage as a biomarker for ultraviolet radiation exposure and oxidative stress. Br J Dermatol. 2013;2:9–14.
18. Bossi P, Resteghini C, Perrone F, Cortelazzi B, Pilotti S, Maurichi A, et al. Prolonged response using gefitinib followed by sirolimus for advanced cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2012;67(5):226–8.
19. Boukamp P. Non-melanoma skin cancer: what drives tumor development and progression? Carcinogenesis. 2005;26:1657–67.
20. Brash DE. Preprocancer. Science. 2015;348(6237):867–8.
21. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A. 1991;88(22):10124–8.
22. Brash DE, Zhang W, et al. Colonization of adjacent stem cell compartments by mutant keratinocytes. Semin Cancer Biol. 2005;15(2):97–102.
23. Brittan M et al. Bone marrow cells engraft within the epidermis and proliferate in vivo with no evidence of cell fusion. J Pathol. 2005;205(1):1–13.
24. Britten CD. PI3K and MEK inhibitor combinations: examining the evidence in selected tumor types. Cancer Chemother Pharmacol. 2013;71(6):1395–409.
25. Brown VL, Harwood CA, Crook T, Cronin JG, Kelsell DP, Proby CM. p16INK4a and p14ARF tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma. J Invest Dermatol. 2004;122(5):1284–92.
26. Brown K, Strathdee D, et al. The malignant capacity of skin tumours induced by expression of a mutant H-ras transgene depends on the cell type targeted. Curr Biol. 1998;8(9): 516–24.
27. Brudnik U, Branicki W, et al. The contribution of melanocortin 1 receptor gene polymorphisms and the agouti signalling protein gene 8818A>G polymorphism to cutaneous melanoma and basal cell carcinoma in a Polish population. Exp Dermatol. 2009; 18(2):167–74.
28. Bruegger C, Kempf W, et al. MicroRNA expression differs in cutaneous squamous cell carcinomas and healthy skin of immunocompetent individuals. Exp Dermatol. 2013;22(6): 426–8.

29. Brunton VG, Frame MC. Src and focal adhesion kinase as therapeutic targets in cancer. Curr Opin Pharmacol. 2008;8(4):427–32.
30. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330–7.
31. Cao W, Wu W, Shi F, Chen X, Wu L, Yang K, et al. Integrated analysis of long noncoding RNA and coding RNA expression in esophageal squamous cell carcinoma. Int J Genomics. 2013;2013:480534. doi:10.1155/2013/480534.
32. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16.
33. Chaudhary SC, Kurundkar D, Elmets CA, Kopelovich L, Athar M. Metformin, an antidiabetic agent reduces growth of cutaneous squamous cell carcinoma by targeting mTOR signaling pathway. Photochem Photobiol. 2012;88(5):1149–56.
34. Chen YW, Kao SY, Wang HJ, Yang MH. Histone modification patterns correlate with patient outcome in oral squamous cell carcinoma. Cancer. 2013;119(24):4259–67. doi:10.1002/cncr.28356.
35. Clausen OP, Aass HC, et al. Are keratoacanthomas variants of squamous cell carcinomas? A comparison of chromosomal aberrations by comparative genomic hybridization. J Invest Dermatol. 2006;126(10):2308–15.
36. Colmont CS, Harding KG, et al. Human skin cancer stem cells: a tale of mice and men. Exp Dermatol. 2012;21(8):576–80.
37. Connolly K, Manders P, Earls P, Epstein RJ. Papillomavirus-associated squamous skin cancers following transplant immunosuppression: one Notch closer to control. Cancer Treat Rev. 2014;40(2):205–14. doi:10.1016/j.ctrv.2013.08.005.
38. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF, et al. Actinic keratoses: natural history and risk of malignant transformation in the veterans affairs topical tretinoin chemoprevention trial. Cancer. 2009;115(11):2523–30.
39. Dajee M, Lazarov M, et al. NF-kappaB blockade and oncogenic Ras trigger invasive human epidermal neoplasia. Nature. 2003;421(6923):639–43.
40. Darr OA, Colacino JA, Tang AL, McHugh JB, Bellile EL, Bradford CR, et al. Epigenetic alterations in metastatic cutaneous carcinoma. Head Neck. 2015;37(7):994–1001. doi:10.1002/hed.23701.
41. de Gruijl FR, Koehl GE, et al. Early and late effects of the immunosuppressants rapamycin and mycophenolate mofetil on UV carcinogenesis. Int J Cancer. 2010;127(4):796–804.
42. Demehri S, Turkoz A, Kopan R. Epidermal Notch1 loss promotes skin tumorigenesis by impacting the stromal microenvironment. Cancer Cell. 2009;16(1):55–66. doi:10.1016/j.ccr.2009.05.016.
43. Denzer N, Vogt T, et al. Vitamin D receptor (VDR) polymorphisms and skin cancer: a systematic review. Dermatoendocrinol. 2011;3(3):205–10.
44. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26(35):5705–12.
45. Dixit V, Mak TW. NF-kappaB signaling. Many roads lead to Madrid. Cell. 2002;111(5):615–9.
46. Dotto GP. Notch tumor suppressor function. Oncogene. 2008;27(38):5115–23.
47. Durham SE, Krishnan KJ, et al. Mitochondrial DNA damage in non-melanoma skin cancer. Br J Cancer. 2003;88(1):90–5.
48. Durinck S, Ho C, et al. Temporal dissection of tumorigenesis in primary cancers. Cancer Discov. 2011;1(2):137–43.
49. Dwyer T, Stankovich JM, Blizzard L, FitzGerald LM, Dickinson JL, Reilly A, et al. Does the addition of information on genotype improve prediction of the risk of melanoma and non-melanoma skin cancer beyond that obtained from skin phenotype? Am J Epidemiol. 2004;159(9):826–33.

50. Dziunycz PJ, Lazarova Z, Duncan N, Wong S, Neuberg M, Hofbauer GF, et al. EGFRvIII expression in squamous cell carcinoma of the skin. JAMA Dermatol. 2013;149:1240–2.
51. Dziunycz P et al. Squamous cell carcinoma of the skin shows a distinct microRNA profile modulated by UV radiation. J Invest Dermatol. 2010;130(11):2686–9.
52. Einspahr JG, Calvert V, et al. Functional protein pathway activation mapping of the progression of normal skin to squamous cell carcinoma. Cancer Prev Res (Phila). 2012;5(3): 403–13.
53. Euvrard S, Morelon E, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367(4):329–39.
54. Fabbri G, Rasi S, Rossi D, Trifonov V, Khiabanian H, Ma J, et al. Analysis of the chronic lymphocytic leukemia coding genome: role of NOTCH1 mutational activation. J Exp Med. 2011;208(7):1389–401.
55. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363(9):809–19.
56. Fogarty GB, Conus NM, et al. Characterization of the expression and activation of the epidermal growth factor receptor in squamous cell carcinoma of the skin. Br J Dermatol. 2007;156(1):92–8.
57. Foote MD, McGrath M, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann Oncol. 2014;25(10):2047–52.
58. Gerstenblith MR, Goldstein AM, Tucker MA. Hereditary genodermatoses with cancer predisposition. Hematol Oncol Clin North Am. 2010;24(5):885–906.
59. Giacchero D, Barriere J, et al. Efficacy of cetuximab for unresectable or advanced cutaneous squamous cell carcinoma–a report of eight cases. Clin Oncol (R Coll Radiol). 2011;23(10): 716–8.
60. Giglia-Mari G, Sarasin A. TP53 mutations in human skin cancers. Hum Mutat. 2003;21(3):217–28.
61. Gogia R, Binstock M, Hirose R, Boscardin WJ, Chren MM, Arron ST. Fitzpatrick skin phototype is an independent predictor of squamous cell carcinoma risk after solid organ transplantation. J Am Acad Dermatol. 2013;68(4):585–91.
62. Goode EL, Ulrich CM, et al. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev. 2002;11(12):1513–30.
63. Goudie DR, D'Alessandro M, Merriman B, Lee H, Szeverényi I, Avery S, et al. Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1. Nat Genet. 2011;43(4):365–9.
64. Greenberg ES, Chong KK, Huynh KT, Tanaka R, Hoon DS. Epigenetic biomarkers in skin cancer. Cancer Lett. 2014;342(2):170–7. doi:10.1016/j.canlet.2012.01.020.
65. Guba M, von Breitenbuch P, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med. 2002;8(2):128–35.
66. Gudbjartsson DF, Sulem P, Stacey SN, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet. 2008;40:886–91.
67. Guinea-Viniegra J, Zenz R, et al. Differentiation-induced skin cancer suppression by FOS, p53, and TACE/ADAM17. J Clin Invest. 2012;122(8):2898–910.
68. Hameetman L, Commandeur S, et al. Molecular profiling of cutaneous squamous cell carcinomas and actinic keratoses from organ transplant recipients. BMC Cancer. 2013;13:58. doi:10.1186/1471-2407-13-58.
69. Han J, Colditz GA, et al. Polymorphisms in the MTHFR and VDR genes and skin cancer risk. Carcinogenesis. 2007;28(2):390–7.
70. Han J, Kraft P, et al. Melanocortin 1 receptor variants and skin cancer risk. Int J Cancer. 2006;119(8):1976–84.
71. Han J, Qureshi AA, Nan H, Zhang J, Song Y, Guo Q, et al. A germline variant in the interferon regulatory factor 4 gene as a novel skin cancer risk locus. Cancer Res. 2011;71(5): 1533–9.

72. Hannigan A, Smith P, et al. Epigenetic downregulation of human disabled homolog 2 switches TGF-beta from a tumor suppressor to a tumor promoter. J Clin Invest. 2010;120(8):2842–57.
73. Harbottle A, Birch-Machin M. Real-time PCR analysis of a 3895 bp mitochondrial DNA deletion in nonmelanoma skin cancer and its use as a quantitative marker for sunlight exposure in human skin. Br J Cancer. 2006;94(12):1887–93.
74. Heath CH, Deep NL, et al. Phase 1 study of erlotinib plus radiation therapy in patients with advanced cutaneous squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2013;85(5):1275–81.
75. Heidorn SJ, Milagre C, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. Cell. 2010;140(2):209–21.
76. Hombach S, Kretz M. The non-coding skin: exploring the roles of long non-coding RNAs in epidermal homeostasis and disease. Bioessays. 2013;35(12):1093–100. doi:10.1002/bies.201300068.
77. Hoogendijk-can den Akker JM, Harden PN, Hoitsma AJ, Proby CM, Wolterbeek R, Bouwes Bavinck JN, et al. Two-year randomiszed controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. J Clin Oncol. 2013;31(10):1317–23.
78. Hu B, Castillo E, et al. Multifocal epithelial tumors and field cancerization from loss of mesenchymal CSL signaling. Cell. 2012;149(6):1207–20.
79. Huang SM, Bock JM, et al. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res. 1999;59(8):1935–40.
80. Huarte M, Rinn JL. Large non-coding RNAs: missing links in cancer? Hum Mol Genet. 2010;19(R2):R152–61.
81. Inman GJ. Switching TGFbeta from a tumor suppressor to a tumor promoter. Curr Opin Genet Dev. 2011;21(1):93–9.
82. Jacobs MS, Persons DL, Fraga GR. EGFR and MYC gene copy number aberrations are more common in squamous cell carcinoma than keratoacanthoma: a FISH study. J Cutan Pathol. 2013;40(5):447–54.
83. Jayaraman SS, Rayhan DJ, Hazany S, Kolodney MS. Mutational landscape of basal cell carcinomas by whole-exome sequencing. J Invest Dermatol. 2014;134(1):213–20. doi:10.1038/jid.2013.276.
84. Jin Y, Jin C, Salemark L, Wennerberg J, Persson B, Jonsson N. Clonal chromosome abnormalities in premalignant lesions of the skin. Cancer Genet Cytogenet. 2002;136(1):48–52.
85. Jin H et al. A homing mechanism for bone marrow-derived progenitor cell recruitment to the neo-vasculature. J Clin Invest. 2006;116(3):652–62.
86. Jonason AS, Kunala S, et al. Frequent clones of p53-mutated keratinocytes in normal human skin. Proc Natl Acad Sci U S A. 1996;93(24):14025–9.
87. Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
88. Kanitz A, Imig J, Dziunycz PJ, Primorac A, Galgano A, Hofbauer GF, et al. The expression levels of microRNA-361-5p and its target VEGFA are inversely correlated in human cutaneous squamous cell carcinoma. PLoS One. 2012;7(11):e49568.
89. Kessenbrock K, Plaks V, et al. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell. 2010;141(1):52–67.
90. Khavari PA. Modelling cancer in human skin tissue. Nat Rev Cancer. 2006;6(4):270–80.
91. Kim DJ, Angel JM, Sano S, DiGiovanni J. Squamous cell carcinoma of the skin shows a distinct microRNA profile modulated by UV radiation. Oncogene. 2009;28(7):950–60.
92. Kim H, Casta A, Tang X, Luke CT, Kim AL, et al. Loss of hairless confers susceptibility to UVB-induced tumorigenesis via disruption of NF-kappaB signaling. PLoS One. 2012;7(6):e22761871.

93. Knoch J, Kamenisch Y, Kubisch C, Berneburg M. Rare hereditary diseases with defects in DNA-repair. Eur J Dermatol. 2012;22(4):443–55. doi:10.1684/ejd.2012.1654.
94. Kopan R, Ilagan MX. The canonical Notch signaling pathway: unfolding the activation mechanism. Cell. 2009;137(2):216–33.
95. Kretz M, Siprashvili Z, Chu C, Webster DE, et al. Control of somatic tissue differentiation by the long non-coding RNA TINCR. Nature. 2013;493:231–5.
96. Kridel R, Meissner B, Rogic S, Boyle M, Telenius A, Woolcock B, et al. Whole transcriptome sequencing reveals recurrent NOTCH1 mutations in mantle cell lymphoma. Blood. 2012;119(9):1963–71.
97. Kurundkar D, Srivastava RK, et al. Vorinostat, an HDAC inhibitor attenuates epidermoid squamous cell carcinoma growth by dampening mTOR signaling pathway in a human xenograft murine model. Toxicol Appl Pharmacol. 2013;266(2):233–44.
98. Laing ME, Cummins R, O'Grady A, O'Kelly P, Kay W, Murphy GM. Aberrant DNA methylation associated with MTHFR C677T genetic polymorphism in cutaneou squamous cell carcinoma in renal transplant patients. Br J Dermatol. 2010;163(2):345–52.
99. Lambert SR, Harwood CA, et al. Metastatic cutaneous squamous cell carcinoma shows frequent deletion in the protein tyrosine phosphatase receptor Type D gene. Int J Cancer. 2012;131(3):E216–26.
100. Lambert SR, Mladkova N, Gulati A, Hamoudi R, Purdie K, Cerio R, et al. Key differences identified between actinic keratosis and cutaneous squamous cell carcinoma by transcriptome profiling. Br J Cancer. 2014;110(2):520–9.
101. Lapouge G, Youssef KK, et al. Identifying the cellular origin of squamous skin tumors. Proc Natl Acad Sci U S A. 2011;108(18):7431–6.
102. Lazarov M, Kubo Y, et al. CDK4 coexpression with Ras generates malignant human epidermal tumorigenesis. Nat Med. 2002;8(10):1105–14.
103. le Pelletier F, Soufir N, de La Salmoniere P, Janin A, Basset-Seguin N. p53 Patches are not increased in patients with multiple nonmelanoma skin cancers. J Investig Dermatol. 2001;117(5):1324–5.
104. Lee CS, Bhaduri A, et al. Recurrent point mutations in the kinetochore gene KNSTRN in cutaneous squamous cell carcinoma. Nat Genet. 2014;46(10):1060–2.
105. Lee JH, Pyon JK, Kim DW, Lee SH, Nam HS, Kim CH, et al. Elevated c-Src and c-Yes expression in malignant skin cancers. J Exp Clin Cancer Res. 2010;29:116. doi:10.1186/1756-9966-29-116.
106. Lee CH, Wu SB, et al. Involvement of mtDNA damage elicited by oxidative stress in the arsenical skin cancers. J Invest Dermatol. 2013;133(7):1890–900.
107. Lefort K, Mandinova A, et al. Notch1 is a p53 target gene involved in human keratinocyte tumor suppression through negative regulation of ROCK1/2 and MRCKalpha kinases. Genes Dev. 2007;21(5):562–77.
108. Leufke C, Leykauf J, et al. The telomere profile distinguishes two classes of genetically distinct cutaneous squamous cell carcinomas. Oncogene. 2014;33(27):3506–18. doi:10.1038/onc.2013.323.
109. Lewis CM, Glisson BS, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. Clin Cancer Res. 2012;18(5):1435–46.
110. Li YY, Hanna GJ, Laga AC, et al. Genomic analysis of metastatic cutaneous squamous cell carcinoma. Clin Cancer Res. 2015;21(6):1447–56. doi:10.1158/1078-0432.CCR-14-1773.
111. Li W, Marshall C, et al. Srcasm modulates EGF and Src-kinase signaling in keratinocytes. J Biol Chem. 2005;280(7):6036–46.
112. Li J, Wang K, et al. Array comparative genomic hybridization of keratoacanthomas and squamous cell carcinomas: different patterns of genetic aberrations suggest two distinct entities. J Invest Dermatol. 2012;132(8):2060–6.
113. Lim YZ, South AP. Tumour-stroma crosstalk in the development of squamous cell carcinoma. Int J Biochem Cell Biol. 2014;53C:450–8. doi:10.1016/j.biocel.2014.06.012.

114. Lin W, Qureshi AA, Kraft P, Nan H, Guo Q, Hu FB, et al. ASIP genetic variants and the number of non-melanoma skin cancers. Cancer Causes Control. 2011;22(3):495–501.
115. Marcinkiewicz KM, Gudas LJ. Altered histone mark deposition and DNA methylation at homeobox genes in human oral squamous cell carcinoma. J Cell Physiol. 2014;229(10):1405–16. doi:10.1002/jcp.24577.
116. Martincorena I, Roshan A, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science. 2015;348(6237):880–6.
117. Martins VL, JVyas JJ, et al. Increased invasive behaviour in cutaneous squamous cell carcinoma with loss of basement-membrane type VII collagen. J Cell Sci. 2009;122(Pt 11):1788–99.
118. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011;29(25):3419–26.
119. Maurer A, Herschberger E, et al. Low incidence of EGFR and HRAS mutations in cutaneous squamous cell carcinomas of a German cohort. Exp Dermatol. 2011;20(10):848–50.
120. Moriyama T, Ohuchida K, Mizumoto K, Yu J, Sato N, Nabae T, et al. MicroRNA-21 modulates biological functions of pancreatic cancer cells including their proliferation, invasion, and chemoresistance. Mol Cancer Ther. 2009;8(5):1067–74.
121. Morris RJ, Coulter K, Tryson K, Steinberg SR. Evidence that cutaneous carcinogen-initiated epithelial cells from mice are quiescent rather than actively cycling. Cancer Res. 1997;57(16):3436–43.
122. Mortier L, Marchetti P, et al. Progression of actinic keratosis to squamous cell carcinoma of the skin correlates with deletion of the 9p21 region encoding the p16(INK4a) tumor suppressor. Cancer Lett. 2002;176(2):205–14.
123. Murao K, Kubo Y, Ohtani N, Hara E, Arase S. Epigenetic abnormalities in cutaneous squamous cell carcinomas: frequent inactivation of the RB1/p16 and p53 pathways. Br J Dermatol. 2006;155(5):999–1005.
124. Nan H, Kraft P, et al. Genetic variants in pigmentation genes, pigmentary phenotypes, and risk of skin cancer in Caucasians. Int J Cancer. 2009;125(4):909–17.
125. Nan H, Qureshi AA, et al. Melanoma susceptibility variants on chromosome 20q11.22 are associated with pigmentary traits and the risk of nonmelanoma skin cancer. Br J Dermatol. 2010;162(2):461–3.
126. Nandakumar V, Vaid M, Tollefsbol TO, Katiyar SK. Aberrant DNA hypermethylation patterns lead to transcriptional silencing of tumor suppressor genes in UVB-exposed skin and UVB-induced skin tumors of mice. Carcinogenesis. 2011;32(4):597–604. doi:10.1093/carcin/bgq282.
127. Ng Y-Z, Dayal JHS, South AP. Genetic predisposition to cutaneous squamous cell carcinoma. In: Caterina AM La Porta, editor. Skin cancers – risk factors, prevention and therapy. Croatia: InTech; 2011. ISBN: 978-953-307-722-972. http://www.intechopen.com/books/skin-cancers-risk-factors-prevention-and-therapy/genetic-predisposition-to-cutaneous-squamous-cell-carcinoma.
128. Nguyen BC, Lefort K, Mandinova A, Antonini D, Devgan V, Della Gatta G, et al. Cross-regulation between Notch and p63 in keratinocyte commitment to differentiation. Genes Dev. 2006;20:1028–42.
129. Nikolaou V, Stratigos AJ, Tsao H. Hereditary nonmelanoma skin cancer. Semin Cutan Med Surg. 2012;31(4):204–10.
130. Oberholzer PA, Kee D, et al. RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. J Clin Oncol. 2012;30(3):316–21.
131. Olascz EB, Seline LN, Schock AM, et al. MicroRNA-135b regulates Leucine Zipper Tumor suppressor 1 in cutaneous squamous cell carcinoma. PLoS One. 2015;10(5):e0125412.
132. Ortiz-Urda S, Garcia J, Green CL, et al. Type VII collagen is required for Ras-driven human epidermal tumorigenesis. Science. 2005;307:1773–6.

133. Padilla RS, Sebastian S, et al. Gene expression patterns of normal human skin, actinic keratosis, and squamous cell carcinoma: a spectrum of disease progression. Arch Dermatol. 2010;146(3):288–93.
134. Patel GK, Yee CL, et al. Identification and characterization of tumor-initiating cells in human primary cutaneous squamous cell carcinoma. J Invest Dermatol. 2012;132(2):401–9.
135. Pelisson I, Soler C, et al. A possible role for human papillomaviruses and c-myc, c-Ha-ras, and p53 gene alterations in malignant cutaneous lesions from renal transplant recipients. Cancer Detect Prev. 1996;20(1):20–30.
136. Pelizzola M, Ecker JR. The DNA methylome. FEBS Lett. 2011;585(13):1994–2000.
137. Perrem K, Lynch A, Conneely M, Wahlberg H, Murphy G, Leader M, et al. The higher incidence of squamous cell carcinoma in renal transplant recipients is associated with increased telomere lengths. Hum Pathol. 2007;38:351–8.
138. Pickering CR, Zhou JH, Lee J, et al. Mutational landscape of aggressive squamous cell carcinoma. Clin Cancer Res. 2015;20:3842–8.
139. Poage GM, Houseman EA, Christensen BC, Butler RA, Avissar-Whiting M, McClean MD, et al. Global hypomethylation identifies Loci targeted for hypermethylation in head and neck cancer. Clin Cancer Res. 2011;17(11):3579–89.
140. Poligone B, Hayden MS, Chen L, Pentland AP, Jimi E, Ghosh S. A role for NF-κB activity in skin hyperplasia and the development of keratoacanthomata in mice. PLoS One. 2013;8(8):e71887. doi:10.1371/journal.pone.0071887.
141. Popp S, Waltering S, et al. Genetic characterization of a human skin carcinoma progression model: from primary tumor to metastasis. J Invest Dermatol. 2000;115(6):1095–103.
142. Portela A, Esteller M. Epigenetic modifications and human disease. Nat Biotechnol. 2010;28:1057–68.
143. Pourreyron C, Chen M, McGrath JA, Salas-Alanis JC, South AP, Leigh IM. High levels of type VII collagen expression in RDEB cSCC keratinocytes increases PI3K and MAPK signalling, cell migration and invasion. Br J Dermatol. 2014;170(6):1256–65. doi:10.1111/bjd.12715.
144. Prior SL, Griffiths AP, et al. A study of mitochondrial DNA D-loop mutations and p53 status in nonmelanoma skin cancer. Br J Dermatol. 2009;161(5):1067–71.
145. Purdie KJ, Harwood CA, et al. Single nucleotide polymorphism array analysis defines a specific genetic fingerprint for well-differentiated cutaneous SCCs. J Invest Dermatol. 2009;129(6):1562–8.
146. Purdie KJ, Lambert S, Teh MT, Chaplin T, Molloy G, Raghavan M, et al. Allelic imbalances and microdeletions affecting the PTPRD gene in cutaneous squamous cell carcinomas detected using single nucleotide polymorphism microarray analysis. Genes Chromosomes Cancer. 2007;46:661–9.
147. Ra SH, Li X, et al. Molecular discrimination of cutaneous squamous cell carcinoma from actinic keratosis and normal skin. Mod Pathol. 2011;24(7):963–73.
148. Ratushny V, Gober MD, et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. J Clin Invest. 2012;122(2):464–72.
149. Rehman I, Quinn AG, Healy E, Rees JL. High frequency of loss of heterozygosity in actinic keratoses, a usually benign disease. Lancet. 1994;344(8925):788–9.
150. Rehman I, Quinn AG, et al. Low frequency of allelic loss in skin tumours from immunosuppressed individuals. Br J Cancer. 1997;76(6):757–9.
151. Rehman I, Takata M, Wu YY, Rees JL. Genetic change in actinic keratosis. Oncogene. 1996;12:2483–90.
152. Ren Q, Kari C, Quadros MR, Burd R, McCue P, et al. Malignant transformation of immortalized HaCaT keratinocytes through deregulated nuclear factor kappa B signaling. Cancer Res. 2006;66:5209–15.
153. Restivo G, Nguyen BC, Dziunycz P, Ristorcelli E, Ryan RJ, Özuysal ÖY, et al. IRF6 is a mediator of Notch pro-differentiation and tumour suppressive function in keratinocytes. EMBO J. 2011;30(22):4571–85. doi:10.1038/emboj.2011.325.

154. Ridd K, Bastian BC. Somatic mutation of epidermal growth factor receptor in a small subset of cutaneous squamous cell carcinoma. J Invest Dermatol. 2010;130:901.
155. Ridky TW, Chow JM, Wong DJ, Khavari PA. Invasive three-dimensional organotypic neoplasia from multiple normal human epithelia. Nat Med. 2010;16(12):1450–5.
156. Ridky TW, Khavari PA. Pathways sufficient to induce epidermal carcinogenesis. Cell Cycle. 2004;3(5):621–4.
157. Rittie L, Kansra S, et al. Differential ErbB1 signaling in squamous cell versus basal cell carcinoma of the skin. Am J Pathol. 2007;170(6):2089–99.
158. Roh MR, Zheng Z, et al. Differential expression patterns of MMPs and their role in the invasion of epithelial premalignant tumors and invasive cutaneous squamous cell carcinoma. Exp Mol Pathol. 2012;92(2):236–42.
159. Ruczinski I, Jorgensen TJ, Shugart YY, Schaad YB, Kessing B, Hoffman-Bolton J, et al. A population-based study of DNA repair gene variants in relation to non-melanoma skin cancer as a marker of a cancer-prone phenotype. Carcinogenesis. 2012;33(9):1692–8.
160. Sand M, Skrygan M, Georgas D, et al. Microarray analysis of microRNA expression in cutaneous squamous cell carcinoma. J Dermatol Sci. 2012;68(3):119–26.
161. Saridaki Z, Liloglou T, Zafiropoulos A, Koumantaki E, Zoras O, Spandidos DA. Mutational analysis of CDKN2A genes in patients with squamous cell carcinoma of the skin. Br J Dermatol. 2003;148(4):638–48.
162. Smilek P, Neuwirthova J, Jarkovsky J, Dusek L, Rottenberg J, Kostrica R, et al. Epidermal growth factor receptor (EGFR) expression and mutations in the EGFR signaling pathway in correlation with anti-EGFR therapy in head and neck squamous cell carcinomas. Neoplasma. 2012;59(5):508–15.
163. Somoano B, Niendorf KB, Tsao H. Hereditary cancer syndromes of the skin. Clin Dermatol. 2005;23(1):85–106.
164. South AP, Cho RJ, et al. The double-edged sword of Notch signaling in cancer. Semin Cell Dev Biol. 2012;23(4):458–64.
165. South AP, Purdie KJ, Watt SA, Haldenby S, den Breems NY, Dimon M, et al. NOTCH1 mutations occur early during cutaneous squamous cell carcinogenesis. J Invest Dermatol. 2014;134(10):2630–8. doi:10.1038/jid.2014.154.
166. Stahl PL, Stranneheim H, et al. Sun-induced nonsynonymous p53 mutations are extensively accumulated and tolerated in normal appearing human skin. J Invest Dermatol. 2011;131(2):504–8.
167. Stransky N, Egloff NM, et al. The mutational landscape of head and neck squamous cell carcinoma. Science. 2011;333(6046):1157–60.
168. Su F, Viros A, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med. 2012;366(3):207–15.
169. Sully K, Akinduro O, Philpott MP, Naeem AS, Harwood CA, Reeve VE, et al. The mTOR inhibitor rapamycin opposes carcinogenic changes to epidermal Akt1/PKBa isoform signaling. Oncogene. 2013;32:3254–62.
170. Sweeny L, Dean NR, et al. EGFR expression in advanced head and neck cutaneous squamous cell carcinoma. Head Neck. 2012;34(5):681–6.
171. Tang X, Zhu Y, et al. CP-31398 restores mutant p53 tumor suppressor function and inhibits UVB-induced skin carcinogenesis in mice. J Clin Invest. 2007;117(12):3753–64.
172. Tarutani M, Cai T, et al. Inducible activation of Ras and Raf in adult epidermis. Cancer Res. 2003;63(2):319–23.
173. Teh MT, Gemenetzidis E, Patel D, Tariq R, Nadir A, Bahta AW, et al. FOXM1 induces a global methylation signature that mimics the cancer epigenome in head and neck squamous cell carcinoma. PLoS One. 2012;7(3):e34329. doi:10.1371/journal.pone.0034329.
174. Toll A, Salgado R, Yebenes M, Martin-Ezquerra G, Gilaberte M, Baro T, et al. MYC gene numerical aberrations in actinic keratosis and cutaneous squamous cell carcinoma. Br J Dermatol. 2009;161:1112–8.

175. Toll A, Salgado R, et al. Epidermal growth factor receptor gene numerical aberrations are frequent events in actinic keratoses and invasive cutaneous squamous cell carcinomas. Exp Dermatol. 2010;19(2):151–3.
176. Tsai HC, Baylin SB. Cancer epigenetics: linking basic biology to clinical medicine. Cell Res. 2011;21:502–17.
177. Uribe P, Gonzalez S. Epidermal growth factor receptor (EGFR) and squamous cell carcinoma of the skin: molecular bases for EGFR-targeted therapy. Pathol Res Pract. 2011;207(6): 337–42.
178. Van Haren R, Feldman D, et al. Systematic comparison of nonmelanoma skin cancer microarray datasets reveals lack of consensus genes. Br J Dermatol. 2009;161(6):1278–87.
179. Venza I, Visalli M, Tripodo B, De Grazia G, Loddo S, Teti D, et al. FOXE1 is a target for aberrant methylation in cutaneous squamous cell carcinoma. Br J Dermatol. 2010;162(5):1093–7. doi:10.1111/j.1365-2133.2009.09560.x.
180. Verneuil L, Varna M, Ratajczak P, Leboeuf C, Plassa LF, Elbouchtaoui M, et al. Human skin carcinoma arising from kidney transplant-derived tumour cells. J Clin Invest. 2013;123(9):3797–801.
181. Vogelstein B, Papdopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer genome landscapes. Science. 2013;339:1546–58.
182. Voskamp P, Bodmann CA, Rebel HG, Koehl GE, Tensen CP, Bouwes Bavinck JN, et al. Rapamycin impairs UV induction of mutant-p53 overexpressing cell clusters without affecting tumor onset. Int J Cancer. 2012;131(6):1267–76.
183. Wang NJ, Sanborn Z, et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc Natl Acad Sci U S A. 2011;108(43):17761–6.
184. Wheless L, Kistner-Griffin E, et al. A community-based study of nucleotide excision repair polymorphisms in relation to the risk of non-melanoma skin cancer. J Invest Dermatol. 2012;132(5):1354–62.
185. Winship IM, Dudding TE. Lessons from the skin-cutaneous features of familial cancer. Lancet Oncol. 2008;9(5):462–72.
186. Worsham MJ, Stephen JK, Chen KM, Havard S, Shah V, Gardner G, et al. Delineating an epigenetic continuum in head and neck cancer. Cancer Lett. 2014;342(2):178–84. doi:10.1016/j.canlet.2012.02.018.
187. Xu N, Zhang L, et al. MicroRNA-125b down-regulates matrix metallopeptidase 13 and inhibits cutaneous squamous cell carcinoma cell proliferation, migration, and invasion. J Biol Chem. 2012;287(35):29899–908.
188. Yadav V, Denning MF. Fyn-induced cutaneous carcinogenesis with modulation of Notch1 and p53. Cancer Res. 2011;50(5):346–52.
189. Yamane K, Jinnin M, et al. Down-regulation of miR-124/-214 in cutaneous squamous cell carcinoma mediates abnormal cell proliferation via the induction of ERK. J Mol Med (Berl). 2013;91(1):69–81.
190. Yanofsky VR, Mitsui H, Felsen D, Carucci JA. Understanding dendritic cells and their role in cutaneous carcinoma and cancer immunotherapy. Clin Dev Immunol. 2013;2013:624123. doi:10.1155/2013/624123.
191. Zandi R, Larsen AB, Andersen P, Stockhausen MT, Poulsen HS. Mechanisms for oncogenic activation of the epidermal growth factor receptor. Cell Signal. 2007;19(10):2013–23.
192. Zhang W, Hanks AN, et al. UVB-induced apoptosis drives clonal expansion during skin tumor development. Carcinogenesis. 2005;26(1):249–57.
193. Zhang X, Makino T, et al. Activation of the extracellular signal-regulated kinases signaling pathway in squamous cell carcinoma of the skin. Biosci Trends. 2007;1(3):156–60.
194. Zhang M, Song F, Liang L, Nan H, Zhang J, Liu H, et al. Genome-wide association studies identify several new loci associated with pigmentation traits and skin cancer risk in European Americans. Hum Mol Genet. 2013;22(14):2948–59.

195. Zhang L, Stokes N, et al. Specific microRNAs are preferentially expressed by skin stem cells to balance self-renewal and early lineage commitment. Cell Stem Cell. 2011;8(3):294–308.
196. Zhao L, Li W, Marshall C, Griffin T, Hanson M, Hick R, et al. Srcasm inhibits Fyn-induced cutaneous carcinogenesis with modulation of Notch1 and p53. Cancer Res. 2009;69(24): 9439–47. doi:10.1158/0008-5472.CAN-09-2976.
197. Zhou M, Liu W, et al. A novel onco-miR-365 induces cutaneous squamous cell carcinoma. Carcinogenesis. 2013;34(7):1653–9.

Chapter 4
Molecular and Cellular Interplay in SCC Including Immunomodulation and Clinical Implications

Valerie Yanofsky, John A. Carucci, and Günther F.L. Hofbauer

Introduction

CSCC is the second most common form of cancer found in the United States, and accounts for approximately 20% of all non-melanoma skin cancers. Several important risk factors for the development of SCC include skin type, with Fitzpatrick types I and II skin being the highest risk, cumulative exposure to UV radiation, age, and immune status [1, 2]. These are covered in detail in Chaps. 1 and 2. In particular, the incidence of SCC is thought to be over 100 times greater in immunosuppressed solid-organ transplant recipients (OTR) as compared to the general population [3]. The epidemiology and clinical management of SCC in the context of immunosuppression is covered fully in Chap. 10 but is briefly reviewed by way of introduction here.

SCC lesions found in OTRs may display more aggressive clinical behavior [4] than that seen in the immunocompetent. Transplant-associated SCC (TSCC) often occurs in patients at a younger age, and may demonstrate increased rates of local recurrence, which may reach as high as 13.4 %, as well as elevated metastatic rates approximating 8 % within the first 24 months post-excision [5, 6]. In some cases, OTRs may develop hundreds of rapidly growing SCC, a phenomenon known as

V. Yanofsky, BS
Ronald O. Perelman Department of Dermatology, NYU-Langone Medical Center,
550 First Avenue, New York, NY 10016, USA
e-mail: valerie.yanofsky@med.einstein.yu.edu

J.A. Carucci, MD, PhD (✉)
Ronald O. Perelman Department of Dermatology, New York University Langone Medical Center, 240 East 38th Street, 12th Floor, New York, NY 10016, USA
e-mail: john.carucci@nyumc.org

G.F.L. Hofbauer, MD
Dermatologische Klinik, Universitätsspital Zürich,
Gloriastrasse 31, Zürich, ZH 8091, Switzerland

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_4

catastrophic carcinomatosis, which can result in extensive local tissue damage and widespread disease [4, 7]. Metastatic SCC in OTRs is often fatal, with some studies showing a 3-year mortality as high as 46 % [8, 9]. SCC lesions in immune suppressed patients may therefore be considered to be "high-risk" tumors. See Chaps. 1, 3, and 10 for a thorough discussion of clinical data related to SCC and immunosuppression, and Chap. 2 for definitions of high-risk SCC.

Although high-risk SCC lesions found in immunocompromised hosts may present as a single solitary tumor, the far more common clinical picture involves multiple lesions, which arise consistently on chronically photo-damaged skin [5, 10]. This gives rise to the notion of "field cancerization," which refers to a broad area of skin that may appear clinically and histopathologically normal, but has in fact been transformed through exposure to multiple carcinogens, such as UV rays and immunosuppressive agents, to become tumorigenic. These areas typically contain distinct molecular and immune profiles, and may be affected by multiple subclinical and clinical actinic keratosis (AK) and in situ (epidermal) SCC lesions [11, 12]. Extensive skin damage associated with field cancerization provides a rationale for the initiation of field therapy, which represents a multi-pronged approach aimed at targeting an entire field rather than individual lesions in an effort to eradicate both clinically apparent and subclinical AK, in situ, and dermally invasive SCC lesions [13, 14]. Field therapy (covered in Chap. 5) may lead to markedly improved long term outcomes for patients with field cancerization.

Comparing and contrasting SCC development in immune competent patients with high-risk SCC in OTRs provides us a unique opportunity to explore the tumor microenvironment, and the precise molecular changes which may underlie the disparate clinical behaviors seen between these two populations. Although high-risk SCC can develop in patients without known immune dysfunction (see Chap. 2), the OTR model allows us to gain a greater understanding of the generation of antitumor immunity, and the various factors which may contribute to field cancerization and catastrophic carcinogenesis. This chapter will therefore highlight the important molecular pathways and key immune features which may give rise to SCC lesions. In particular, we will focus on the novel molecular interactions and distinct immune phenotypes seen in immunosuppressed OTRs as a proposed mechanism underlying the development of high-risk SCC tumors. As this chapter focuses on molecular pathways and cellular interactions, see Chap. 3 for a discussion of genetic and epigenetic changes impacting SCC production and prognosis.

Cellular Pathways of SCC Formation

All SCC lesions are believed to begin via the repeated, uncontrolled division of transformed keratinocytes [15]. Ultraviolet (UV) exposure is accepted as the main pathogenic factor inducing a primary mutation in keratinocytes, which may ultimately lead to the development of SCC. This process is believed to occur in a classic, stepwise fashion, in which a single transformed clone gains a growth advantage

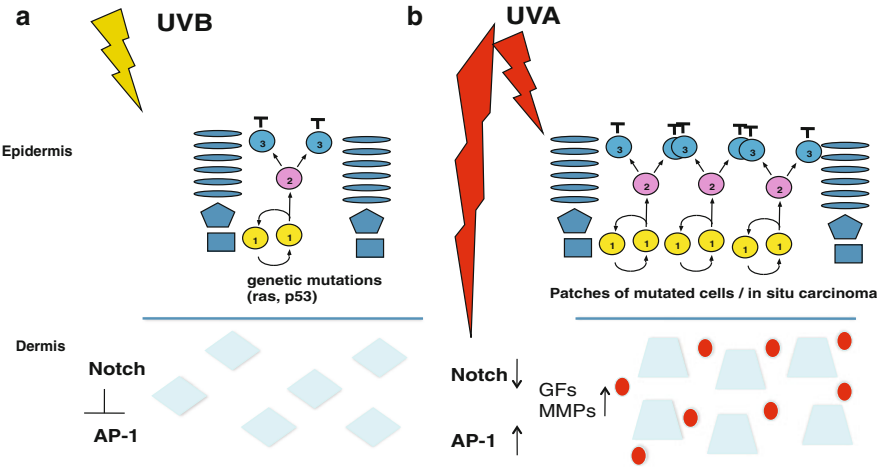


Fig. 4.1 *The cellular pathways of SCC formation and field cancerization*. (**a**) UV exposure results in a primary genetic mutation in keratinocytes, which promotes cellular proliferation and the acquisition of further mutations. This ultimately results in the formation of precursor SCC lesions. (**b**) Normal appearing skin adjacent to tumor tissue may contain unique molecular and genetic profiles, resulting in a tumorigenic focus. For example, Notch1, a regulator of keratinocyte differentiation, has been shown to be down-regulated in the dermis underlying actinic keratosis lesions. This results in increased expression of AP-1 family transcription factors, leading to elevated levels of pro-tumor cytokines. Kindly provided by Prof. Gian-Paolo Dotto, MD PhD

which allows it to acquire more genetic alterations [16]. Accumulation of transformed clones results in a microscopic focus of abnormal cells within the skin, which form precursor SCC lesions known as actinic keratosis (AK) or Bowen's disease (SCC in situ, Fig. 4.1a). These lesions are confined locally by the skin's basement membrane, and are therefore prevented from invading adjacent tissues [15–17]. Ultimately, further mutations enable the tumor to progress and breach the basement membrane, which results in the infiltration of nearby structures and subsequent metastasis.

This model is likely incomplete since some SCC, particularly very high-risk, poorly differentiated and sarcomatoid tumors do not appear to arise from a prior AK or in situ SCC lesion. Other mechanisms probably exist which can initiate SCC carcinogenesis, including viral HPV tumor promotion which plays a role in anogenital and nail fold SCC, but likely has a minimal role in UV-induced SCC. Still, since most SCCs do arise within sun-exposed regions and many occur in clinically actinically damaged skin, the UV model is likely relevant to most SCCs as further explained below.

UV rays most commonly induce a mutation or deletion of the p53 gene, resulting in an inactivation of its tumor-suppressor protein product [18]. This protein is thought to play a prominent role in protecting the integrity of the genome by triggering apoptosis of mutated cells during the cell cycle. Deletion of this gene therefore promotes unchecked progression through the cell cycle and resistance to cellular death [19]. Accordingly, $p53^{-/-}$ mice will have an increased propensity for developing AK-like lesions and SCC secondary to UV exposure [20]. The presence of p53 mutations

have been found in a significant percentage of CSCC lesions, as well as in AKs, demonstrating that dysplastic lesions may acquire genetic mutations prior to becoming SCC [21]. In fact, the prevalence of p53 mutations is over 15-fold higher in clinically unremarkable sun-exposed skin as compared to non-exposed skin, which further supports the notion of field cancerization which may be subclinical and sets the stage for the acquisition of new mutations, which may drive tumor development and progression [22]. UV-induced p53 mutations are occurring constantly in our skin and are also constantly being repaired via DNA repair mechanisms. The devastating effects of failure of this natural repair system are seen in xeroderma pigmentosum. This disease is due to defects in DNA repair and results in aggressive SCCs beginning in childhood which invariably lead to death.

While keratinocytes in chronically sun-exposed areas of the skin may show multiple changes detectable before cancer formation occurs, other cells may similarly be involved in a close interplay in the process of field cancerization. For instance, the Notch1 gene is known to be a master regulator of differentiation in many tissues, and has been found to contribute to keratinocyte homeostasis in the epidermis [23]. Notch1 has also been shown, however, to play a key role in the differentiation of dermal fibroblast cells. Accordingly, a site-specific deletion of CSL/RBP-Jκ in the mouse dermis led to the formation of multiple SCC lesions, reenacting the clinically observed phenomenon of field cancerization [24]. Furthermore, human skin may demonstrate similar patterns of Notch1 downregulation in dermal tissue underlying AK lesions, with a corresponding increase in the AP-1 family transcription factors such as c-Jun and Fos (Fig. 4.1b).

Another factor which may play an important role in the promotion of field cancerization is the presence of chronic inflammation. Notch 1 is a regulatory gene which contributes to keratinocyte homestasis [23]. In a mouse model of field cancerization with impaired dermal Notch signaling, widespread low-grade inflammation could be observed long before the presence of multiple tumors though the mechanism by which this occurs is not known.

This link between chronic inflammation and SCC seen in the laboratory is consistent with the clinical occurrence of SCC within chronically inflamed or damaged skin such as is seen in Marjolin's ulcers and the devastating condition of recessive dystrophic epidermolysis bullosa in which aggressive SCC forms within the chronically scarred tissues and is the leading cause of death in this disease. SCC formation could be reduced in the Notch 1 mouse model above via the use of broad anti-inflammatory agents such as cyclooxygenase-2 inhibitors prior to tumor development which resulted in a dramatic reduction if not total suppression of tumor formation [24].

Inflammation therefore appears to be a critical precursor for the induction of field cancerization in this model. Similarly, inflammation was shown to be a key player in the chemical carcinogenesis model of SCC formation through the presence of the RAGE receptor, and its ligands S100A8/A9 [25]. S100A8/A9 belong to the calcium-binding family of S100 proteins which are commonly expressed in inflammatory diseases at large, e.g. S100A7 (psoriasin) in psoriasis. Among other ligands

they may bind to the receptor for advanced glycation end products (RAGE), thus mediating a pro-inflammatory effect. Both the RAGE receptor and its ligands appear to be upregulated in SCC lesions, and expression levels may vary following the use of immunosuppressive drugs in organ transplant recipients. This suggests a possible role for RAGE and S100A8/A9 in the formation of high-risk SCC lesions associated with OTRs [26].

Carcinogenic Impact of Medication on Keratinocytes

While light skin type and cumulative UV exposure are thought to be the principal risk factors for the development of SCC, the administration of certain medications is also known to play a pivotal role in SCC formation. In particular, the risk of developing SCC in OTRs on chronic immunosuppressive therapy is thought to be 100-fold greater than that of the general population [3]. The effect of immunosuppression itself and the subsequent decreased immune surveillance it entails may facilitate SCC formation.

In addition to the impact of immunosuppressive drugs on the immune system, direct drug-induced effects extending beyond immunosuppression have recently been identified in keratinocytes, and may serve as potential contributors to the formation of high-risk SCCs in OTRs. These mechanisms are discussed below.

Calcineurin Inhibition Drives SCC Formation through the Promotion of ATF3 in Keratinocytes

Calcineurin inhibitors (cyclosporine A and tacrolimus) were amongst the first immunosuppressive agents used to prevent transplant rejection in OTRs, and they remain at the cornerstone of modern transplant medicine. They are thought to exert their immunosuppressive effect largely through the inhibition of calcineurin, which prevents the activation of lymphocytes and thereby suppresses the initiation of an adaptive immune response. The expression of calcineurin is not unique to lymphocytes of the immune system, however, and has been found in multiple different cells of the body. Cyclosporine A may therefore exert widespread systemic effects in addition to its role in immune suppression.

In keratinocytes, calcineurin has recently been shown to inhibit the expression of Activating Transcription Factor 3 (ATF3), a member of the enlarged AP-1 family of transcription factors. ATF3 expression has been shown to play a role in the pathogenesis of several different epithelial cancers, and therefore may be of potential interest in keratinocytes as well. Subsequent experimentation has shown calcineurin inhibition to directly result in increased ATF3 expression, which in turn, results in increased binding of ATF3 to various sites in the promoter region of p53. This results in the

effective inhibition of p53 mRNA expression [27]. As mentioned previously, p53 is a key tumor suppressor gene in charge of cell cycle regulation, and loss of p53 function is known to catalyze tumor formation in epithelial cells [19]. Furthermore, in vivo experiments conducted in mice have shown that the use of cyclosporine A resulted in a sharp increase in both ATF3 mRNA and protein levels, with a corresponding downregulation of p53 protein expression. This led to a subsequent increase in epithelial tumor formation [27]. This newly described mechanism for calcineurin inhibition in keratinocytes may help explain the disproportionate increase in keratinocyte-derived cancers relative to overall malignancies seen in OTRs.

In contrast to systemic calcineurin inhibition with cyclosporine A, topical calcineurin inhibitors such as tacrolimus and pimecrolimus, widely used in the treatment of atopic dermatitis and other inflammatory skin disease, have yet to be associated with any increased incidence of SCC [28, 29]. While the exact mechanism underlying this observed discrepancy is not fully understood, it is thought that the inhibition of calcineurin in epidermal keratinocytes alone may be insufficient to incite the development of squamous cell carcinoma itself. Rather, SCC formation may rely on the synergistic effect of the local dermal and inflammatory microenvironment in order to overcome host tumor defenses mounted by the body's immune system. These systemic cellular host immune defenses are impaired by systemic but not topical calcineurin inhibition which may explain why systemic inhibition with oral drugs (notably cyclosporine A) is associated with SCC formation while topical inhibition has not emerged in association with increased cutaneous carcinogenesis to date.

Azathioprine Photosensitizes Skin to UVA and Facilitates Direct DNA Damage of Keratinocytes in OTR

Another medication commonly used to prevent transplant rejection in OTRs is the anti-metabolite compound azathioprine (AZA). AZA works by incorporating the metabolite 6-thioguanine (6-TG) into cells during de novo DNA synthesis, thereby blocking effective synthesis and impairing cellular function. More recently, the newer purine analogues mycophenolic acid and mycophenolate mofetil have become the first-line anti-metabolite agents used in transplantation medicine. AZA continues to be used, however, in older patients with long-standing immunosuppressive regimens, as well as those with chronic inflammatory conditions such as inflammatory bowel disease [30].

While patients on azathioprine do not typically complain of photosensitivity, experimental data have previously identified AZA as a potent photosensitizer in the ultraviolet A (UVA) range [31]. More importantly, keratinocytes under the influence of AZA were shown to be directly susceptible to DNA damage induced by UVA. This is particularly significant since it was previously believed that only ultraviolet B (UVB) rays were powerful enough to induce direct DNA damage, as evidenced by UVB signature mutations such as the cyclobutane pyrimidine dimer and 6-4 photoproduct formation commonly found in the skin. Further experiments effectively

demonstrated, however, that AZA treatment may result in clinically demonstrable UVA-induced photosensitivity [32]. Accordingly, clinical studies have shown that switching renal transplant recipients from AZA to alternative anti-metabolites such as mycophenolate mofetil can improve UVA-related photosensitivity in as little as 3 months [33]. Furthermore, UVA exposure in these patients, once switched to mycophenolate, did not inflict the same degree of molecular damage, as measured by p53 induction in photo-exposed skin as they had suffered while on azathioprine.

Interestingly, a long-term follow up conducted on a small group of renal transplant recipients was able to detect the persistence of the AZA metabolite 6-TG in circulating lymphocytes as long as 2 years after discontinuation of the drug, with a continued further improvement of photosensitivity in two out of four patients. These latter observations suggest that azathioprine may continue to exert a carcinogenic effect long beyond its period of use. While no formal data incriminate azathioprine as an isolated culprit for the increased incidence of SCC seen in OTRs, it may still be prudent to limit its use, especially in light-skinned patients, and to consider switching away from azathioprine if SCC occurs, based on the current evidence highlighted above [34].

The Tumor Microenvironment in High-Risk SCC

The body's immune system is equipped with all the necessary components to effectively identify, target, and eradicate malignant SCC cells. The generation of such anti-tumor immunity, however, is a complex process which is dependent on the precise and dynamic interplay of several critical immune mediators. Furthermore, the nature of an immune response may be molded by a variety of chemical signals present in the surrounding microenvironment [35].

Typically, the initiation of anti-tumor immunity begins with dendritic cells, which are considered professional antigen-presenting cells and serve as an important link between the innate and adaptive immune systems [36]. These cells will recognize and process specific tumor-associated antigens, with subsequent presentation to naïve CD4+ and CD8+ T-cells. This results in the generation and activation of antigen-specific effector T cells, including T-helper (Th) and cytotoxic T cells (Tc), which may directly attack invading cancer cells [37]. Accordingly, any defect or suppression of function in the above-mentioned immune cells may result in defective or impaired anti-tumor immunity. In the remainder of this chapter, we will systematically describe the presence and function of key immune cells, including dendritic cells, macrophages, and effector T cells, which are found in the SCC tumor microenvironment. We will further highlight the distinct immune features observed in transplant-associated SCC (TSCC) as compared to SCC, which may be contributing to the impaired immunity and accelerated tumor growth seen clinically. Additionally, we will characterize the unique soluble factors and signaling molecules present in the SCC microenvironment, which may be interacting with immune cell function to promote neoplastic transformation and protect the tumor from host immunity.

Dendritic Cells in the Tumor Microenvironment

Dendritic cells (DC) are considered to be professional antigen-presenters based on their ability to sample the surrounding environment for foreign invaders, and present associated antigens in the context of MHC class II and co-stimulatory molecules [36]. Their prevalence in the peripheral tissues such as the skin supports their role as gatekeepers of immunity. Cutaneous DCs may be loosely subdivided into three main subsets, which can be distinguished based on their location and differential expression of surface molecules in the steady state. These include: (1) epidermal Langerhans cells (LCs) which patrol the epidermis; (2) dermal myeloid dendritic cells (mDCs) which patrol the dermis; and (3) plasmacytoid dendritic cells (pDCs) which are antigen presenting cells that circulate in blood and lymphatics [38, 39].

DCs are thought to be the first immune cells to encounter local tumor antigen in SCC, and are therefore critical for the initiation of tumor immunity. Indeed, we have previously studied the presence of DCs in SCC lesions, and found significantly reduced quantities of both LCs and mDCs as compared to normal skin (Fig. 4.2). This suggests a disruption in DC-generated immunity in SCC, which may in part account for a more tumor permissive environment [40, 41].

In addition to the decreased amount of mDCs, we have also evaluated both the phenotype and function of mDCs extracted from SCC lesions compared to those taken from peritumoral or healthy skin. We found that tumor-associated mDCs were, in fact, poor stimulators of T cell proliferation and activation when compared to their peritumoral or healthy skin counterparts. Furthermore, this discrepancy was directly the result of defective mDC function and not due to impaired DC maturation. This was evidenced by comparable levels of the DC maturation markers CD83 and CD86 in tumoral, peritumoral, and healthy-skin mDCs [40]. Consistent with our findings, tumor-associated mDCs extracted from BCC lesions have also been shown to be deficient activators of the T cell response when compared to normal cutaneous mDCs [42]. Although the precise mechanism underlying this observed effect remains unclear, we have shown the SCC immune microenvironment to be rich in soluble immunosuppressive factors such as IL-10, TGF-β, and VEGF-A [40]. These molecules were found to be elevated in both lesional tissue and adjacent peritumoral skin, which supports the notion that normal-appearing skin adjacent to tumor sites may in fact contain a unique pro-tumoral composition. Additionally, IL-10, TGF-β and VEGF-A have been linked to the direct inhibition of mature mDC stimulatory function [43]. This suggests tumor cells may secrete immunosuppressive molecules which effectively suppress proper mDC function, resulting in the impaired generation of anti-tumor immunity.

In contrast to the impaired mDC function seen in SCC, LCs harvested from SCC lesions have actually been shown to have an enhanced ability to stimulate CD4+ and CD8+ T cell proliferation in vitro when compared to cells taken from matched, non-tumor bearing skin [44]. Furthermore, SCC-derived LCs may efficiently polarize the T cell population towards a predominantly Th1 response, which results in the increased secretion of IFN-γ. This is thought to be a critical mediator in the successful

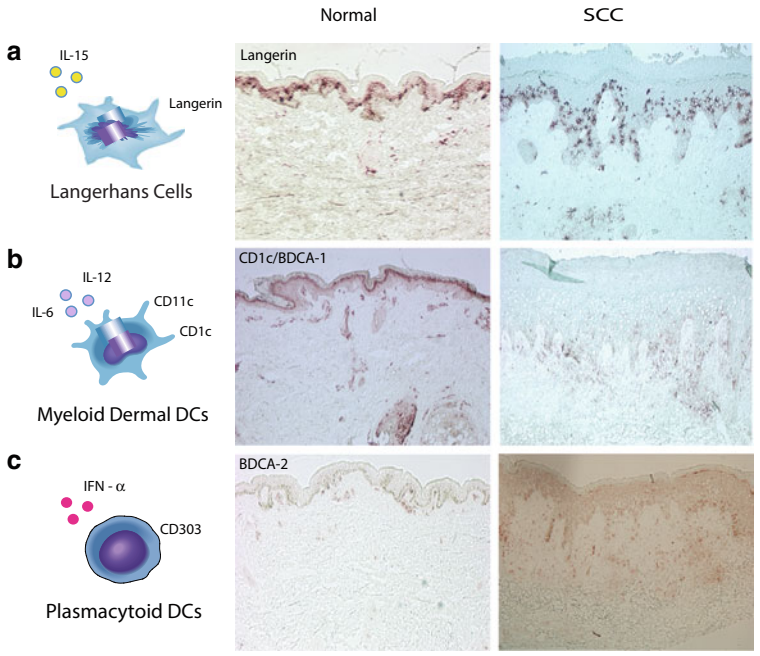


Fig. 4.2 *The distribution of cutaneous dendritic cell subsets in normal skin versus human squamous cell carcinoma* (*SCC*). The human skin contains three main subsets of DCs which can be distinguished based on location and the differential expression of surface molecules in the steady state (*left*). Representative immunohistochemistry (*right*) demonstrating the relative distribution of DC subsets in normal skin versus SCC, including (**a**) Langerhans cells (**b**) dermal myeloid DCs and (**c**) plasmacytoid DCs

generation of anti-tumor immunity [45]. It would therefore appear that the SCC microenvironment may actually serve to promote, rather than inhibit, LC activation and the initiation of an anti-tumor response. Accordingly, subsequent study has revealed that non-tumor LCs cultured in the presence of tumor supernatant (TSN) will lead to the increased proliferation of both CD8+ and CD4+ T cells, with a shift towards a Th1 cell response [44].

Despite the stimulatory effect of the SCC microenvironment on LC function, and the enhanced type 1 anti-tumor response generated in vitro, LCs remain incapable of preventing SCC tumor growth in vivo. This effect may be due to a variety of different reasons, including the dramatically reduced number of LCs found in both lesional and peritumoral skin [40, 41, 46]. Additionally, these cells may have impaired patterns of migration, and defective mechanisms of T cell priming in the draining lymph nodes. This would effectively prevent the activation of a T cell response and subsequently inhibit the launch of a full-scale immune attack [47, 48]. In fact, current research has shown that the application of TSN directly to SCC lesions in mice resulted in a markedly diminished migration of LCs to draining lymph nodes in vivo [41, 49]. Finally, much of our knowledge concerning LC

function in the SCC microenvironment is derived from the study of migrating cells taken from pre-existing tumors. The role of LCs in the tumor initiation stage thus remains largely unknown. Several recent studies have suggested LCs may actually accelerate SCC development in mutated keratinocytes, resulting in a pro-tumor effect in cutaneous carcinomas [50, 51].

While the SCC tumor microenvironment is distinctive in that it contains markedly low levels of mDCs and LCs, it is also notable for containing relatively large quantities of pDCs [40]. These cells are thought to be the primary foot soldier of the innate immune system due to their tremendous ability to produce interferon-α (IFNα) in response to foreign invasion [52]. This cytokine has been shown to have both antiviral and antitumor effects, and may therefore be beneficial in tumor eradication [53]. Additionally, it has recently been shown that pDCs are capable of recognizing, processing, and cross-presenting foreign antigen to CD8+ T cells [54, 55]. Although this process is found to be less efficient in pDCs when compared to their mDC counterparts, these findings support the notion that pDCs may, in fact, be effective activators of the anti-tumor immune response [56]. Accordingly, it has been shown that the elevated amounts of pDCs are indeed associated with increased clearance of BCC lesions following treatment with imiquimod [57]. Further research is currently needed in order to more accurately define the role of pDCs in human cutaneous carcinomas.

Recently, a novel subtype of mDCs has been identified which is associated mainly with an inflammatory response. These highly specialized DCs are characterized by the secretion of inflammatory mediators such as TNF, iNOS, IL-20 and IL-23, and are hence labeled TIP-DCs [39, 40]. The presence of TIP-DCs has been previously described in psoriasis, where it was shown that treatment of psoriatic lesions with the anti-CD11a agent efalizumab strongly reduced their influx into the affected areas. This suggests that these cells may be playing an active role in driving keratinocyte hyperproliferation [58]. Alternatively, TIP-DCs have been shown to exert a direct immunosuppressive effect by catalyzing the metabolism of L-arginine, which results in the subsequent production of nitric oxide and reactive oxygen species. In particular, reduced concentration of L-arginine has been shown to prevent the development of antigen-specific T cells, and nitric oxide may inhibit activated T cell proliferation [59]. We have previously evaluated the SCC microenvironment for the presence of TIP-DCs, and found a significant influx of these cells in the dermal regions surrounding SCC tumor nests. While their precise role in SCC remains somewhat unclear, TIP-DCs may be contributing to immune dysfunction through the secretion of immunosuppressive cytokines which inhibit effector T cell production.

Effector T Cells in the Tumor Microenvironment

Following antigen uptake and processing, peripheral DCs will migrate through the afferent lymphatics to nearby lymph nodes for presentation to naïve T cells. Binding of T cells to the MHC-antigen complex and co-stimulatory molecules on the DC

surface results in the activation and subsequent differentiation of T cells into highly specific effector cells [60]. Typically, these cells can be subdivided into one of three categories based on the distinct molecules they produce. These include: (1) cytotoxic CD8+ T cells (Tc), which bind to MHC class I molecules on the DC surface, and release specialized cytotoxins including perforin, granzymes, and IFN-γ in response to cytosolic pathogens; (2) CD4+ Th1 cells, which bind to MHC class II molecules and release IL-2, IFN-γ and other activating molecules, thereby enhancing the anti-tumor function of macrophages, natural killer cells (NK) and Tc cells; and (3) CD4+ Th2 cells, which also bind to MHC class II molecules, and drive B-cell dependent humoral immunity through the release of B cell growth factors IL-4 and IL-5 [61–64]. Tc and Th1 cells are generally thought to be the key mediators of anti-tumor immunity.

Since T-cell mediated immunity is critical in controlling tumor growth, we have previously characterized the presence of tumor-associated CD4+ and CD8+ T cells in SCC as compared to those found in transplant-associated SCC (TSCC) and normal skin. Not surprisingly, we found a significantly greater number of CD8+ T cells associated with both SCC and TSCC as compared to normal skin [65]. Previous research has shown that CSCC is commonly associated with increased T cell infiltrates, however the clinical persistence of cancer suggests that these T cells are unable to destroy the tumor [66, 67]. Interestingly, however, our results show fewer numbers of CD8+ T cells in TSCC as compared to SCC lesions. This decrease in anti-tumor Tc cells may be one of several factors contributing to the increased proliferative behaviors seen in TSCC. Accordingly, recent studies have indeed shown reduced amounts of tumor-infiltrating CD8+ T cells to be associated with more aggressive tumor phenotypes and increased risk of lymph node metastasis [68].

In addition to increased CD8+ T cells in the SCC and TSCC microenvironment, we have also found a significantly increased number of Foxp3+ regulatory T cells (Tregs) in tumor tissue as compared to normal skin [65]. These cells are known to promote immune tolerance, and are thought to be critical for the prevention of autoimmunity [69, 70]. Recent evidence has shown, however, that Tregs may also play a role in the suppression of an appropriate anti-tumor response through the direct inhibition of effector T cell proliferation and cytokine production [71–73]. Additionally, DCs co-cultured with Tregs have been shown to down-regulate the expression of co-stimulatory molecules, which may impair their ability to stimulate T cell proliferation and contribute to immune system dysfunction [74–76]. In fact, recent studies have shown that increased levels of Tregs are correlated with a poor prognosis and decreased survival rates in a variety of cancers, including gastric, breast and ovarian carcinoma [71, 77, 78]. Of note, when evaluating the presence of Tregs in SCC and TSCC, we actually found an increased ratio of Tregs to CD8+ Tc cells in TSCC as compared to SCC [65]. This disruption of the Treg to Tc cell balance may further exacerbate the immune impairment seen in SCC, which may result in a severely compromised ability to launch an immune attack. This may again be contributing to the more aggressive tumor phenotypes seen in TSCC.

Another significant disparity that is found between the immune microenvironment in TSCC as compared to SCC is a decreased percentage of IFN-γ secreting

CD4+ T cells (Th1) in TSCC [65]. This is somewhat consistent with our previous research, which has shown the TSCC microenvironment to contain a predominantly Th2 phenotype [74]. As mentioned previously, Th1 cells are thought to be critical for the generation of anti-tumor immunity, thus decreased levels may contribute to the more tumor permissive environment seen in TSCC [65, 79]. More interestingly, however, we found the TSCC microenvironment to contain a significant increase in the percentage of CD8+ interleukin-22 (IL-22) producing cells as compared to non-transplant associated SCC (Fig. 4.3a) [65]. IL-22 is a member of the IL-10 family of cytokines, and has been implicated in a number of benign keratinocyte hyperproliferative conditions such as psoriasis and atopic dermatitis [80–84]. Recent evidence, however, suggests that IL-22 may also play a role in driving the growth of a number of malignant processes, such as mantle cell lymphoma, hepatocellular carcinoma, colon carcinoma and pancreatic cancer [85–89]. While the precise nature of IL-22 in SCC remains to be defined, we have provided evidence that IL-22 administration may in fact enhance the proliferation of CSCC cells in vitro (Fig. 4.3b). More specifically, we found treatment with IL-22 resulted in an eight-fold increase in cell numbers as compared to those cells grown without IL-22 supplementation (Fig. 4.3c) [65]. Furthermore, the SCC microenvironment was associated with increased gene expression of IL-22, and increased protein expression of IL-22, the IL-22 receptor, and associated downstream modulator pSTAT-3 [65]. These findings serve to reinforce the importance of the IL-22 pathway in SCC and TSCC, and support the notion that increased IL-22 may be driving accelerated SCC growth in organ transplant recipients.

Macrophages, Immune Suppressive Molecules, and Other Competing Forces in the SCC Microenvironment

Tumor behavior is not simply a function of cancer or immune cells themselves, but rather is dependent on the composition of the local surroundings. The tumor microenvironment can thus be thought of as the collection of cells, soluble factors, signaling molecules and extracellular matrix components that together may serve to regulate neoplastic transformation and tumor progression [90]. We have previously described the unique DC and effector T cell components which make up the SCC microenvironment. We will now focus on the presence of macrophages, associated soluble factors, and immunosuppressive molecules, which may also be contributing to the complex immune environment seen in SCC.

Macrophages are considered to be the body's principal phagocytic cells, and like DCs, they are thought to play a key role in the initiation of both the innate and the adaptive immune response. They are often one of the major populations of leukocytes found in solid tumors, where they have been shown to alternatively promote or inhibit tumor growth [91–93]. In particular, tumor-associated macrophages (TAMs) have been shown to promote early eradication of tumor cells in vitro [94]. They are also, however, associated with a negative prognosis in several human cancers, and

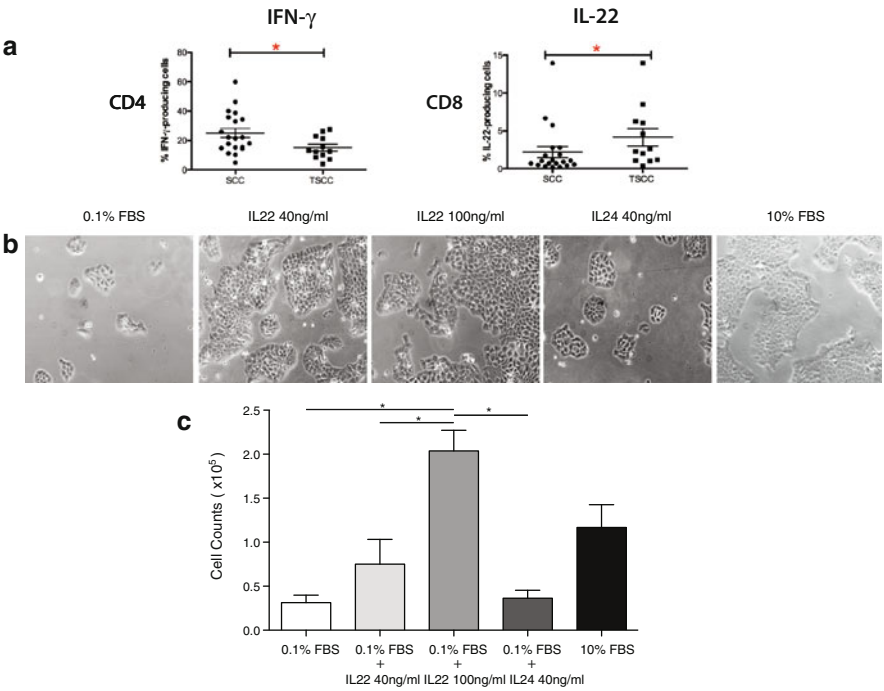


Fig. 4.3 *Transplant-associated SCC (TSCC) contains a unique immune phenotype which may be driving accelerated SCC growth.* (**a**) We stimulated T cell "crawl outs" taken from SCC and TSCC and determined T cell phenotype through intracellular cytokine staining. We found TSCC lesions to contain a significant decrease in CD4+ IFN-γ producing cells, and a significant increase in CD8+ IL-22 producing cells ($p < 0.05$). (**b**) IL-22 was found to drive accelerated SCC growth in vitro. A431 cells were cultured in full media (10 % FBS) or in serum starvation media (0.1 % FBS) with or without the addition of the indicated cytokines for 72 h. Cells cultured in full media, and in starvation media supplemented with IL-22 (40 and 100 ng/ml) show considerably greater proliferative behavior with increased colony formation when compared to those grown in starvation media alone or supplemented with IL-24 (40 ng/ml) (**c**) Cell counts were performed after 72 h of cultivation in the indicated conditions. The addition of 100 ng/ml IL-22 to the starvation media resulted in a hyperproliferation of tumor cells and eightfold increase in cell numbers when compared to those grown in serum starvation alone, or serum starvation supplemented with IL-22 (40 ng/ml) or IL-24 (40 ng/ml) (one-way ANOVA, $p < 0.001$)

have been shown to release angiogenic factors which may directly contribute to tumor growth [93, 95]. We have previously shown that TAMs are significantly upregulated in the SCC microenvironment as compared to normal skin. Additionally, the phenotype and function of TAMs in SCC was found to be heterogeneous, with evidence for both anti- and pro-tumor function [35]. For instance, TAMs were found to have upregulated expression of the IFN-γ receptor, which reflects an enhanced ability to respond to IFN-γ with antigen presentation and the initiation of a Th1 immune response. This would be expected to prevent tumor progression [96]. Conversely, TAMs were also found to produce factors which encouraged tumorigenesis.

These include the pro-lymphangiogenic vascular endothelial growth factor-C (VEGF-C), as well as matrix metalloproteinases (MMPs) 9 and 11, which promote local invasion and metastatic spread through the degradation of the extracellular matrix [35, 97]. MMPs may also release matrix-sequestered angiogenic factors which encourage tumor growth [98]. The abundant influx of TAMs in the SCC microenvironment may therefore be serving to promote tumor growth and carcinogenesis.

As mentioned above, the SCC microenvironment contains a large amount of TAMs which may secrete pro-tumoral factors such as VEGF-C. VEGF-C is a critical mediator of lymphangiogenesis, and is thought to stimulate the proliferation and increased survival of lymphatic endothelial cells [99]. Additionally, increased lymphatic vessel density (LVD) and VEGF-C expression have been shown to be effective predictors of lymph node metastasis in several different cancers, including oral and supraglottic SCC, as well as melanoma [100–102]. Accordingly, we have shown the SCC tumor microenvironment to contain increased LVD in the juxtatumoral dermis, as well as an upregulation of several different lymphangiogenesis genes. SCC lesions also contained increased levels of VEGF-C as compared to normal skin, likely the result of secretion by associated TAMs. Moreover, these findings were not only present in SCC lesions, but also apparent in matched adjacent non-tumor bearing skin. This supports the concept of field cancerization, and may facilitate the recurrence and metastasis of SCC tumors despite treatment with excision and seemingly clear margins [97].

Finally, endothelial cells lining local blood vessels are often the first contact that many blood-borne elements, including certain immune cells, have with a tumor. Endothelial cell integrity may therefore play a key role in tumor development by allowing various immune components to gain entry to the tumor microenvironment [103]. Recent research has suggested that reduced expression of endothelial E-selectin in the local SCC tumor vasculature may result in aberrant T cell homing and increased infiltration of Tregs into the tumor [66]. Additionally, we have shown that the SCC tumor microenvironment contains significantly greater expression of the endothelial protein CD200, a known immunosuppressive protein which often regulates immune cell entry into areas of immune privilege, such as the brain, retina and hair follicle [104–106]. This effect can be manipulated in human cancers to confer pathologic immune privilege to tumor cells, thereby helping the tumor evade immune detection. Furthermore, we found several factors released from SCC lesions were actually capable of inducing the expression of CD200 on endothelial cells in vitro. This may help explain our finding that nearly all vessels in SCC expressed CD200, whereas very few did in normal skin [104]. We also saw a significant increase in the expression of CD200 receptor (CD200R) on myeloid cells in the SCC microenvironment, which may, in part, help account for the mDC dysfunction seen in SCC [40, 104]. Taken together, these results suggest that CD200, and its interaction with CD200R on myeloid cells, may be a critical mechanism of immune evasion in SCC.

Summary and Conclusions

Squamous cell carcinoma (SCC) remains a significant cause of morbidity and mortality in organ transplant recipients (OTRs). Lesions in this patient population tend to be more numerous, rapidly growing, and more aggressive when compared to SCC from immune competent patients, with elevated rates of recurrence and metastases [4, 7]. Additionally, extensive body surface area involvement often renders surgery, the primary treatment modality, difficult or disfiguring. There thus exists a real need for the development of effective medical therapies for the treatment of filed cancerization and aggressive SCC in OTRs. This process is dependent, however, on a thorough and comprehensive understanding of SCC pathogenesis and the various factors which may allow tumor cells to evade immune detection. Furthermore, targeting specific lesions themselves may be inadequate in the context of field cancerization, which suggests that normal appearing skin adjacent to tumor tissue may actually contain unique genetic mutations which render the area tumorigenic.

Comparing low-risk SCC tumor development in immune competent patients versus high-risk transplant-associated SCC (TSCC) provides us with a novel opportunity to explore the intricacies of the tumor immune microenvironment, and allows us to gain a greater understanding of the various factors which may drive SCC proliferation. SCC lesions are thought to occur as a direct result of chronic exposure to carcinogenic stimuli such as UV light. This eventually results in a genomic mutation in keratinocytes, which confers a growth advantage such that the transformed cell may continue to acquire new mutations. These rapidly-proliferating mutated cells will ultimately form a microscopic tumor focus within the skin. While this process of tumor development is thought to be consistent for all SCC lesions, there are various tumorigenic factors which may catalyze cellular damage and increase carcinogenesis. For instance, the use of immunosuppressive agents such as Cyclosporine A and Azathioprine may be directly driving SCC formation through the respective inhibition of the p53 tumor suppressor protein and photosensitization of the skin to UVA. These medications are commonly used in OTRs, and may, in part, explain the high prevalence of SCC seen in this population.

Additionally, the immune microenvironment associated with SCC is thought to be a dynamic milieu, comprised of opposing forces driving tumor promotion and tumor suppression (Fig. 4.4). We have found SCC lesions to contain a significantly reduced number of mDCs and LCs when compared to normal skin, as well as an increased number of pDCs. Furthermore, mDC function appears to be impaired in SCC lesions, with an inability to stimulate an appropriate T cell response. Other unique features of the tumor microenvironment include increased amounts of Tregs, which is further highlighted by an increased ratio of Tregs to CD8+ Tc cells in transplant-associated SCC (TSCC). TSCC lesions also contain a significantly decreased amount of CD4+ IFN-γ producing cells, as well as a significantly increased amount of CD8+ IL-22 producing cells. The former is thought to be a key mediator of anti-tumor immunity, and may help explain the more tumor permissive environment seen in TSCC. The latter has been shown to directly drive SCC proliferation in vitro, and may therefore contribute to the more aggressive tumor phenotypes seen in TSCC.

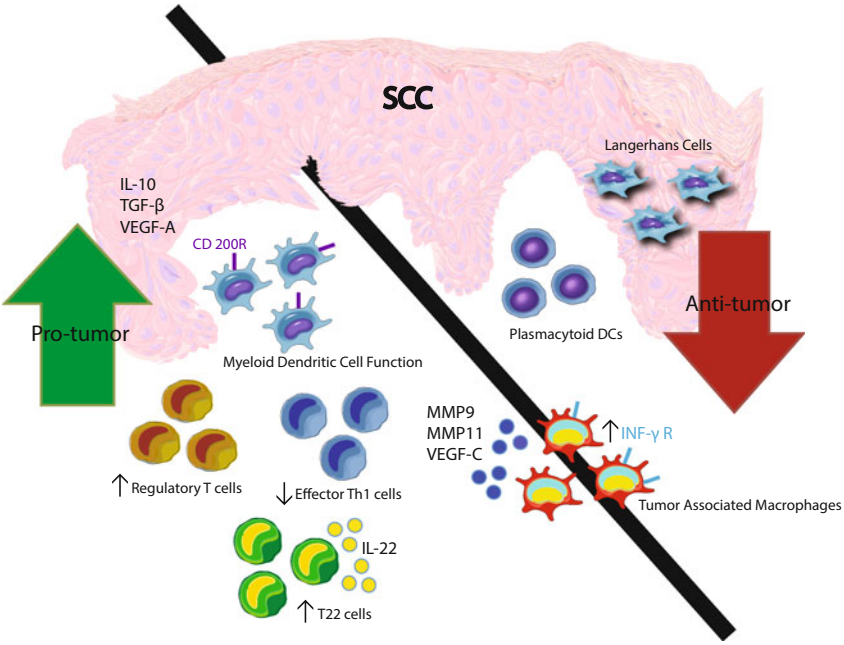


Fig. 4.4 *The SCC immune microenvironment is a dynamic milieu comprised of competing forces driving tumor progression and tumor suppression*. The SCC microenvironment is associated with an increased influx of pDCs, which secrete the anti-tumoral cytokine IFNα. The tumor microenvironment also works to promote LC function and enhance their ability to stimulate effector T cells. Conversely, mDC function is suppressed in SCC lesions. SCC is also associated with an influx of Tregs, which may create a more tumor permissive environment. Additionally, TSCC will contain a significant decrease in Th1 cells as well as a significant increase in T22 cells, which serve to further promote tumor proliferation. Tumor associated macrophages display heterogeneous behavior. On the one hand they demonstrate an enhanced ability to respond to IFN-γ and stimulate Th1. They also, however, secrete pro-angiogenic immunosuppressive factors such as MMP 9, MMP 11 and VEGF-C

High-risk SCC lesions may therefore be attributed to a number of different factors, which taken together serve to promote both a decrease in immune surveillance, as well as an increase in mutagenic and proliferative signals. Furthermore, aberrant gene patterns in the surrounding tissue increase the likelihood of tumor recurrence and new tumor formation. Treatment of these lesions may therefore require a comprehensive, multi-pronged approach aimed at targeting individual lesions themselves, the surrounding tumor microenvironment, and the affected field in order to effectively eradicate lesions and ensure a more long term tumor-free survival.

References

1. Leblanc Jr KG, Hughes MP, Sheehan DJ. The role of sirolimus in the prevention of cutaneous squamous cell carcinoma in organ transplant recipients. Dermatol Surg. 2011;37(6):744–9.
2. Ulrich C, et al. Skin cancer in organ transplant recipients--where do we stand today? Am J Transplant. 2008;8(11):2192–8.
3. Lindelof B, et al. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol. 2000;143(3):513–9.
4. Carucci JA. Cutaneous oncology in organ transplant recipients: meeting the challenge of squamous cell carcinoma. J Invest Dermatol. 2004;123(5):809–16.
5. Martinez JC, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermatol. 2003;139(3):301–6.
6. Ong CS, et al. Skin cancer in Australian heart transplant recipients. J Am Acad Dermatol. 1999;40(1):27–34.
7. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47(1):1–17. quiz 18-20.
8. Carroll RP, et al. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis. 2003;41(3):676–83.
9. Gogia R, et al. Fitzpatrick skin phototype is an independent predictor of squamous cell carcinoma risk after solid organ transplantation. J Am Acad Dermatol. 2013;68(4):585–91.
10. Winkelhorst JT, et al. Incidence and clinical course of de-novo malignancies in renal allograft recipients. Eur J Surg Oncol. 2001;27(4):409–13.
11. Idezuki T. Field cancerization and field therapy - the therapy of actinic keratosis by imiquimod. Gan To Kagaku Ryoho. 2013;40(1):1–5.
12. Stockfleth E. Topical management of actinic keratosis and field cancerisation. G Ital Dermatol Venereol. 2009;144(4):459–62.
13. Berman B, Cohen DE, Amini S. What is the role of field-directed therapy in the treatment of actinic keratosis? Part 1: overview and investigational topical agents. Cutis. 2012;89(5):241–50.
14. Dakubo GD, et al. Clinical implications and utility of field cancerization. Cancer Cell Int. 2007;7:2.
15. de Gruijl FR, van Kranen HJ, Mullenders LH. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B. 2001;63(1-3):19–27.
16. Ratushny V, et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. J Clin Invest. 2012;122(2):464–72.
17. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67.
18. Brash DE, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A. 1991;88(22):10124–8.
19. Lane DP. Cancer. p53, guardian of the genome. Nature. 1992;358(6381):15–6.
20. Jiang W, et al. p53 protects against skin cancer induction by UV-B radiation. Oncogene. 1999;18(29):4247–53.
21. Ziegler A, et al. Sunburn and p53 in the onset of skin cancer. Nature. 1994;372(6508):773–6.
22. Nakazawa H, et al. UV and skin cancer: specific p53 gene mutation in normal skin as a biologically relevant exposure measurement. Proc Natl Acad Sci U S A. 1994;91(1):360–4.
23. Restivo G, et al. IRF6 is a mediator of Notch pro-differentiation and tumour suppressive function in keratinocytes. EMBO J. 2011;30(22):4571–85.
24. Hu B, et al. Multifocal epithelial tumors and field cancerization from loss of mesenchymal CSL signaling. Cell. 2012;149(6):1207–20.
25. Gebhardt C, et al. RAGE signaling sustains inflammation and promotes tumor development. J Exp Med. 2008;205(2):275–85.

26. Djerbi N, et al. Influence of cyclosporin and prednisolone on RAGE, S100A8/A9, and NFkappaB expression in human keratinocytes. JAMA Dermatol. 2013;149(2):236–7.
27. Wu X, et al. Opposing roles for calcineurin and ATF3 in squamous skin cancer. Nature. 2010;465(7296):368–72.
28. Lerche CM, et al. Topical pimecrolimus and tacrolimus do not accelerate photocarcinogenesis in hairless mice after UVA or simulated solar radiation. Exp Dermatol. 2009;18(3):246–51.
29. Hui RL, et al. Association between exposure to topical tacrolimus or pimecrolimus and cancers. Ann Pharmacother. 2009;43(12):1956–63.
30. Timmer A, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;9:CD000478.
31. O'Donovan P, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005;309(5742):1871–4.
32. Perrett CM, et al. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. Br J Dermatol. 2008;159(1):198–204.
33. Hofbauer GF, et al. Reversal of UVA skin photosensitivity and DNA damage in kidney transplant recipients by replacing azathioprine. Am J Transplant. 2012;12(1):218–25.
34. Hofbauer GF, Bouwes Bavinck JN, Euvrard S. Organ transplantation and skin cancer: basic problems and new perspectives. Exp Dermatol. 2010;19(6):473–82.
35. Pettersen JS, et al. Tumor-associated macrophages in the cutaneous SCC microenvironment are heterogeneously activated. J Invest Dermatol. 2011;131(6):1322–30.
36. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998; 392(6673):245–52.
37. Figdor CG, et al. Dendritic cell immunotherapy: mapping the way. Nat Med. 2004;10(5): 475–80.
38. Chu CC, Di Meglio P, Nestle FO. Harnessing dendritic cells in inflammatory skin diseases. Semin Immunol. 2011;23(1):28–41.
39. Zaba LC, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. J Invest Dermatol. 2009;129(2):302–8.
40. Bluth MJ, et al. Myeloid dendritic cells from human cutaneous squamous cell carcinoma are poor stimulators of T-cell proliferation. J Invest Dermatol. 2009;129(10):2451–62.
41. Galan A, Ko CJ. Langerhans cells in squamous cell carcinoma vs. pseudoepitheliomatous hyperplasia of the skin. J Cutan Pathol. 2007;34(12):950–2.
42. Nestle FO, et al. Human sunlight-induced basal-cell-carcinoma-associated dendritic cells are deficient in T cell co-stimulatory molecules and are impaired as antigen-presenting cells. Am J Pathol. 1997;150(2):641–51.
43. Mimura K, et al. Vascular endothelial growth factor inhibits the function of human mature dendritic cells mediated by VEGF receptor-2. Cancer Immunol Immunother. 2007;56(6): 761–70.
44. Fujita H, et al. Langerhans cells from human cutaneous squamous cell carcinoma induce strong type 1 immunity. J Invest Dermatol. 2012;132(6):1645–55.
45. Jiang J, Wu C, Lu B. Cytokine-induced killer cells promote antitumor immunity. J Transl Med. 2013;11:83.
46. Takahara M, et al. Stromal CD10 expression, as well as increased dermal macrophages and decreased Langerhans cells, are associated with malignant transformation of keratinocytes. J Cutan Pathol. 2009;36(6):668–74.
47. Lucas AD, Halliday GM. Progressor but not regressor skin tumours inhibit Langerhans' cell migration from epidermis to local lymph nodes. Immunology. 1999;97(1):130–7.
48. van de Ven R, et al. Characterization of four conventional dendritic cell subsets in human skin-draining lymph nodes in relation to T-cell activation. Blood. 2011;118(9):2502–10.
49. Mittelbrunn M, et al. Solar-simulated ultraviolet radiation induces abnormal maturation and defective chemotaxis of dendritic cells. J Invest Dermatol. 2005;125(2):334–42.
50. Lewis J, et al. The contribution of Langerhans cells to cutaneous malignancy. Trends Immunol. 2010;31(12):460–6.
51. Modi BG, et al. Langerhans cells facilitate epithelial DNA damage and squamous cell carcinoma. Science. 2012;335(6064):104–8.

52. Cella M, et al. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. Nat Med. 1999;5(8):919–23.
53. Pfeffer LM, et al. Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. Cancer Res. 1998;58(12):2489–99.
54. Hoeffel G, et al. Antigen crosspresentation by human plasmacytoid dendritic cells. Immunity. 2007;27(3):481–92.
55. Tel J, et al. Human plasmacytoid dendritic cells efficiently cross-present exogenous Ags to CD8+ T cells despite lower Ag uptake than myeloid dendritic cell subsets. Blood. 2013; 121(3):459–67.
56. Tel J, et al. Natural human plasmacytoid dendritic cells induce antigen-specific T-cell responses in melanoma patients. Cancer Res. 2013;73:1063–75.
57. Urosevic M, et al. Disease-independent skin recruitment and activation of plasmacytoid predendritic cells following imiquimod treatment. J Natl Cancer Inst. 2005;97(15):1143–53.
58. Lowes MA, et al. Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). Proc Natl Acad Sci U S A. 2005;102(52):19057–62.
59. Huang FP, et al. Nitric oxide regulates Th1 cell development through the inhibition of IL-12 synthesis by macrophages. Eur J Immunol. 1998;28(12):4062–70.
60. Steinman RM, Banchereau J. Taking dendritic cells into medicine. Nature. 2007;449(7161): 419–26.
61. Janeway Jr CA. How the immune system protects the host from infection. Microbes Infect. 2001;3(13):1167–71.
62. Huang SJ, et al. Imiquimod enhances IFN-gamma production and effector function of T cells infiltrating human squamous cell carcinomas of the skin. J Invest Dermatol. 2009;129(11): 2676–85.
63. Martinez-Sosa P, Mendoza L. The regulatory network that controls the differentiation of T lymphocytes. Biosystems. 2013;113:96–103.
64. Walton S, Mandaric S, Oxenius A. CD4 T cell responses in latent and chronic viral infections. Front Immunol. 2013;4:105.
65. Zhang S, et al. Increased Tc22 and Treg/CD8 ratio contribute to aggressive growth of transplant associated squamous cell carcinoma. PLoS One. 2013;8(5):e62154.
66. Clark RA, et al. Human squamous cell carcinomas evade the immune response by down-regulation of vascular E-selectin and recruitment of regulatory T cells. J Exp Med. 2008;205(10):2221–34.
67. Halliday GM, et al. Spontaneous regression of human melanoma/nonmelanoma skin cancer: association with infiltrating CD4+ T cells. World J Surg. 1995;19(3):352–8.
68. Kim ST, et al. Tumor-infiltrating lymphocytes, tumor characteristics, and recurrence in patients with early breast cancer. Am J Clin Oncol. 2012;36:224–31.
69. Yu P, Fu YX. Tumor-infiltrating T lymphocytes: friends or foes? Lab Invest. 2006;86(3): 231–45.
70. Rutella S, Lemoli RM. Regulatory T cells and tolerogenic dendritic cells: from basic biology to clinical applications. Immunol Lett. 2004;94(1–2):11–26.
71. Beyer M, Schultze JL. Regulatory T cells in cancer. Blood. 2006;108(3):804–11.
72. Thornton AM, Shevach EM. CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. J Exp Med. 1998;188(2):287–96.
73. Ng WF, et al. Human CD4(+)CD25(+) cells: a naturally occurring population of regulatory T cells. Blood. 2001;98(9):2736–44.
74. Kosmidis M, et al. Immunosuppression affects CD4+ mRNA expression and induces Th2 dominance in the microenvironment of cutaneous squamous cell carcinoma in organ transplant recipients. J Immunother. 2010;33(5):538–46.
75. Cederbom L, Hall H, Ivars F. CD4+CD25+ regulatory T cells down-regulate co-stimulatory molecules on antigen-presenting cells. Eur J Immunol. 2000;30(6):1538–43.

76. Bluth MJ, et al. Regulatory T cells are associated with the human cutaneous SCC microenvironment and suppress activation of naive T cells stimulated by CD3/28. J Invest Dermatol. 2010;130:S58.
77. Bates GJ, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol. 2006;24(34):5373–80.
78. Wolf D, et al. The expression of the regulatory T cell-specific forkhead box transcription factor FoxP3 is associated with poor prognosis in ovarian cancer. Clin Cancer Res. 2005; 11(23):8326–31.
79. Ikeda H, Old LJ, Schreiber RD. The roles of IFN gamma in protection against tumor development and cancer immunoediting. Cytokine Growth Factor Rev. 2002;13(2):95–109.
80. Zhang N, Pan HF, Ye DQ. Th22 in inflammatory and autoimmune disease: prospects for therapeutic intervention. Mol Cell Biochem. 2011;353(1–2):41–6.
81. Wolk K, et al. Biology of interleukin-22. Semin Immunopathol. 2010;32(1):17–31.
82. Witte E, et al. Interleukin-22: a cytokine produced by T, NK and NKT cell subsets, with importance in the innate immune defense and tissue protection. Cytokine Growth Factor Rev. 2010;21(5):365–79.
83. Jabbari A, Johnson-Huang LM, Krueger JG. Role of the immune system and immunological circuits in psoriasis. G Ital Dermatol Venereol. 2011;146(1):17–30.
84. Nograles KE, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. J Allergy Clin Immunol. 2009;123(6): 1244–52. e2.
85. Gelebart P, et al. Interleukin 22 signaling promotes cell growth in mantle cell lymphoma. Transl Oncol. 2011;4(1):9–19.
86. Jiang R, et al. Interleukin-22 promotes human hepatocellular carcinoma by activation of STAT3. Hepatology. 2011;54(3):900–9.
87. Ziesche E, et al. The interleukin-22/STAT3 pathway potentiates expression of inducible nitric-oxide synthase in human colon carcinoma cells. J Biol Chem. 2007;282(22):16006–15.
88. Huber S, et al. IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. Nature. 2012;491(7423):259–63.
89. Curd LM, Favors SE, Gregg RK. Pro-tumour activity of interleukin-22 in HPAFII human pancreatic cancer cells. Clin Exp Immunol. 2012;168(2):192–9.
90. Swartz MA, et al. Tumor microenvironment complexity: emerging roles in cancer therapy. Cancer Res. 2012;72(10):2473–80.
91. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol. 2005;5(12):953–64.
92. Wang YC, et al. Notch signaling determines the M1 versus M2 polarization of macrophages in antitumor immune responses. Cancer Res. 2010;70(12):4840–9.
93. Steidl C, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. N Engl J Med. 2010;362(10):875–85.
94. Romieu-Mourez R, et al. Distinct roles for IFN regulatory factor (IRF)-3 and IRF-7 in the activation of antitumor properties of human macrophages. Cancer Res. 2006;66(21):10576–85.
95. Lin EY, Pollard JW. Tumor-associated macrophages press the angiogenic switch in breast cancer. Cancer Res. 2007;67(11):5064–6.
96. Hung K, et al. The central role of CD4(+) T cells in the antitumor immune response. J Exp Med. 1998;188(12):2357–68.
97. Moussai D, et al. The human cutaneous squamous cell carcinoma microenvironment is characterized by increased lymphatic density and enhanced expression of macrophage-derived VEGF-C. J Invest Dermatol. 2011;131(1):229–36.
98. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer. 2002;2(3):161–74.
99. Hamada K, et al. VEGF-C signaling pathways through VEGFR-2 and VEGFR-3 in vasculoangiogenesis and hematopoiesis. Blood. 2000;96(12):3793–800.

100. Baek SK, et al. Prognostic significance of vascular endothelial growth factor-C expression and lymphatic vessel density in supraglottic squamous cell carcinoma. Laryngoscope. 2009;119(7): 1325–30.
101. Sugiura T, et al. VEGF-C and VEGF-D expression is correlated with lymphatic vessel density and lymph node metastasis in oral squamous cell carcinoma: implications for use as a prognostic marker. Int J Oncol. 2009;34(3):673–80.
102. Boone B, et al. The role of VEGF-C staining in predicting regional metastasis in melanoma. Virchows Arch. 2008;453(3):257–65.
103. Franses JW, et al. Stromal endothelial cells directly influence cancer progression. Sci Transl Med. 2011;3(66):66ra5.
104. Belkin DA, et al. CD200 upregulation in vascular endothelium surrounding cutaneous squamous cell carcinoma. JAMA Dermatol. 2013;149(2):178–86.
105. Meuth SG, et al. CNS inflammation and neuronal degeneration is aggravated by impaired CD200-CD200R-mediated macrophage silencing. J Neuroimmunol. 2008;194(1-2):62–9.
106. Broderick C, et al. Constitutive retinal CD200 expression regulates resident microglia and activation state of inflammatory cells during experimental autoimmune uveoretinitis. Am J Pathol. 2002;161(5):1669–77.

Part III
Management of High-Risk SCC

Chapter 5
Management of Patients with Multiple SCCs/ Field Cancerization

Sasha Jenkins Haberle, Lauren Rimoin, Myrto Georgia Trakatelli, and Fiona Zwald

Background: The Concept of Field Cancerization

In the multi-step model of carcinogenesis, it is theorized that actinic keratoses (AK) represent a step in the transformation of normal skin to cutaneous squamous cell carcinoma (CSCC) [1]. The molecular and genetic bases of this process are covered in Chaps. 3 and 4. Over the past decade, there has been increasing evidence that the conventional lesion-directed therapy of AKs (predominantly liquid–nitrogen cryotherapy) has failed to address the clinically negligible but potentially biologically significant preneoplastic changes in surrounding skin [2]. Although actinic keratosis are precancerous [3, 4], the exact probability of a given AK undergoing malignant transformation is unknown [5]. There is a histologic continuum between AK and in situ CSCC which is not clinically obvious and patients with AK will also often have CSCC in the same region of sun-damaged skin. The reported risk of progression to CSCC for individual lesions ranges from 0.025 to 16 % per year [6]. The 10-year risk of malignant transformation of at least one AK on a given patient is 10.2 % [7]. The relative risk of malignant transformation depends ultimately on factors related to the

S.J. Haberle, MD, MPH
Department of Dermatology, Dermatologists of Southwest Ohio, INC, Cincinnati, OH, USA

L. Rimoin, MD
Department of Dermatology, Emory University, Atlanta, GA, USA

M.G. Trakatelli, MD, PhD
Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece

St. Pierre Hospital, Bruxelles, Belgium

F. Zwald, MD, MRCPI (✉)
Piedmont Transplant Institute, Piedmont Hospital, Atlanta, GA, USA
e-mail: Fiona.zwald@gmail.com

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_5

AK itself (for example, thickness), as well as patient characteristics (for example, drug therapy, degree of pigmentation, immune status) [8]. Though not all CSCCs arise from pre-existing AK, approximately 50 % of CSCCs appear to arise from a prior AK lesion [8]. Yet doctors are unable to predict accurately which AKs will progress to CSCCs, nor are they able to recognize premalignant changes in clinically normal-appearing surrounding skin that has been subjected to equivalent ultraviolet exposure and other underlying risk factors [9, 10].

Given the high number of CSCCs arising from AKs, there has been a paradigm shift in which the idea of treating individual AKs has given way to a preference for treatment of a larger field of sun-damaged skin that contains molecular and/or cytological changes that may eventually give rise to carcinoma, a process known as "field cancerization." Within such fields of marked sun-damage, patients may have numerous areas in different stages of cancer development including AK, CSCC in situ, and dermally invasive CSCC (Fig. 5.1) [11]. The concept of field cancerization was first described in the gastrointestinal literature in 1953 as the development of clinically occult areas that express multifocal premalignant genetic mutations before progressing to pathologic dysplasia and eventually to primary and recurrent tumors [1]. The idea of field cancerization clearly applies to the development of

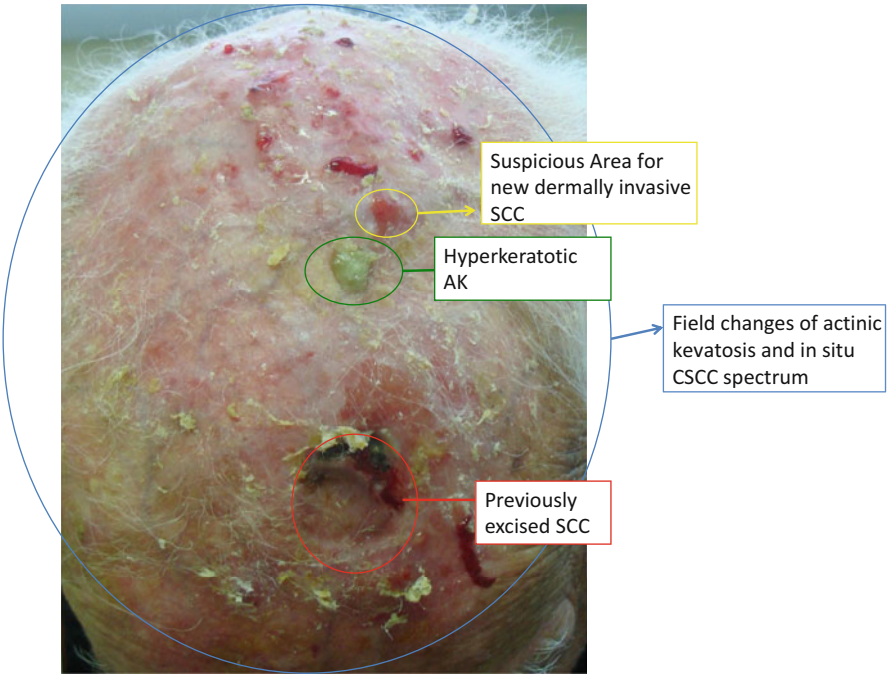


Fig. 5.1 Field cancerization with scar of SCC excision and various lesions consistent with the spectrum of field cancerization: actinic keratosis, hyperkeratotic actinic keratosis, in situ CSCC, and dermally invasive CSCC

non-melanoma skin cancers in actinically damaged skin, and dermatologists are now armed with numerous ways of treating all AKs in a given field rather than spot-treating clinically obvious AKs. The idea of chemoprevention is the use of various agents to prevent, suppress, and reverse the progression of cancer. The implementation of topical therapies, procedural ablative techniques, and systemic prophylactic treatment has been shown to successfully reduce overall burden of premalignant disease in the treatment of clinical and subclinical lesions in large areas of sun-damaged (actinically-damaged) skin.

While initial clearance after field therapy is typically evaluated in studies as a 75 % or greater reduction in total AK lesions, the true goal in these patients should be sustained clearance [12]. Unfortunately, 25–75 % of immunocompetent patients show regrowth of premalignant lesions and subsequently require retreatment within 1 year [13]. The challenge of significant regrowth despite impressive initial clearance can be met by implementing regular cyclical treatment of AKs [12]. This chapter will explore various modalities that may be employed in a repeated rotation for the treatment of larger areas of field cancerization [14]. It should be noted that the combination of lesion-directed cryotherapy and field-directed therapy have been shown to be more effective in maintaining long-term clearance of AKs than field-directed modalities alone [15, 16].

At-Risk Populations

Specific populations are at a greater risk of developing large areas of premalignant change, making them particularly favorable candidates for field cancerization therapy. Table 5.1 summarizes dermatologic conditions associated with increased risk of developing multiple and/or high risk NMSC where chemoprevention should be considered [17]. The highest burden of AKs and CSCCs is seen in older patients with Fitzpatrick skin types I to III and a history of chronic sun exposure [11]. Additional environmental risk factors include frequent sunburns, tanning salon use, exposure to ionizing radiation, cigarette smoking, and arsenic exposure [11]. Certain genetic conditions such as xeroderma pigmentosum and albinism also predispose patients to AKs and CSCCs. Other clinical situations, such as chronic non-healing wounds, longstanding inflammatory diseases like discoid lupus erythematosus, and the presence of porokeratoses also increase one's risk of multiple non-melanoma skin cancer. Geographic location is an important factor to consider, as AKs are more frequently seen in high UV index countries/regions with fair-skinned populations. For example, the prevalence of men aged 30–70 in Australia with AK is just over 55 %, whereas the prevalence in a similar demographic in Europe is only 15 % [18].

Another important group to consider in those at high-risk for multiple AKs and CSCCs are immunosuppressed individuals, particularly solid-organ-transplant recipients (SOTR) and individuals with chronic lymphocytic leukemia (CLL) or AIDS. Accounting for nearly 40 % of all post-transplant neoplasms, skin cancers

Table 5.1 Risk factors for developing numerous and/or high-risk cutaneous squamous cell carcinoma

1. Immunosuppresion • Solid organ-transplant recipients • Other patients on chronic immunosuppressive therapies (e.g. rheumatoid arthritis, colitis) • Hematologic malignancies, particularly chronic lymphocytic leukemia • Infection with human immunodeficiency virus
2. Chronic radiation or excessive ultraviolet light exposure • Severe photodamage • Psoriasis post-PUVA treatment • Chronic radiation dermatitis
3. Genetic syndromes with increased risk of nonmelanoma skin cancer • Xeroderma pigmentosum • Epidermodysplasia verruciformis • Bazex syndrome • Epidermolysis bullosa

are the number one diagnosed malignancy in SOTR [19, 20]. Over half of SOTR are diagnosed with at least one skin cancer, which tend to act more aggressively than skin cancers in immunocompetent people [21]. Similarly, those with CLL have an eight- to tenfold increased risk of skin cancer, with CSCCs occurring more often than BCCs [22].

Immunosuppressed individuals are estimated to have double the risk of CSCC metastasis (approximately 12.9 %) than their immunocompetent counterparts [22]. While sun exposure tends to be the most significant risk factor in these patients and CSCC is rare in immunosuppressed persons with minimal UV exposure or darker skin types, multi-drug immunosuppressive therapy and longer duration of immunosuppression have also been linked to greater CSCC risk [23].

Predictors of Appearance of Multiple CSCCs

There are various risk factors that may predispose to one or numerous CSCC (Table 5.1) and patients often present with a combination of these factors as their coexistence has a synergistic effect for tumor appearance. Many high-risk patients will develop progressively more CSCCs after their first one. The reported cumulative 3-year risk of subsequent CSCC in patients with a prior SCC is 18 % [24], at least a tenfold increase in incidence compared with the incidence of first tumors in a comparable general population.

Predictors of future CSCC in high-risk populations have not been firmly established [24] making management of these patients a continuous challenge. Although increasing age and male sex are strong predictors of CSCC and basal cell carcinoma (BCC) risk in the general population, they do not seem to be strong risk factors for CSCC/BCC after a CSCC/BCC.

In a recent publication [25], in an attempt to better define predictive factors for the appearance of new primary CSCC, a cohort study of a population at high risk of keratinocyte cancers (defined by having heavily sun-damaged skin and at least 3.6 keratinocyte cancers in the 5 years prior to enrollment) were followed for a median duration of 3.7 years for occurrence of CSCC on the face or ears. The most important independent risk factors in this group were number of invasive CSCCs in the 5 years before enrollment, number of actinic keratosis (AK) at enrollment, and total occupational time of outdoor UV exposure. Since the risk of subsequent CSCC may increase with number of previous CSCCs, patients with multiple previous CSCCs merit more frequent examination.

Premalignant and Malignant Lesion Surveillance

While all dermatologists can agree that close follow-up is crucial in individuals with multiple AKs and CSCCs, there are no established guidelines advising how often this should occur. The general consensus suggests that patients with actinic damage should be seen at the very least on a semi-annual to annual basis to determine if ablative treatments have worked, if new AKs have arisen, or if transformation to CSCC has occurred. Physicians should consider history of skin cancer, immune status, extent of past or current sun exposure, age, and comorbidities when deciding on the length of follow up intervals. These recommendations change with particularly high-risk individuals. For example, a dermatologist may evaluate a solid organ transplant patient (SOTR) prior to transplantation to establish a baseline, but follow up recommendations range depending on other risk factors. Those with a history of metastatic CSCC or melanoma should be evaluated every 1–3 months, while those with no history of skin cancer may be evaluated annually, or even every other year for those with darker skin types [21]. Regardless of the interval, each evaluation should consist of a total body skin exam and education regarding sun protection and skin self-exams. Table 5.2 summarizes recommended frequency of dermatology visits for SOTR [24].

Distinguishing Premalignant Lesions from Invasive CSCC

Ideally, dermatologists could confidently and effectively distinguish low risk premalignant lesions, high-risk premalignant lesions, and invasive CSCCs in a clinical setting. However, a 2010 study comparing clinical diagnoses to pathologic diagnoses of AKs versus early CSCCs showed a meager 55 % clinical-pathologic agreement, suggesting that dermatologists should be vigilant and thorough in their

Table 5.2 Follow-up intervals for total body skin examination for solid organ transplantation

Patient risk factor	Interval for total body skin examination (no. of months)
No skin cancer/field disease	12
Field disease	6
One nonmelanoma skin cancer	3–6
Multiple nonmelanoma skin cancers	3
High-risk squamous cell carcinoma or melanoma	2
Metastatic squamous cell carcinoma or melanoma	2

Table 5.3 Factors associated with increased risk of invasive squamous cell carcinoma arising from actinic keratosis

Lesion related	AK characteristics/appearance	Hyperkeratotic, rapidly proliferative or changing, inflammed, tender, bleeding, ulcerated, indurated
	AK number/size	Presence of multiple lesions, large surface area
	AK location	Lip, ear, extremities
Patient related	Characteristics	Male gender, older age, light skin
	Concomitant medical conditions/ medications	Agents that increase sun sensitivity, history of skin cancer, organ transplantation and other settings of chronic immunosuppression, lymphoma and leukemia

treatment of individuals with multiple AKs as one cannot always clinically differentiate between AK, CSCC in situ, and CSCC with early superficial dermal invasion [25]. A recent summary of data regarding clinical indicators of malignant transformation indicates that lesions with induration, bleeding, rapid enlargement in diameter, erythema, and ulceration suggest a risk of malignant transformation to invasive CSCC [26]. Failure to clear with topical therapy is a very important indicator of dermal invasion and is a major reason why topical field therapy (described below) greatly aids the identification of dermally invasive CSCC which do not respond. Other risk factors for progression of AK to CSCC include location (lips, nose, ears, eyelids), male gender, older age, history of skin cancer, fair skin, and presence of hyperkeratosis [27]. Table 5.3 summarizes factors reported as associated with increased risk of invasive squamous cell carcinoma arising from actinic keratosis.

Premalignant lesions such as verruca, AKs, and porokeratoses should be treated aggressively at first development. If these lesions are tender, or have an atypical or enlarging appearance, they should be biopsied for histological evaluation. It must also be emphasized that any lesion that persists after standard treatment must be biopsied.

Patient Education

Studies have shown that people's understanding of skin cancer and the adoption of sun-protection practices is generally low [28]. The ever-increasing incidence of AK and CSCC indicates that the use of sun-protection practices is inadequate, and attempts to improve these behaviors have not always achieved the desired results [29]. A systematic review showed that behavioral counseling could influence sun-protective behavior [28] and thus, this should be carried out keeping in mind that counseling needs to be tailored to the population targeted in order to be effective. Sun-associated behavior modification post-organ transplantation has been proven to reduce the risk of developing CSCC and BCC, even in those patients with a history of prior CSCC [30]. Vitamin D deficiency is a real consequence of aggressive photoprotection, and patients using strict sun protection should be screened and supplemented accordingly. The American Academy of Dermatology recommends daily supplementation with 1000 IU of D3 in adults who regularly and properly practice photoprotection. Given that sun protection reduces risk of CSCC, it is of paramount importance that dermatologic consultations for follow up of field cancerization also serve to raise awareness in the patients of their heightened risk of skin cancer and provide them with skin-care education and protective strategies. Skin-care education is essentially comprised of photoprotection education, and self -skin examination (SSE) education. The advice given to the patients should be repeated at each follow-up consultation and reinforced with written information and/or pamphlets and images [31]. Photoprotection education aims to minimize UV exposure and subsequently the development of new AK and CSCC in patients with previous CSCC and/or BCC. Counseling should explain the importance of UV in skin carcinogenesis and teach the hallmarks of photoprotection that are sun avoidance during peak ultraviolet hours, proper use of sunscreen and protective clothing and avoidance of suntanning. High risk patients should be instructed to wear clothing covering as much skin surface as possible (wide-brim hat, sunglasses, long-sleeved tops and trousers when possible), to avoid exposure to the sun and seek the shade, especially between 11 a.m. and 4 p.m., to avoid the use of tanning beds and to use sunscreen on the chronically sun-exposed sites such as the ears, neck and hands. Sunscreen should protect against both UVA and UVB rays with a sun protection factor of at least 30 (SPF30), and emphasis of reapplication should be discussed [31].

Another important component of skin-care education is teaching the patient how to perform a self-skin examination and describing the possible signs that should alert him to consult his dermatologist. To enhance early detection and treatment, high-risk patients should be educated in the clinical appearance of common benign, premalignant, and malignant skin lesions. Patients should be encouraged to perform self-skin examination monthly looking for skin cancer and precursors. They should be advised to look for any new or changing growths including pink patches or spots, scaly growths, bleeding spots, or changing moles. A practical advice approach is that a growth occurring for >4 weeks or a wound or irritated region that fails to heal within 4 weeks merits dermatological evaluation. In addition, for high-risk patients (high risk squamous cell carcinoma or metastatic disease) a self- examination of the lymph nodes every month is recommended [32].

Chemoprevention Therapies

Topical Therapies

The use of topical therapy is critical in management of patients with field disease and history of multiple CSCCs. As discussed previously, it can be difficult to spot-treat individual clinically apparent actinic keratosis when they are numerous and the use of topical therapies to treat larger surface areas of actinically damaged skin has proven to be a useful method in managing patients. In addition to eliminating dysplastic cells in the epidermis and allowing less damaged, healthier cells to replace them, field treatment helps clinicians to identify dermally-invasive CSCCs which don't respond to topical therapy and that may require surgical excision. In this section, we will discuss the various types of topical therapy that can be used for field therapy.

Cryotherapy

The use of liquid nitrogen on premalignant actinic keratosis is the most widely used treatment. The mechanism of action of cryotherapy involves rapid cooling, resulting in intracellular ice crystal formation, followed by a slow thaw that results in cell damage [33]. Additional cycles lead to more damage. The response rate of a single treatment cycle for actinic keratosis ranges from 68 to 76.2 % [34–36], while the response rate of lesions retreated at 3 or 6 months increased to 86.1–87 % [34, 37]. The use of cryotherapy is helpful in patients that have a limited number of discrete lesions, but in areas of field cancerization it can be challenging to distinguish individual lesions and the affected area may be larger thus making cryotherapy a less suitable and impractical treatment modality.

Topical Retinoids

Retinoids are natural and synthetic derivatives of vitamin A. Retinoids act through either the retinoic acid receptors or the retinoid X receptors, and have been shown to have antiproliferative and cancer preventive properties [38]. There have been a few trials looking at the use of topical retinoids in prevention of CSCC and BCC. A double-blind placebo-controlled trial in 13 renal transplant patients demonstrated no significant difference in the number of actinic keratosis following 6 weeks of twice a day application of tretinoin 0.03 % cream, calcipotriol cream 50 μg/g, combination of the two creams and placebo [39]. A randomized double-blind placebo-controlled trial of 1131 patients at the department of Veterans Affairs did not demonstrate a reduction of development of CSCC and BCC using topical tretinoin 0.1 % cream [40]. Given the evidence, routine use of topical retinoid therapy for chemoprevention of CSCC and BCC is not supported.

Topical 5-Fluorouracil

Topical 5-flourouracil (5-FU) is an antimetabolite that has been used for nearly 50 years in the treatment of preamalignant skin disease in the immunocompetent population and is commonly used for field treatment in solid organ transplant recipients (SOTRs). Its effect is mediated by disruption of RNA synthesis as well as via inhibition of thymidylate synthetase leading to decreased synthesis of DNA which particularly affects the rapidly proliferating cells of AK and in situ CSCC [41, 42]. It is available in 2 and 5 % solution, 5 % cream, and 0.5 % cream, all of which are approved by the FDA for treatment of actinic keratoses. The 5 % fluorouracil (5-FU) is also approved for the treatment of superficial basal cell carcinoma. The 5 % strength is typically used for treatment of field cancerization.

Literature supports an improved clearance rate of AKs in immunocompetent patients compared to immunosuppressed patients. The clearance of AK lesions in immunocompetent patients using 5 % 5-FU cream is about 93.8 % at 24 weeks. An average of 49 % of patients treated with 5 % 5-FU had 100 % clearance of all lesions, while only 34.8 % of patients treated with 0.5 % 5-FU had complete clearance [43]. Yet despite its widespread use in the immunosuppressed including the transplant population, there is a paucity of randomized controlled trials examining the efficacy of 5-FU in the immunosuppressed. A single study performed in 2007 compared the use of MAL-PDT with a typical 3 week course of twice daily application of 5-FU in transplant recipients and found that the 5-FU group experienced only an 11 % rate of complete clearance of the treated fields, with a mean decrease in lesional area of 79 % [44]. This is in marked contrast to prior studies of 5-FU in immunocompetent hosts, where rates of complete clearance of the treated field as high as 90 % have been reported, and is likely secondary to the background immunosuppression seen in SOTRs [45].

5-flourouracil can be used repeatedly, even in transplant patients and no studies to date have reported adverse effects on organ graft function. 5-FU has clearly been shown to reduce the number of AKs, however the results are not long-lasting and treatment needs to be repeated in cycles, usually every 6–18 months. Lastly, the use of topical 5-FU in preventing CSCC has not been studied.

Imiquimod 5 %

Imiquimod is a member of the imidazoquinoline group, possesses antiviral and antitumor activities, and is approved by the FDA for treatment of condyloma acuminata, AKs, and superficial BCCs less than 2 cm on the neck, body, or extremities in immunocompetent adults. Its activity is thought to be mediated in part by interactions with Toll-like receptor (TLR) 7 and stimulation of both innate and adaptive immune responses [46–48]. It is available in 5 % cream and 3.75 % cream, but typically the 5 % cream is used for field therapy.

Imiquimod has been studied in both the immunocompetent and immunosuppressed patient population. A double-blind randomized vehicle-control trial using

5 % imiquimod cream three times per week for 18 weeks demonstrated a complete response rate of 43 % for AKs. In addition, a small-randomized placebo-controlled trial of 31 patients with CSCC in situ showed a resolution of 73 % of cases using imiquimod 5 % cream with no recurrences in a 9 month period [49]. A 2007 study examining the efficacy and safety of topical 5 % imiquimod in organ transplant recipients demonstrated reduced cutaneous dysplasia with complete clearance rates of AKs as high as 62 % in treated patients. No adverse effects on graft organ function were noted during or following treatment with imiquimod on areas of 100 cm^2 three times per week over 16 weeks [50]. Combination with 5 % 5-flourouracil (imiquimod applied Monday, Wednesday, and Friday and 5-FU applied twice daily on off days) may enhance efficacy of each individual agent and has been used successfully to treat lower extremities in situ CSCC in renal transplant recipients [51]. Immunosuppressed patients using 5 % imiquimoid should look for inflammation. If no inflammation is present during treatment duration, application under occlusion can be tried. However, if there is still no inflammation, then treatment should be changed to another agent.

Similar to topical 5-FU, imiqiumod is successful in prevention and treatment of AKs and field disease therapy but has not been studied for chemoprevention of CSCC. Also like topical 5-FU, the results of imiquimod are not long-lasting, and repetitive cycles of imiquimod are necessary in treating patients with field disease therapy. A drawback of imiquimod relative to 5-FU is the small packets in which it is dispensed precluding treatment of larger areas of field cancerization. Treatment of larger areas has been associated with very severe and limiting flu-like symptoms thought due to a systemic cytokine release [52, 53].

Diclofenac Sodium

Diclofenac is a nonsteroidal anti-inflammatory drug, an inhibitor of cyclooxygenase 2, formulated as a 3 % topical gel in 2.5 % hyaluronate sodium. It has been used for the treatment of AKs for more than a decade. Its use has been studied in both immunocompetent and immunosuppressed individuals. A meta-analysis of twice daily application of topical diclofenac vs. placebo revealed that 39.6 % of patients experienced complete AK lesion clearance at 30 days after the end of treatment, in comparison with 12 % of patients treated with a placebo gel [54]. Complete lesion clearance rates (for two separate trials) 30 days after a 90-day treatment with diclofenac were 47 and 34 %, in comparison with 19 and 18 % for the placebo groups [55]. A randomized placebo controlled trial of 32 SOTR using twice daily application of topical diclofenac cream for 16 weeks demonstrated a complete clearance of AK lesions of 41 % in the treated group and 0 % in the placebo group [56]. Furthermore, none of the treated patients developed an invasive CSCC in the study area within 24 months of treatment.

The most common adverse effects reported after treatment with 3 % diclofenac in 2.5 % hyaluronic acid gel are pruritus, contact dermatitis, dry skin, rash, and scaling. Treatment is generally well-tolerated [54]. Treatment of AK using 3 % diclofenac in

2.5 % hyaluronic gel appears to be well tolerated, but with lower efficacy than other topical treatments reviewed, and thus is not recommended as first line therapy for treatment of field disease.

Ingenol Mebutate

Ingenol mebutate is a recently approved topical medication for the treatment of actinic keratoses. The 0.015 % gel formulation is used once daily for 3 consecutive days on the scalp or face, while the 0.05 % gel formulation is used once daily for 2 consecutive days on the trunk or extremities. It is derived from the milkweed plant, *Euphorbia peplus*, and is a hydrophobic macrocyclicditerpene ester. The proposed mechanism of action in immunocompetent hosts involves rapid lesion necrosis and specific neutrophil-mediated, antibody-dependent cellular cytotoxicity [57]. Clearance rates with ingenol mebutate in immunocompetent hosts may be lower than those achieved with topical imiquimod and 5-FU, but with the major advantage of a 2 or 3 day treatment course. Recent clinical trials have shown a 38–42 % complete clearance using short-course field therapy (2–3 days) on actinic keratoses on the trunk or extremities (0.05 % concentration) and in 37–47 % on the face or scalp (0.015 % concentration) [58]. The sustained clearance rate after 12 months was 46.1 % on the face or scalp and 44 % on the trunk or extremities [59]. Adverse effects are similar to those seen with other topical treatments for premalignant skin disease and includes erythema, flaking, scaling, crusting, swelling, vesiculation, pustulation, erosions or ulceration [60]. The main advanatage of the use of ingenol mebutate in field therapy is the shorter treatment course and mild to moderate skin reactions, allowing for increased patient compliance. The primary drawback as with imiquimod, is that the medication is dispensed in very small packets that can treat approximately a 10 cm^2 field making it impractical for treatment of large zones of field cancerization. Ingenol mebutate has not yet been studied exclusively in SOTRs or other immunosuppressed patient populations and it remains to be seen what role it will play in field therapy treatment.

Chemotherapy Wraps

Patient compliance with topical medications may represent a challenge in treating field cancerization given the frequency and duration of treatment required. In addition management of multiple squamous cell carcinomas and actinic keratosis in certain areas, such as the lower legs, feet, forearms and hands is problematic as topical medications are generally less effective in these areas. An off label use of 5 %-fluorouracil under occlusion (chemowraps) was first described as a preoperative adjuvant for biopsy proven CSCCs in diffusely solar damaged lower legs [59]. Patients were treated with weekly wraps between 4 and 20 weeks with a decrease in clinical lesions lasting from 4 weeks to 3 years. Application of 5 %-fluorouracil under occlusion applied weekly and left in place for 5–7 days, is also a useful modality for treating large areas of severe actinic damage [61, 62].

Table 5.4 Use of chemowraps

1. Wash affected area (either leg or arm) with soap and water
2. Apply thick coat of 5 % 5-fluorouracil (should be white) • For the forearms, start on the dorsal hand and extend to below the elbow • For the lower leg, start on the midfoot and extend to the upper calf • For both areas, treat circumferentially, both affected and non-affected skin
3. For the lower leg, apply a Vaseline gauze on the anterior of ankle to minimize friction with movement
4. Apply a zinc-impregnated gauze, such as (Unna paste) with a 50 % overlap over 5-FU
5. Cover with Kerlix with minimal overlap
6. Cover with 6-in. coban or self-adhering wrap
7. Patient removes wrap after 1 week, washes area and returns to clinic for reapplication or is taught to do above steps at home
8. Continue as necessary, usually for 4 weeks but up to 12 is possible if tolerated

Table 5.4 and Fig. 5.2 provide an explanation of technique, but in brief, topical 5-flourouracil is applied to affected areas on the forearms, dorsal hands, and/or legs and feet under occlusion. The patient returns to the office for regular weekly assessments by the dermatologist, care being taken to avoid the occurrence of superficial infection or deep dermal ulceration. To further enhance efficacy, hyperkeratotic crusts should be removed prior to application of 5-FU to allow for better penetration of medication into epidermis. A small amount of local anesthesia may be required. Patients may also be trained to apply wraps themselves or with the aid of family members. Digital photos may be sent to trained office nursing staff and reviewed by physicians as needed between visits. This may sometimes allow patients to complete treatment at home safely if weekly office visits are impractical.

After the end of treatment, a healing period of approximately 4 weeks should be allowed. Any lesions that remain should be biopsied to rule out invasive CSCC Chemowraps are successful for a number of reasons including the following: improved compliance; increased total dose of 5-fluorouracil to the epidermis; higher potency secondary to occlusion; compression allowing for healing of 5-fluoruracil induced damage [63].

Photodynamic Therapy

Photodynamic therapy (PDT) is an appropriate method of field cancerization therapy, particularly in individuals with multiple AKs and those who have difficulty adhering to topical regimens. PDT employs a topical photosensitizer such as 5-aminolevulinic acid (5-ALA) or methyl aminolevulinate (MAL), heme-precursors that are selectively absorbed into rapidly proliferating, iron-deficient tumor cells of epithelial origin [64]. This process preferentially photosensitizes atypical cells in AKs and in situ CSCC, avoiding more extensive cutaneous side effects [65]. This photosensitizing step is followed by exposure to a non-coherent light source 1–3 h later;

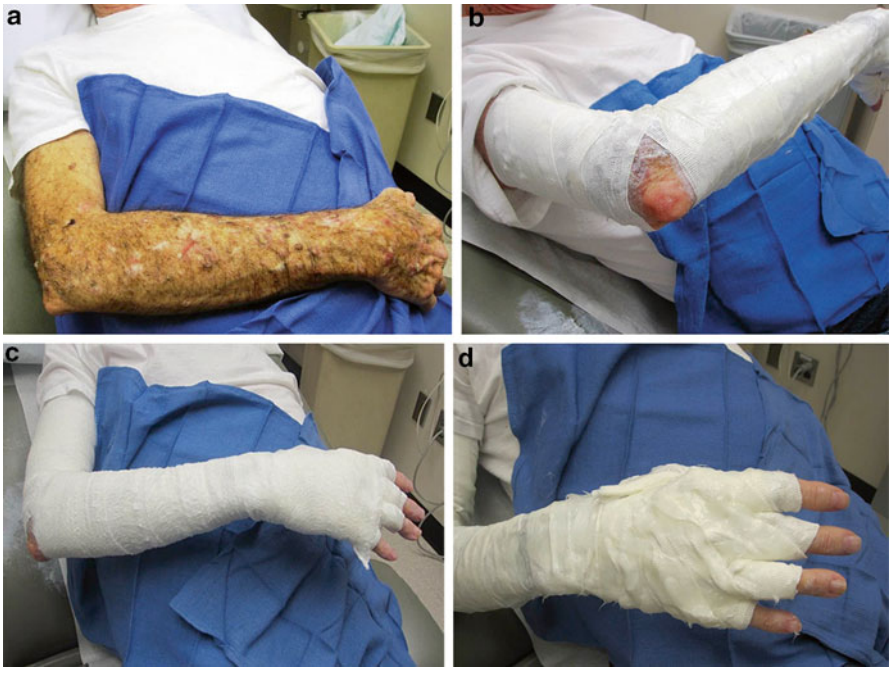


Fig. 5.2 (**a**) Right arm of renal transplant recipient demonstrating extensive field disease with numerous actinic keratoses and lesions clinically suggestive of squamous cell carcinoma in situ. (**b**) Chemowrap in place demonstrating sparing of the elbow to allow for use of the arm and improve patient mobility. (**c**) Chemowrap in place demonstrating individual wrapping of the fingers to allow for patient's use of the hand. (**d**) Close up view of individual wrapping of the hand

light is absorbed by the photosensitizing agent which subsequently generates reactive oxygen species to induce tissue damage in photosensitized cells [64]. Standard protocol for MAL-PDT includes a single treatment for AKs with possible repeat treatment in 3 months, compared to the required two treatments 1 week apart for BCC and in situ CSCC (Bowen's disease) [66]. In the United States, blue light is approved in combination with 5-ALA for the treatment of non-hyperkeratotic AKs; however, red light is recommended for the treatment of in situ CSCC and invasive CSCC up to a thickness of 2–3 mm [64]. However, cure rates for invasive CSCC treated with PDT are lower than with surgical excision. Either broadband lamps or light emitting diodes (LEDs) may be used, although LEDs offer practical advantages in safety and ease of use, with an advantage in treating larger areas and possible greater depth of photodynamic activity compared to broadband light [67].

The use of PDT using MAL has shown complete response rates up to 90 % at 3 months and 78 % at 1 year with excellent cosmesis and few side effects [35, 68, 69]. A 2009 randomized, double-blind, placebo-controlled study multicenter trial showed that PDT using a red light-emitting diode with topical MAL was significantly superior in completely eradicating AKs than placebo PDT (83.3 % vs. 28.7 %) [67].

PDT is an effective option for high-risk individuals such as the immunosuppressed population. Three separate studies evaluating the efficacy of topical PDT with MAL and non-coherent red light for AKs in transplant patients demonstrated complete clearance rates of 64–89 % and a 71–76 % decrease in number of AKs [46, 70, 71]. These studies all followed similar protocols which involved curettage of lesions prior to treatment, and use of non-coherent red light ([44, 70, 71]) A small study followed 12 high-risk OTR who received cyclic PDT using 20 % 5-aminolevuinic acid and blue light every 4–8 weeks over 2 years and monitored development of further CSCC compared to pre-treatment; median reduction in invasive and in situ CSCC at 12- and 24-months post-transplant was 79 and 95 % respectively, showing promise for this treatment modality [72].

The major side effect of PDT is pain during illumination. Pain is less with shorter incubation times of MAL or ALA but shorter incubation time must be balanced against efficacy. Optimal protocols are not yet precisely defined and vary amongst practitioners. Other side effects include erythema, crusting of lesions, and edema, similar to other topical therapies. Because the phototoxic reaction is limited to the epidermis, the cosmetic outcome is excellent, again similar to other topical therapies [12]. Pain can also be minimized with daylight PDT which uses daylight instead of an artificial light source to activate the topical photosensitizers [73]. This technique requires at least 2 h of daylight exposure, which is felt to achieve the same effective light dose as red LED lamps. Sunscreen must be used on the entire sun-exposed area (including treatment areas). Three Northern European trials conducted in 2006 through 2008 showed equivalent efficacy of daylight PDT on treating multiple AKs compared to conventional PDT [74–76]. Another disadvantage in the United States is that PDT is reimbursed at a low rate by most insurers such that the significant nursing and equipment costs are not covered. Subsequently medical practices that perform PDT treatments often do so at a financial loss and so it is not widely offered. Hopefully PDT will become more accessible to patients in the future as it is one of the most efficacious and convenient treatments available for field cancerization and may be cost effective in some patient subsets if it prevents CSCC. This merits further study.

Chemical Peels

Chemical peels are a type of field-directed ablation treatment modality. They can be used either alone or in conjunction with another treatment, such as 5 % 5-fluorouracil. Depending on the strength of the chemical peel agent used, chemical peels remove skin to a variety of depths. The use of medium depth chemical peels (35–40 % trichloroacetic acid) in trials has been shown to decrease actinic damage at 6 weeks and 6 months [77]. Chemical peels can be used as an alternative to patient applied topical medications for field therapy on the scalp and face when patient compliance is an issue. Caution is advised for use of chemical peeling on the neck and upper extremities due to high risks of scarring and dyspigmentation.

Sunscreen

Patient education regarding adequate sun protective measures and appropriate sunscreen application is one of the most important tools in the management and prevention of skin cancer patients at risk for multiple CSCCs and areas of field cancerization, especially SOTR. Sun protection counseling is discussed more fully earlier in this chapter in the patient education section.

Combination Topical Therapies

Though not rigorously studied, combinations of the above modalities may be used. For example, in patients who cannot tolerate prolonged 5-FU or chemowraps, light curetting followed by 3–5 days of 5-FU and then PDT can produce very good results in a short period of time. In addition, topical therapies may be combined with systemic therapies below for optimal control of field cancerization.

Systemic Therapies

Acitretin

Systemic retinoids, specifically acitretin, have demonstrated utility in the suppression of AK and CSCC development, particularly in immunosuppressed patients [38]. This is the result of multiple downstream effects secondary to the binding of acitretin to the nuclear retinoid receptor, including promotion of cell maturation and differentiation as well as down-regulation of proto-oncogene expression [78–80]. Retinoids are used as prophylaxis to prevent morbidity from multiple AKs, CSCCs and BCCs. They have not been shown to decrease the risk of recurrence or mortality from existing CSCCs.

Chemoprevention with acitretin should be considered in patients developing multiple CSCCs and/or BCCs annually (5–10 per year). In addition, in solid organ transplant recipients (SOTRs) or other immusuppresed patients, acitretin use should be considered in those with extensive actinic damage and a history of multiple skin cancers or high-risk CSCC, and in patients with eruptive keratoacanthomas [81]. The development of multiple CSCCs has been reported as a common side effect of vemurafenib and dabrafenib, BRAF inhibitors used in treating metastatic melanoma [82]. It is thought that this might be a result of a paradoxical activation of the MAPK pathway, which occurs in the setting of hyperactivating RAS mutations [83]. The use of acitretin for chemoprevention of CSCC has been successful in patients treated with these new BRAF inhibitor medications [84]. Given that the peak of developing these lesions in patients on BRAF inhibitors is in the first 12–24 weeks, it is important to start using these medications early in the treatment course [84, 85]. Table 5.5 highlights circumstances for consideration of oral chemoprevention in patients.

Table 5.5 Use of retinoids for chemoprevention

Circumstances for starting oral chemoprophylaxis	History of aggressive or high-risk CSCC along with actinic damage
	Patients developing multiple CSCC per year (5–10 annually)
	Patients on BRAF inhibitors who are light skinned with history of UV exposure
Contraindications	Pregnancy and/or lactation
	Women of childbearing potential not on adequate contraception
	Moderate-to-severe liver dysfunction
	Severe kidney dysfunction
	Uncontrollable hyperlipidemia, especially hypertriglyceridemia
	Concomitant medications that interfere with retinoids
	Concomitant hepatotoxic drugs
	Alcohol abuse
Acitretin dosing schedule	Start with 10 mg every day
	Every 2–4 weeks increase the dose by 10–20 mg/day
	Target dose is 15–25 mg/day
Recommended monitoring guidelines	At baseline: history, physical exam, fasting lipid panel, comprehensive metabolic panel (CMP) and complete blood count (CBC), pregnancy test if applicable
	Fasting lipids, CMP, and CBC at week 2 and week 4, then monthly for first 3 months of therapy

The side effect profile of acitretin therapy in SOTRs is similar to that seen in the immunocompetent population and includes mucocutaneous xerosis (dryness), elevated serum lipids, and transaminitis. These effects appear to be dose related [86]. Initiation of therapy at low doses (10 mg every day) and increasing at 10 mg increments at 2–4 week intervals to a goal dose of 20–25 mg daily can minimize side effects by preventing sudden onset of severe mucocutaneous symptoms. Baseline fasting lipids, comprehensive metabolic panel and complete blood count should be obtained and rechecked at 2–4 weeks and then at monthly intervals for the first 3 months of therapy. Acitretin is a teratogen for up to 2 years after it cessation. It is pregnancy category X and should never be used during pregnancy. The use of retinoids in women of childbearing age must be carefully weighed against these risks and regular pregnancy testing and strict contraception practices are critical. The use of two contraceptive methods is recommended 1 month prior to initiation of therapy, during therapy and for 3 years after stopping therapy. Other contraindications to use include severe lipid abnormalities that are refractory to standard therapies. It is important to recognize that this is a long-term therapy; cessation of treatment results in prompt recurrence and sometimes even re-bound effect of pre-malignant/malignant skin disease that can be difficult to control [87, 88]. Table 5.5 summarizes the use of retinoids for chemoprevention [17].

Capecitabine

Capecitabine (an oral form of 5-fluorouracil) is the first FDA approved oral chemotherapeutic and was initially used in patients with metastatic breast cancer and later in patients with both metastatic and primary colon cancer. In 2006, Peramiquel et al. reported inflammation and regression of actinic keratoses in patients receiving capecitabine and shortly thereafter the use of this medication was explored in patients at high risk for cSCC, including SOTRs [89].

Capecitabine is a pro-drug of 5-fluorouracil and the final step in its conversion is mediated in peripheral tissues by thymidine phosphorylase, which is expressed at greater levels in some carcinomas. It is usually dosed at 1 g/m^2/day for 14 days of a 21-day cycle. Prior to starting therapy, liver and renal function panels should be checked, and then lab values should be checked monthly for 3 months, and then every other month [61]. Use of capecitabine is typically performed in conjunction with a multi-disciplinary team.

Two retrospective reviews examined the use of low-dose oral capecitabine in SOTRs with multiple cSCCs and/or BCCs [90, 91]. In these studies patients were treated in repeated 3-week cycles of 1–1.5 g/m^2 daily for 14 days, followed by 7 days of no treatment. The first study, which included only three patients, reported a dramatic decrease in the number of malignant skin lesions requiring excision in the 6 months following study onset compared to the 6 months immediately prior (only 1 lesion excised compared to a total of 35 excisions in the preceding 6 months) [90]. The second retrospective study of 15 solid organ transplant recipients demonstrated a significant decrease in the incidence of cSCCs in 80 % of treated patients using a similar treatment regimen [91]. In addition, 40 % of patients had reduction in the rate of BCC occurrence, and 53.3 % of patients had a decrease in number of AKs. No evidence of rebound after stopping therapy was reported. However, in this study 73 % of patients eventually developed grade 3 or 4 toxicities, most commonly fatigue (40 %), hand-foot syndrome (20 %), and diarrhea (20 %), and 33 % of patients had discontinued treatment by 1 year due to such side-effects [91]. A final case series of 10 solid organ transplant recipients treated with a similar regimen of oral capecitabine (0.5–1.5 g/m) for days 1–14 of a 21 day treatment cycle showed a significant reduction in development of cSCCs per month, as well as actinic keratoses [92]. Similar side effects were demonstrated with two patients (20 %) requiring discontinuation. No cases of graft organ rejection were reported in these publications.

These early reports of capecitabine in organ transplant patients suggest that overall this is a relatively safe treatment, especially at low doses. However, prospective studies are needed to characterize optimal dosing regimens as well as capecitabine's long-term safety and efficacy. Use of capecitabine is typically performed in collaboration with medical oncology (and the transplant team in the case of transplant patients) due to the potential for side-effects, it is generally used when other treatment modalities have proven to be infective in controlling cutaneous field cancerization.

Summary

Managing patients with field disease who develop multiple cutaneous squamous cell carcinomas can be very challenging. These challenging patients require close follow-up with frequent skin checks and monitoring of their skin disease as well as sun protection education. It is extremely important to not only treat individual lesions, but also to treat regions of field cancerization with field therapy. Though not definitively proven to decrease subsequent formation of invasive CSCC, preliminary data indicate treatment of field disease may minimize CSCC formation. Additionally, clearance of extensive field disease can help to clarify the physical exam so that dermally invasive lesions in need of biopsy and surgical clearance can be more readily identified as they are no longer camouflaged by a severely actinically-damaged background. Improving the appearance of very damaged skin likely has significant psychological and social benefits to patients as well.

Multiple treatment modalities may be used for field directed therapy, including topical and systemic medications. Typically, topically applied therapies such as imiquimod, 5FU, or PDT may be used in rotation with destructive modalities, such as cryotherapy, ED&C, and surgical excision. In certain circumstances, application of chemowraps (5FU under occlusion) might be indicated for difficult to treat field disease. In addition, systemic medications might be indicated for chemoprevention in a subtype of patients, such as immunosuppressed individuals. Early biopsy of lesions that persist despite these therapies is essential in successful management of these challenging patients.

References

1. Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. J Drugs Dermatol. 2012;11(12):1462–7.
2. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res. 2003;63:1727–30.
3. Boddie AW, Fischer EP, Byers RM. Squamous carcinoma of the lower lip in patients under 40 years of age. South Med J. 1977;70(6):711–2.
4. Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. Dermatology. 1994;189(1):52–4.
5. Holman CD, Armstrong BK, Evans PR, Lumsden GJ, Dallimore KJ, Meehan CJ, et al. Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. Br J Dermatol. 1984;110(2):129–38.
6. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol. 2000;42(1 Pt 2):23–4.
7. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. Arch Dermatol. 1991;127(7):1029–31.
8. Wallingford SC, Russell SA, Vail A, Proby CM, Lear JT, Green AC. Actinic keratoses, actinic field change and associations with squamous cell carcinoma in renal transplant recipients in Manchester, UK. Acta Derm Venereol. 2015;95:830–4.
9. Schwartz R. The actinic keratosis. A perspective and update. Dermatol Surg. 1997;23(11): 1009–19.

10. Mittelbronn MA, Mullins DL, Ramos-Caro FA, Flowers FP. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol. 1998;37:677–81.
11. Czarnecki D, Meehan CJ, Bruce F, Culjak G. The majority of cutaneous squamous cell carcinomas arise in actinic keratoses. J Cutan Med Surg. 2002;6:207–9.
12. Slaughter DP, Southwick HW, SMejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963–8.
13. Ceilley RI, Jorizzo JL. Current issues in the management of actinic keratosis. J Am Acad Dermatol. 2013;68(1):S28–38.
14. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomized study of topical 5% immiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients wtih actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. Br J Dermatol. 2007;157(Suppl):34–40.
15. Ulrich C. Topical treatment of field cancerization. Cancer Treat Res. 2009;146:439–46.
16. Mastrolonardo M. Topical diclofenac 3% gel plus cryotherapy for treatment of multiple and recurrent actinic keratoses. Clin Exp Dermatol. 2009;34:33–5.
17. Dm A. Combination of topical 5-fluorouracil wtih cryotherapy for treatment of actinic keratoses. J Dermatol Surg Oncol. 1983;9:403–4.
18. Soltani-Arabshahi R, Tristani-Firouzi P. Chemoprevention of nonmelanoma skin cancer. Facial Plast Surg. 2013;29(5):373–83.
19. Stockfleth E TD, Braathen L, Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European. J Eur Acad Dermatol Venereol. 2015;29(11):2069–79. doi: 10.1111/jdv.13180. Epub 2015 Sep 14.
20. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003;348(17):1681–91.
21. Barta U, Grafe T, Wollina U. Radiation therapy for extensive actinic keratosis. J Eur Acad Dermatol Venereol. 2000;14(4):293–5.
22. Greenberg J, Zwald F. Management of skin cancer in solid-organ transplant recipients: a multidisciplinary approach. Dermatol Clin. 2011;29(2):231–41.
23. Weinberg AS, Ogle C, Shim EK. Metastatic cutaneous squamous cell carcinoma: an update. Dermatol Surg. 2007;33:885–99.
24. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):253–61. quiz 62.
25. Otley CC. Organization of a specialty clinic to optimize the care of organ transplant recipients at risk for skin cancer. Dermatol Surg. 2000;26(7):709–12.
26. Terushkin V, Braga JC, Dusza SW, Scope A, Busam K, Marghoob AA, Gill M, Halpern AC. Agreement on the clinical diagnosis and management of cutaneous squamous neoplasms. Dermatol Surg. 2010;10:1514–20.
27. TE Quaedvlieg PJ, Thissen MR, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol. 2006;16(4):335–9.
28. Berman B, Cohen DE, Amini S. What is the role of field-directed therapy in the treatment of actinic keratosis? Part 1: overview and investigational topical agents. Cutis. 2012;89(5):241–50.
29. Lin JS, Eder M, Weinmann S, Zuber SP, Beil TL, Plaut D, et al. U.S. Preventive Services Task Force evidence syntheses, formerly systematic evidence reviews. Behavioral counseling to prevent skin cancer: systematic evidence review to update the 2003 US Preventive Services Task Force recommendation. Rockville: Agency for Healthcare Research and Quality (US); 2011.
30. National Cancer Institute Cancer Trends Progress Report - 2011/2012 Update http://progressreport.cancer.gov 22 August 2014.
31. Ulrich C, Jurgensen JS, Degen A, Hackethal M, Ulrich M, Patel MJ, et al. Prevention of nonmelanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol. 2009;161 Suppl 3:78–84.
32. Hofbauer GF, Anliker M, Arnold A, Binet I, Hunger R, Kempf W, et al. Swiss clinical practice guidelines for skin cancer in organ transplant recipients. Swiss Med Wkly. 2009;139(29–30):407–15.

33. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47(1):1–17. quiz 8-20.
34. Shimizu I, Cruz A, Chang KH, Dufresne RG. Treatment of squamous cell carcinoma in situ: a review. Dermatol Surg. 2011;37(10):1394–411.
35. Morton C, Campbell S, Gupta G, Keohane S, Lear J, Zaki I, et al. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. Br J Dermatol. 2006;155(5):1029–36.
36. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat. 2003;14(2):99–9106.
37. Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol. 2002;47(2):258–62.
38. Kaufmann R, Spelman L, Weightman W, Reifenberger J, Szeimies RM, Verhaeghe E, et al. Multicentre intraindividual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. Br J Dermatol. 2008;158(5):994–9.
39. Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. Br J Dermatol. 2005;152(3):518–23.
40. Smit JV, Cox S, Blokx WA, van de Kerhof PC, de Jongh GJ, de Jong EM. Actinic keratoses in renal transplant recipients do not improve with calcipotriol cream and all-trans retinoic acid cream as monotherapies or in combination during a 6-week treatment period. Br J Dermatol. 2002;147(4):816–8.
41. Weinstock MA, Bingham SF, Digiovanna JJ, Rizzo AE, Marcolivio K, Hall R, et al. Tretinoin and the prevention of keratinocyte carcinoma (basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. J Invest Dermatol. 2012;132(6):1583–90.
42. Eaglsterin WH, Weinstien GD, Frost P. Fluorouracil: mechanims of action in human skin and actinic keratoses. I. Effect on DNA synthesis in vivo. Arch Dermatol. 1970;101:132–9.
43. Tsai E, Zackheim H, Kim Y. Topical and intralesional chemotherapeutic agents. In: Wolverton S, editor. Comprehensive dermatologic drug therapy. 2nd ed. Philadelphi: Elsevier; 2007. p. 643–53.
44. Askew DA, Mickan SM, Soyer HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis--a systematic review of randomized controlled trials. Int J Dermatol. 2009;48(5):453–63.
45. Perrett CM, McGregor JM, Warwick J, Karran P, Leigh IM, Proby CM, 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(2):320–8.
46. Pearlman DL. Weekly pulse dosing: effective and comfortable topical 5-fluorouracil treatment of multiple facial actinic keratoses. J Am Acad Dermatol. 1991;25(4):665–7.
47. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol. 2000;43(1 Pt 2):S6–11.
48. Ito T, Amakawa R, Kaisho T, Hemmi H, Tajima K, Uehira K, et al. Interferon-alpha and interleukin-12 are induced differentially by Toll-like receptor 7 ligands in human blood dendritic cell subsets. J Exp Med. 2002;195(11):1507–12.
49. Kovach BT, Stasko T. Use of topical immunomodulators in organ transplant recipients. Dermatol Ther. 2005;18(1):19–27.
50. Patel GK, Goodwin R, Chawla M, Laidler P, Price PE, Finlay AY, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2006;54(6):1025–32.
51. Ulrich C, Busch JO, Meyer T, Nindl I, Schmook T, Sterry W, et al. Successful treatment of multiple actinic keratoses in organ transplant patients with topical 5% imiquimod: a report of six cases. Br J Dermatol. 2006;155(2):451–4.

52. Smith KJ, Germain M, Skelton H. Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% 5-fluorouracil therapy. Dermatol Surg. 2001;27(6):561–4.
53. Cantisani C, Lazic T, Richetta AG, Clerico R, Mattozzi C, Calvieri S. Imiquimod 5% cream use in dermatology, side effects and recent patents. Recent Pat Inflamm Allergy Drug Discov. 2012;6(1):65–9.
54. Hanger C, Dalrymple J, Hepburn D. Systemic side effects from topical imiquimod. N Z Med J. 2005;118(1223):U1682.
55. Pirard D, Vereecken P, Melot C, Heenen M. Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. Arch Dermatol Res. 2005;297(5):185–9.
56. Solaraze. Diclofenac sodium 3% – package insert. Fairfield: Doak Dermatologics; 2004.
57. Ulrich C, Johannsen A, Rowert-Huber J, Ulrich M, Sterry W, Stockfleth E. Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratoses. Eur J Dermatol. 2010;20(4):482–8.
58. Rosen RH, Gupta AK, Tyring SK. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: rapid lesion necrosis followed by lesion-specific immune response. J Am Acad Dermatol. 2012;66(3):486–93.
59. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366(11):1010–9.
60. Lebwohl M, Shumack S, Stein Gold L, Melgaard A, Larsson T, Tyring SK. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. JAMA Dermatol. 2013;149(6):666–70.
61. Mann M, Berk DR, Petersen J. Chemowraps as an adjuvant to surgery for patients with diffuse squamous cell carcinoma of the extremities. J Drugs Dermatol. 2008;7(7):685–8.
62. Ritchie SA, Patel MJ, Miller SJ. Therapeutic options to decrease actinic keratosis and squamous cell carcinoma incidence and progression in solid organ transplant recipients: a practical approach. Dermatol Surg. 2012;38(10):1604–21.
63. Tallon B, Turnbull N. 5% Fluorouracil chemowraps in the management of widespread lower leg solar keratoses and squamous cell carcinoma. Australas J Dermatol. 2013;54(4):313–6.
64. Babilas P, Landthaler M, Szeimies R. Photodynamic therapy in dermatology. Eur J Dermatol. 2006;16(4):340–8.
65. Peng Q, Soler AM, Warloe T, Nesland JM, Giercksky KE. Selective distribution of porphyrins in skin thick basal cell carcinoma after topical application of methyl 5-aminolevulinate. J Photochem Photobiol B. 2001;62(3):140–5.
66. Morton C, Szeimies RM, Sidoroff A, Braathen L. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol. 2013;27:536–44.
67. Szeimies RM, Matheson RT, Davis SA, Bhatia AC, Frambach Y, Klövekorn W, Fesq H, Berking C, Reifenberger J, Thaçi D. Topical methyl aminolevulinate photodynamic therapy using red light-emitting diode light for multiple actinic keratoses: a randomized study. Dermatol Surg. 2009;35(4):586–92.
68. Pariser DM, Lowe NJ, Stewart DM, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results from a prospective randomized multicenter trial. J Am Acad Dermatol. 2003;48:227–32.
69. Tschen EH, Wong DS, Pariser DM, Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. Br J Dermatol. 2006;155:1262–9.
70. Dragieva G, Prinz BM, Hafner J, Dummer R, Burg G, Binswanger U, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol. 2004;151(1):196–200.
71. Piaserico S, Belloni Fortina A, Rigotti P, Rossi B, Baldan N, Alaibac M, et al. Topical photodynamic therapy of actinic keratosis in renal transplant recipients. Transplant Proc. 2007; 39(6):1847–50.

72. Willey A, Mehta S, Lee PK. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy. Dermatol Surg. 2010; 36(5):652–8.
73. Wiegell SR, Wulf HC, Szeimies RM, Basset-Seguin N, Bissonnette R, Gerritsen MJ, Gilaberte Y, Calzavara-Pinton P, Morton CA, Sidoroff A, Braathen LR. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012;26(6):673–9.
74. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PplX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses – a randomized, controlled, single-blinded study. Br J Dermatol. 2008;158:740–6.
75. Wiegell SR, Haedersdal M, Eriksen P, Wulf HC. Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol. 2009;160:1308–14.
76. Wiegell SR, Fabricius S, Stender IM, et al. A randomized, multicentre study of directed daylight exposure times of 1½ vs. 2½ h in daylightmediated photodynamic therapy with methyl aminolevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol. 2011;164:1083–90.
77. Humphreys TR, Werth V, Dzubow L, Kligman A. Treatment of photodamaged skin with trichloroacetic acid and topical tretinoin. J Am Acad Dermatol. 1996;34(4):638–44.
78. Schule R, Rangarajan P, Yang N, Kliewer S, Ransone LJ, Bolado J, et al. Retinoic acid is a negative regulator of AP-1-responsive genes. Proc Natl Acad Sci U S A. 1991;88(14):6092–6.
79. Hansen LA, Sigman CC, Andreola F, Ross SA, Kelloff GJ, De Luca LM. Retinoids in chemoprevention and differentiation therapy. Carcinogenesis. 2000;21(7):1271–9.
80. Wright TI, Spencer JM, Flowers FP. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol. 2006;54(6):933–46. quiz 47-50.
81. Otley CC, Berg D, Ulrich C, Stasko T, Murphy GM, Salasche SJ, et al. Reduction of immunosuppression for transplant-associated skin cancer: expert consensus survey. Br J Dermatol. 2006;154(3):395–400.
82. Anforth R, Fernandez-Penas P, Long GV. Cutaneous toxicities of RAF inhibitors. Lancet Oncol. 2013;14(1):e11–8.
83. Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med. 2012; 366(3):207–15.
84. Anforth R, Blumetti TC, Clements A, Kefford R, Long GV, Fernandez-Penas P. Systemic retinoids for the chemoprevention of cutaneous squamous cell carcinoma and verrucal keratosis in a cohort of patients on BRAF inhibitors. Br J Dermatol. 2013;169(6):1310–3.
85. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012;366(8): 707–14.
86. Patton TJ, Zirwas MJ, Wolverton SE. Systemic retinoids. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 2nd ed. Philadelphia: Elsevier; 2007. p. 275–300.
87. Kovach BT, Sams HH, Stasko T. Systemic strategies for chemoprevention of skin cancers in transplant recipients. Clin Transplant. 2005;19(6):726–34.
88. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):263–79. quiz 80.
89. Peramiquel L, Dalmau J, Puig L, Roe E, Fernandez-Figueras MT, Alomar A. Inflammation of actinic keratoses and acral erythrodysesthesia during capecitabine treatment. J Am Acad Dermatol. 2006;55(5 Suppl):S119–20.
90. Endrizzi BT, Lee PK. Management of carcinoma of the skin in solid organ transplant recipients with oral capecitabine. Dermatol Surg. 2009;35(10):1567–72.
91. Jirakulaporn T, Endrizzi B, Lindgren B, Mathew J, Lee PK, Dudek AZ. Capecitabine for skin cancer prevention in solid organ transplant recipients. Clin Transplant. 2011;25(4):541–8.
92. Endrizzi B, Ahmed RL, Ray T, Dudek A, Lee P. Capecitabine to reduce nonmelanoma skin carcinoma burden in solid organ transplant recipients. Dermatol Surg. 2013;39(4):634–45.

Chapter 6
Management of High-Risk Primary Tumors Including Nodal Staging

Vishal Anil Patel, Christian L. Baum, and Désirée Ratner

Introduction

As discussed in Chap. 1, cutaneous squamous cell carcinoma (CSCC) comprises approximately 20 % of the non-melanoma skin cancers (NMSC) in the United States [29, 35]. Between 87,000 and 760,000 cases have been estimated to occur annually [37]. Multiple countries have reported an incidence rate that has recently been increasing ([9, 23–25]). More important and more concerning, however, may be the recent finding that mortality from CSCC may be just as common as death from many common cancers including melanoma, renal carcinoma and oropharyngeal carcinoma [30, 31]. While most CSCCs are easily treatable and curable, a certain subset of tumors exhibits more aggressive behavior.

As detailed in Chaps. 1 and 2, approximately 4 % of patients with CSCC develop nodal metastases and 1.5 % of patients die from their disease [9]. Based on estimated incidence data, there were approximately 5604–12,572 patients CSCC patients developing nodal metastasis and 3932–8791 deaths from CSCC in the United States in 2012 [31]. Early identification of the CSCC subsets that carry a substantial risk of recurrence and metastasis and therefore require closer monitoring and more aggressive treatment is the critical first step in the management of this disease process. Chapter 2 discusses in detail risk factors that have been proposed to

V.A. Patel, MD (✉)
Department of Dermatology, Columbia University/New York Presbyterian,
161 Fort Washington, 12th Floor, New York, NY 10032, USA
e-mail: Vap2109@columbia.edu

C.L. Baum, MD
Department of Dermatology, Mayo Clinic,
200 First Street, S.W., Rochester, MN 55905, USA

D. Ratner, MD
Department of Dermatology, Beth Israel Medical Center, St. Luke's Hospital and Roosevelt Hospital, 325 W. 15th Street, New York, NY 10011, USA

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_6

help identify high-risk CSCC and even very high-risk CSCC [46] and how they have impacted tumor-staging systems. We will briefly touch upon and review those aspects as they relate to high-risk CSCC management. This chapter describes treatment options that have been validated as being effective for high-risk CSCC, specifically focusing on conventional excisional surgery, radiation therapy, and Mohs micrographic surgery (MMS). We will also briefly discuss the use of radiation, chemotherapy, and targeted molecular inhibitors as adjuvant therapy for primary tumors. The use of these treatments for locally advanced and metastatic CSCC is described in later chapters. Lastly, we will discuss the role of sentinel lymph node biopsy in the work up of high-risk CSCC.

Identification of High Risk CSCC

Identifying high-risk CSCC is critical so that appropriate treatment can occur as early as possible after diagnosis. However, determining the appropriate management for high-risk tumors may at times be challenging due to the lack of specific prognostic and outcome data for the various risk factors [37]. There is currently a debate regarding which and how many risk factors are sufficient to diagnose a high-risk lesion. Current National Comprehensive Cancer Network (NCCN) guidelines suggest that the presence of any one risk factor in any given CSCC warrants wide excision with a 10 mm margin or MMS [46]. However, the American Joint Committee on Cancer (AJCC) requires a lesion to be >2 cm in diameter or have 2 or more high-risk factors to be considered high-risk [65]. These systems were derived via expert consensus opinion regarding available published data. The Brigham and Women's CSCC staging system proposed in 2013 is derived from cohort outcome data and has proposed a more stringent designation for high-risk CSCC [26]. It is detailed in Chap. 2 and below.

As a result of these differing definitions of high-risk CSCC in the literature and the profound lack of clinical trial data, approaches to management of high-risk tumors may vary greatly between expert clinicians. Improved prognostic stratification as detailed in Chap. 2 and clinical trials of new drugs (described in Chaps. 3 and 9) should soon provide clinicians with more guidance. Meanwhile, for the purposes of our discussion of management options for high-risk CSCC, we encourage readers to consider the data presented in Chaps. 1 and 2 and below to form their own definition of high-risk CSCC and apply the treatments outlined herein to such cases based on the clinician's estimated risk of recurrence, metastasis, and death as derived from currently available data.

A certain subset of CSCC exhibits more aggressive clinical behavior than high-risk tumors as broadly defined by the NCCN (see Chap. 2 for NCCN definition). A tumor may be considered very high risk (Table 6.1) if it displays lymphovascular, perineural ("named nerve"), parotid, cartilaginous, or bony invasion, or if the patient develops in-transit metastasis, or regional or distant metastasis [51]. Furthermore, if a tumor is characterized by a greater number of high risk features, it may be considered very high risk as well ([31, 45]).

Table 6.1 Very high-risk CSCC features

Very high-risk CSCC characteristics
Lymphovascular invasion
Perineural invasion of a "named nerve"
Parotid invasion
Cartilaginous invasion
Bony invasion
In-transit metastasis
Regional or distant metastasis

Table 6.2 Risk factors with highest risk of local or distant metastatic disease in studies employing multivariate analyses

High-risk CSCC tumor characteristics
Recurrence after previous treatment
Tumor diameter greater than 2 cm
Large-caliber (≥0.1 mm) perineural invasion
Depth beyond subcutaneous fat
Desmoplasitic, poorly differentiated or undifferentiated histology

When metastatic disease occurs, 80 % of cases involve the regional lymph nodes [14]. Distant organ metastases are relatively rare. Most deaths from CSCC occur due to uncontrolled locoregional disease [9, 31]. Nodal or extensive locoregional spread may occur along nerves or anatomic fusion planes [51]. Presentation of regional or distant metastatic disease most often occurs within 1 or 2 years of diagnosis, but delays beyond 8 years have been reported [9, 14, 59, 67]. When metastases do occur, the most common sites include other cutaneous locations (in-transit or distant), lung, liver, brain, and bones [29].

Predicting metastatic risk is important, since it serves as a means of anticipating, and thereby working to prevent, poor outcomes from a curable illness. Of the high risk features mentioned above, those associated with the highest risk of local or distant metastatic disease are listed in Table 6.2 and include: recurrence after previous treatment, tumor diameter greater than 2 cm, perineural invasion, depth beyond subcutaneous fat, desmoplasia, and poorly differentiated histology [9, 31, 45, 49]. Further effort has gone into defining a special set of risk factors for tumors whose recurrence or metastatic risk is unusually high but which have not yet manifested evidence of recurrence or metastasis [31, 45]. Analogous to the very high-risk factors described above, Miller reviewed available outcome literature in 2010 and characterized these very high-risk cases in which something more than surgery needs to be done as those with perineural invasion, in-transit metastasis, arising in patients with chronic lymphocytic leukemia, having multiple traditional risk factors or radical subsets of traditional risk factors, such as extension into bone, and tumors for which negative surgical margins cannot be obtained [45]. Tumors of this nature may warrant not only adjuvant treatment or more extensive therapeutic options but also more intensive work-up and staging to more accurately define their prognosis and detect subclinical disease spread.

The Brigham and Women's CSCC staging system published in 2013 is based on cohort outcome data from 1818 CSCC patients and attempts to define a subset of CSCC with sufficient risk of recurrence and metastasis to warrant further study of nodal staging and adjuvant therapy. The presence of 2 or more risk factors (defined in the BWH system as tumor diameter ≥2 cm, depth beyond subcutaneous fat, poor differentiation, or invasion of nerve(s) ≥0.1 mm in caliber) conferred a 24 % (95 % CI 16–34 %) risk of nodal metastases and 16 % (95 % CI 10–25 %) risk of death from CSCC [31]. Those with no risk factors or only a single risk factor had a low risk of poor outcomes (1–2 % risk of local recurrence, 0.2–0.6 % risk of nodal metastasis or death). Such patients may not routinely require staging or treatment beyond surgical clearance.

Tumor Staging Options for High-Risk CSCC

Radiologic Staging

Radiologic imaging has not been studied extensively in staging and prognosis of high-risk CSCC. Currently there is no gold standard for radiologic detection of CSCC in subclinical lymph nodes and data on the sensitivity and specificity of possible modalities is generally lacking [37]. All patients with high-risk CSCC should have a thorough manual physical examination of the draining nodal basin. Such examinations via physical palpation have a reported sensitivity of 75.6 % and specificity of 97.5 % for mucosal head and neck squamous cell cancers and are equal in efficacy to MRI [21]. The sensitivity of manual exam may be even higher for CSCC since involved nodes are usually superficial and thus may be more easily detected on physical exam. Ultrasonography (US) and computed tomography (CT) examination however have been shown to be superior to clinical exam alone and should be considered in cases where there is a high suspicion for lymph node disease [3]. Thus, when lymphatic disease is not detected on clinical exam, radiologic imaging may be used to confirm negative lymph node disease status. Imaging modalities that have been utilized include US, CT, magnetic resonance imaging (MRI), and (18) F-fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT). CT is useful for detecting bony or cartilaginous invasion and nodal disease while MRI is generally reserved for soft tissue and neural evaluation and is used less for detection of subclinical nodal disease. Ultrasound examinations are useful for soft tissue and nodal disease evaluation, while PET/CT scans are useful to identify small foci of metastatic disease.

A recent retrospective review compared the diagnostic value of these four different imaging methods as applied to CSCC, and noted that the sensitivity, specificity, and accuracy were 77.0, 99.4, and 95.3 % for CT and MR; 78.4, 98.5, and 94.8 % for US; and 81.1, 98.2, and 95.0 % for PET/CT, respectively. When the imaging modalities were used in combination, there was improved sensitivity (86.5 %), without loss of specificity (99.4 %) or accuracy (97.0 %) [77]. This study illustrates

that no single screening test has yet been validated as a cost-effective screening tool for CSCC, and although combination imaging may increase sensitivity by as much as 10 %, the additive cost may not make such combined modalities cost-effective at this time.

When specifically looking at perineural invasion, detection by CT or MRI is associated with a poor prognosis. Since nerve invasion must be quite advanced to be detected radiologically, routine imaging is likely not of significant value for most asymptomatic patients, but should be performed in those with marked nerve invasion noted at time of excision or in patients with nerve deficits on exam or paresthesias [76].

Recent reports suggest that PET/CT may assist in identifying suspected sentinel lymph nodes for biopsy [33]. Thus, although clear standards for radiologic imaging as part of the routine work up for high-risk CSCC have not been developed, the need for imaging should be evaluated on a case-by-case basis, especially in those patients in whom extensive local invasion, nerve invasion, or distant metastatis is suspected, or in those with a significant risk of nodal metastasis.

Sentinel Lymph Node Biopsy

The relatively predictable metastatic progression of CSCC to regional lymph nodes has served as the rationale to investigate sentinel lymph node biopsy (SLNB) as a staging method to detect microscopic nodal disease. Data related to this technique is lacking. Most published reports exist in the form of case reports and case series, with only one prospective study reported earlier this year [Gore et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2015 May 12]. Based on these limited data, SLNB for CSCC appears to be safe with rare reports of complications such as hematoma, seroma, cutaneous fistula, and infection [56]. SLNB is a relatively easy procedure. Despite the head and neck location commonly being cited as a technically difficult place to perform SLNB, sentinel lymph nodes have been successfully identified in 95–100 % of reported cases. False-negative SLNB results in high-risk CSCC have ranged from 2.4 to 5 % [2, 56, 61]. This is comparable to results from the melanoma literature, where SLNB is considered an acceptable staging procedure [60].

As in melanoma, many have postulated that SLNB can have prognostic significance in the work up of high-risk CSCC patients and aid treatment decisions. However, the appropriate CSCC patients for consideration of SLNB and the impact of SLNB results on outcomes remain incompletely characterized. Among the variables contributing to this ambiguity includes the absence of a uniform definition of high-risk CSCC and associated prognostic estimates as noted above, inconsistent reporting of the clinicopathologic variables, and lack of adjuvant treatment trials making management of CSCC patients with a positive SLNB somewhat uncertain.

Two recent reviews have suggested a positive SLNB rate of 13.7 % (n = 73) of patient with high-risk head and neck CSCC and 12.3 % (n = 130) in patients with non-anogenital high risk CSCC of varying anatomic locations [2, 61]. In the latter report, patients were staged according to the AJCC 7th edition system and the BWH system to examine the utility of the staging systems as predictors of SLNB results. The BWH system more clearly defined which patients were at risk of having positive SLNB with rates of 0, 7.1, 29.4, and 50 % in BWH T1, T2a, T2b, and T3 tumors, respectively. It is worth noting that despite inconsistent reporting of clinicopathologic features, all primary tumors with a positive SLNB were ≥ 2 cm in diameter in both of these reviews. In a limited number of cases with sufficient follow-up, the negative-predictive value of SLNB for CSCC was reported between 95.2 and 100 % for tumors on the head/neck, trunk, and extremities ([2], Kwon et al. 2011). One prospective study has been recently reported showing that of 57 enrolled patients with high risk CSCC who underwent SLNB, 14% were found to have disease within their lymph nodes [20]. This rate of positive lymph node disease is consistent with the previous reported retrospective studies and suggests that patients with high risk CSCC have a tangible risk of disease spread that should be aggressively worked up and managed.

The execution of SLNB is subject to variability related to the surgeon's experience and procedural technique. In many of the published reports, the technique was not described and when it was described the techniques varied. However, Ahmed et al. suggest that both radionucleotide colloid and intraoperative blue dye should be utilized in all future head and neck CSCC SLNB trials since the combination has significantly improved identification of SLNs in melanoma patients compared to blue dye alone [2, 18].

Sentinel lymph node biopsy continues to be investigational for high-risk CSCC until formal trials are available. However, the relatively low risk of the procedure in the context of patients with sufficiently high risk of microscopic nodal disease, namely BWH T2b or higher or tumors with lymphovascular invasion as they have a risk of nodal metastases of at least 20 %, allows physicians to consider SLNB in the management of high-risk CSCC patients. In contrast to melanoma, most CSCC patients die of uncontrolled locoregional disease rather than distant metastases. Distant metastases tend to occur late in the course of disease if at all. Thus, early detection of nodal disease via SLNB may be more beneficial in reducing recurrence and extending life in CSCC patients than it has been in melanoma. Nodal disease, when caught at an early stage, is highly curable in CSCC but much less so with more advanced nodal disease (see Chap. 8). This also suggests that early detection via radiologic imaging and/or SLNB may positively impact CSCC outcomes though this has yet to be proven. Meanwhile, SLNB may provide helpful staging information which would impact management since adjuvant radiation and/or lymphadenectomy are generally offered to patients with nodal disease, usually with excellent results (Chap. 8). However, it should be noted that current data has yet to show that SLNB provides a mortality benefit in those high risk CSCC patients who have poor outcomes [20].

Primary Treatment Options for High-Risk CSCC Primary Tumors

This section will discuss a variety of management options and algorithms for the treatment and follow-up of high-risk primary CSCC. Treatment of locally advanced unresectable disease, nodal disease, and distant metastases is covered primarily in other chapters (Chaps. 7, 8, and 9, respectively). Electrodesiccation and curettage (ED & C) and cryotherapy are not presented as they have limited value for high-risk CSCC and should be discouraged due to the elevated risk of recurrence without proven histologic clearance. Since the management protocol for high-risk CSCC is otherwise largely undefined, treatment recommendations are constantly changing and may vary between expert providers. We therefore present a broad picture with our own personal recommendations on how best to approach and manage high-risk CSCC.

Excisional Surgery

Surgical excision is the treatment of choice for high-risk CSCC. Surgical excision via MMS will be discussed in the next section and is preferred for CSCC with any risk factors (BWH T2a and above) by the authors due to its higher cure rate described below. However, conventional excisional surgery can offer cure rates up to 95 % for the treatment of primary CSCC [66] and can usually be performed in an outpatient setting. Recurrence rates have been noted to be significantly higher for high-risk CSCC treated with conventional excision over MMS (skin and lip SCC (3.1 % vs 10.9 %), ear SCC (5.3 % vs 18.7 %), locally recurrent SCC (10 % vs 23.3 %), SCC with perineural involvement (0 % vs 47 %), SCC greater than 2 cm in diameter (25.2 % vs 41.7 %), and for SCC that is poorly differentiated (32.6 % vs 53.6 %)) [59]. Careful examination of the margins of the excisional specimen is necessary for confirmation of tumor clearance. A pathologist should examine the lateral and deep specimen margins and the surgeon should aid in orienting the lesion by marking one end of the specimen with a suture tie. The NCCN as well as multiple clinical guidelines and authors have approved standard surgical excision as a treatment option for high-risk CSCC. However, the NCCN recommends primary closure or delay of closure until clear margins have been confirmed so that accurate margins can still be obtained on re-excision. The NCCN recommends that re-excisions for positive histologic margins be done via Mohs or permanent section complete circumferential and deep histologic margin assessment (not vertical bread-loaf sections as is done with conventional excision). The recommended clinical margin for conventional excision is 6–10 mm for high-risk CSCC ([11, 15, 46]). Low-risk CSCC can achieve a 95 % clearance rate with 4–6 mm margins of normal skin [11].

High-risk CSCC defined by NCCN as having any high risk feature (size greater than 20 mm on the trunk or extremities, 10 mm on the cheek, forehead, scalp and

neck, or 6 mm on the mask areas of the face, genitalia, hands or feet; poorly defined clinical borders; recurrent tumor; immunosuppressed host; site of prior radiation therapy or chronic inflammation; rapidly growing tumor; neurologic symptoms; poor histologic differentiation; adenoid, acantholytic or desmoplastic subtypes; perineural or vascular involvement; and invasion of Clark level IV or more) requires more and possibly up to 10 mm margins, to achieve 95 % clearance rates [46]. For tumors that have multiple high-risk features (BWH T2b and T3) or fall under the category of very high-risk (Table 6.1), there are no clear data regarding appropriate clinical surgical margins. A minimum of 10 mm is required per multiple national guidelines ([15, 46]). We recommend 6 mm margins when 1 high-risk factor is present (BWH T2a) and 10 mm margins when greater than 2 high-risk factors are present (BWH T2b or T3). Wider margins of 15 mm or more may be necessary to obtain the highest possible cure rate for more worrisome very high-risk lesions (Table 6.1). When possible, erring on the larger margin in high-risk lesions and delaying closures until negative margins are confirmed is advisable. Thus, conventional surgical excision should be reserved for areas in which there is an abundance of adjacent tissue laxity and where tissue sparing is not a concern (e.g. trunk and extremities). Even in such locations, the large wounds created often cannot be closed primarily thus requiring delayed closure pending clear margin confirmation as per NCCN guidelines. These drawbacks of conventional excision limit its use in high-risk CSCC.

Tumors with multiple high-risk features and/or very high-risk features are not ideal candidates for conventional excision due to the above mentioned issues and the elevated risk of recurrence. High-risk tumors should instead be treated with Mohs micrographic surgery (discussed in next section) so that complete circumferential histologic assessment can be performed at the time of excision as well as immediate reconstruction.

Mohs Micrographic Surgery (MMS)

MMS is named after Frederic Mohs, M.D. who developed the technique as a medical student during the mid-1930s. His focus was on tumor removal with complete microscopic examination of the entire resection margin by the surgeon removing the tumor. The process that he initially developed relied upon chemical fixation of the patient's tissue via zinc chloride paste to allow for serial removal and direct histologic visualization of the tumor [47]. Over time, the procedure was modified to incorporate frozen section technology, but the general concept has remained the same [48, 69]. Frederic Mohs' original essential components involve debulking the tumor, then carefully excising a thin disc of tissue around and under the tumor bed. This tissue is marked with color-coded margins to preserve orientation (superior, inferior, medial, lateral) during histologic analysis. The entire epidermis and undersurface of the excised tissue are sectioned, stained, and microscopically evaluated by the micrographic surgeon (see Figs. 6.1 and 6.2).

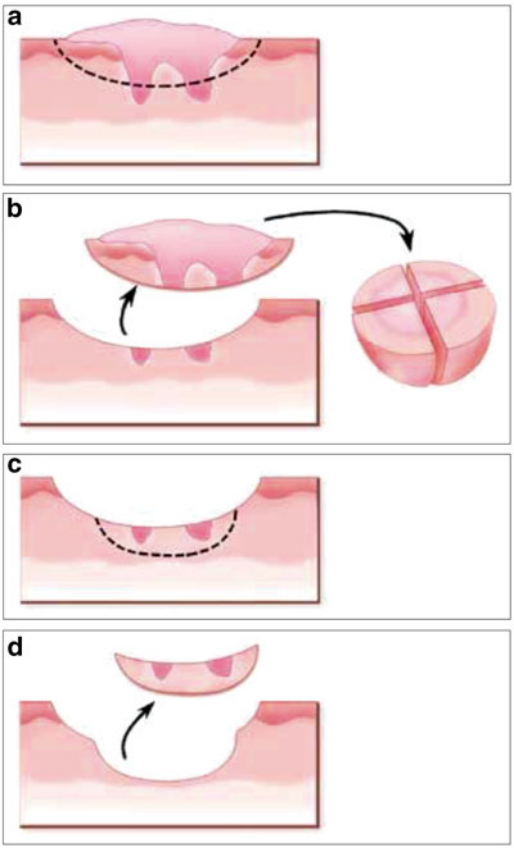


Fig. 6.1 Mohs Microgrpahic Surgery Illustration. (**a**) The roots of a skin cancer may extend beyond the visible portion of the tumor. If these roots are not removed, the cancer will recur. (**b**) The visible portion of the tumor is surgically removed. Removed tumor is divided into segments, each of which is carefully oriented on a "map". The undersurface and edges of each section are then microscopically examined for evidence of remaining cancer. (**c**) If cancer cells are found under the microscope, the surgeon marks their location onto the "map" and returns to the patient to remove another layer of skin-but only precisely where the cancer cells remain. (**d**) The removal process stops when there is no longer any evidence of cancer remaining in the surgical site. Because Mohs surgery removes only tissue containing cancer, it ensures that the healthy tissue is kept intact

In 1974 the technique was improved to allow for rapid high-quality frozen sectioning of the tissue margins, which made it possible to perform multiple excisional stages and repair of the surgical defect on the same day [70]. Any tumor noted on the sections is precisely drawn on a map of the patient's defect [48, 69]. The micrographic surgeon then excises additional tissue from the patient in the areas where the margin is positive and the above process of sectioning, staining and reading the tumor margins is repeated until the tumor is completely removed (see Fig. 6.2).

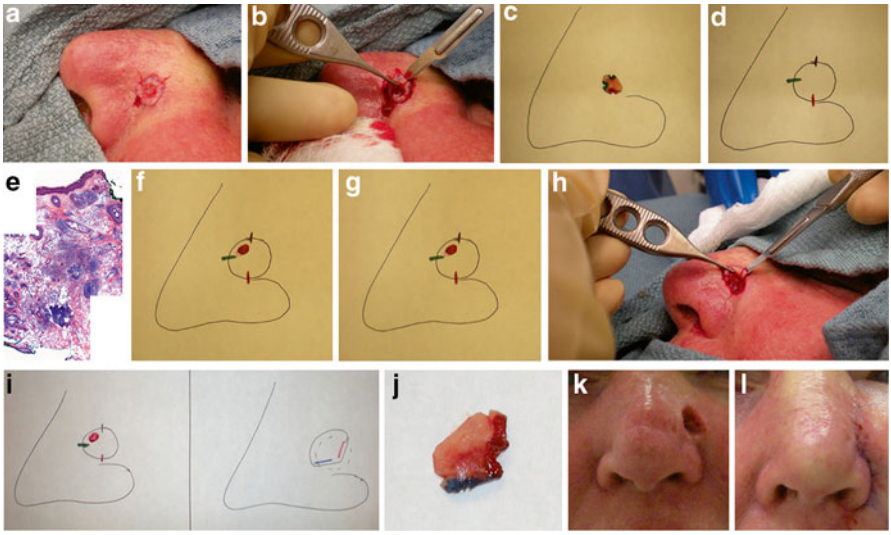


Fig. 6.2 Mohs Micrographic Surgery Technique. (**a**) Clinically visible tumor is debulked and scored hashes made on skin for orientation. (**b**) Tumor is excised with small 1–2 mm border of normal skin. (**c**, **d**) Tissue is placed on map preserving orientation and ink dye is applied to scored hashes and replicated on map diagram. (**e**) Histologic analysis of hematoxylin and eosin stained slides by Mohs surgeon reveals positive margins in deep dermis. (**f**) Remaining tumor is marked on corresponding areas on map diagram. (**g**, **h**) Additional tissue removed from positive areas with the aid of the diagram. (**i**, **j**). Tissue again is inked, mapped, frozen, cut, stained, and read by the surgeon until margins are clear. (**k**, **l**) Wound is reconstructed on the same day using standard reconstructive techniques. (Figure courtesy of Dr. Chrysalyne Schmults)

Horizontal sectioning is the key to the micrographic surgeon's ability to examine the entire surgical margin of the specimen. CSCC specimens are stained via hematoxylin and eosin. However, for more aggressive tumors with perineural invasion or poor differentiation, immunohistochemical staining with cytokeratin may be added to increase the sensitivity of MMS and facilitate tumor identification [78].

Because of the precise MMS mapping technique, only the tissue that requires removal is excised, ensuring maximal normal tissue preservation (see Fig. 6.2). Since the micrographic surgeon directly visualizes the entire marginal surface microscopically, he or she knows exactly where to resect additional tissue (e.g. 4–7 o'clock margin in the subcutaneous fat). Such 3-dimensional precision is difficult to achieve when margin reports are conveyed verbally between pathologists and surgeons without direct visualization of the tumor margin by the surgeon. After confirmation of clear margins, the micrographic surgeon generally performs a repair of the surgical defect immediately. Thus, surgery, pathologic evaluation, and reconstruction of the surgical wound usually occur during the course of a single office visit under local anesthesia, optimizing convenience and minimizing morbidity for the patient, and maximizing cost effectiveness of the procedure.

MMS appropriate usage criteria and indications have been published recently [13]. MMS is the treatment of choice and gold standard for the surgical removal of high-risk CSCC [38]. This is due to the fact that negative margin surgical excisions are associated with significantly lower recurrence rates than those with unknown or unclear surgical margins [28]. The ability to examine 100 % of the surgical margin with MMS validates its superiority to the other treatment modalities discussed above. MMS offers a cure rate of 97 % for primary and 94 % for recurrent CSCCs compared to 92 and 77 % for standard surgical excision [38, 59].

MMS is a more cost-effective, time saving procedure as compared to conventional excision in an operating room or ambulatory surgical center [58]. While the high-risk subgroup of CSCCs is more challenging to treat and has a generally poorer prognosis, MMS is highly effective both in treating these lesions and in preventing local recurrence [7, 55]. Recurrence rates as low as 1.2 % have been reported for high-risk CSCC treated with MMS [55]. This is significantly lower than the recurrence rates of 3.9–5 % associated with conventional excision [28, 38]. When considering specific high-risk features, tumors with a history of recurrence, perineural invasion, diameters greater than 2 cm, and poor differentiation had a lower rate of recurrence when treated with MMS compared to conventional excision (locally recurrent SCC (10 % vs 23.3 %), SCC with perineural involvement (0 % vs 47 %), SCC greater than 2 cm in diameter (25.2 % vs 41.7 %), and for SCC that is poorly differentiated (32.6 % vs 53.6 %)) [59].

Multidisciplinary Surgical Management

Although Mohs surgery is optimal for high-risk CSCC due to its precise margin evaluation, which is particularly helpful in infiltrative and perineural CSCC, most micrographic surgeons operate in outpatient office-based facilities without access to intravenous sedation and general anesthesia. CSCC invading bone or parotid gland or with intracranial perineural extension generally requires some form of sedation during excision and may require extensive reconstruction which cannot be performed under local anesthesia. Many such cases are excised in the operating room with intraoperative frozen section evaluation of selected portions of the margin. However, a significant proportion of high-risk CSCCs excised via conventional excision have positive final histologic margins post surgery (C. Schmults, personal communication, manuscript in preparation), which is associated with poor outcomes as described above.

In such complex cases of locally extensive CSCC, a team approach incorporating Mohs marginal mapping can optimize surgical clearance. In some centers, micrographic surgeon work in operating rooms with head and neck, plastic, craniofacial, or oncologic surgeons. The micrographic surgeon clears as much of the tumor as possible via MMS (see Fig. 6.3). During tissue processing, the other members of the surgical team proceed with local or free flap elevation, parotidectomy, or sentinel node biopsy to help minimize anesthesia time.

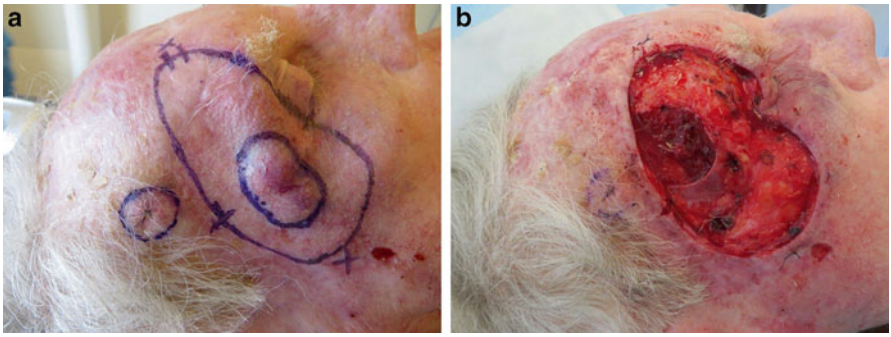


Fig. 6.3 (**a**, **b**) Locally recurrent very high-risk spindle cell SCC with clearance of margins approaching eye and ear. Note X (which is marked with silk suture in operative photo) denotes margin that was cleared along zygoma. Margin along hairline where second in-transit met appeared (note circled area with single central suture) was subsequently cleared by surgical oncology. Repair was performed by plastic surgery with free flap repair

In centers where micrograpahic surgeons do not have tissue-processing facilities adjacent to operating rooms, MMS can still be employed. MMS can be done to establish clear peripheral margins prior to final resection in the operating room. This is done as illustrated by processing a thin but deep (including periosteum) strip of tissue around the tumor periphery via Mohs. The central tumor island is left intact with vascular connection from below if going to OR for definitive resection within 24 h, or via a 5–6 cm portion of perimeter skin left intact if further excision may be delayed (see Fig. 6.4). Once clear peripheral margins are obtained, the wound can be temporarily closed with a basting suture for hemostasis. When the peripheral margins are established in this manner prior to final resection, surgeons can then focus on clearance of the deep margins (e.g. craniotomy, parotidectomy, etc.) in the operating room. This minimizes wait time for intraoperative frozen sections and patient anesthesia time while ensuring precise peripheral margins. Such team approaches can be very useful in the management of very high-risk CSCC.

Primary Radiation Therapy

There is a long history of using radiation therapy as a non-surgical primary treatment option for high-risk CSCC [52]. It has been successfully used in many cases but with overall cure rates generally lower than those reported with surgical excision, particularly Mohs. Cure rates of 80–90 % were reported in a study of medium-sized tumors (1.0–3.0 cm) [39, 62]. An 80 % cure rate was seen in CSCC with incidental perineural invasion [44]. When there is clinical or radiographic evidence of perineural invasion, the cure rates fall to approximately 50 % [44]. Large (>3.0 cm), recurrent, or locally advanced tumors are less responsive to radiation with cure rates falling to 50–88 %, and a high risk for nodal

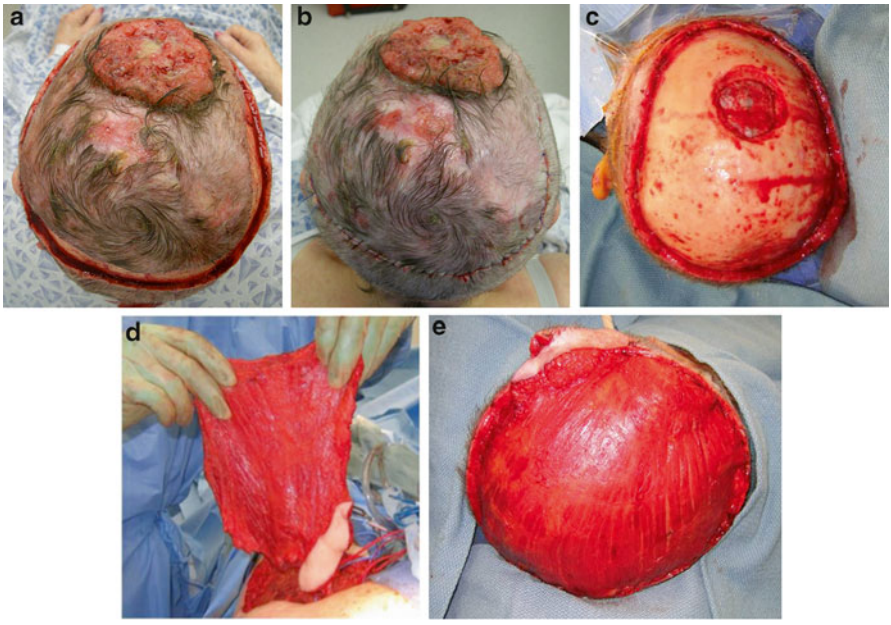


Fig. 6.4 (**a**) Large high-risk CSCC involving bone on pre-op CT treated with strip technique to establish peripheral margin prior to definitive resection and repair in OR via a head and neck surgeon. Multiple smaller CSCCs in field were also included in resection. Tissue is removed including periosteum and processed with vertical sections around perimeter via Mohs technique. Anterior aspect of scalp is left intact to preserve blood supply. (**b**) Temporary basting suture placed to stabilize wound overnight after clear peripheral margins were achieved. (**c**) Next day, tumor and underlying region of involved bone are removed in the OR. (**d**) Latissimus dorsai free flap is elevated. (**e**) Free flap is sutured into place after arterial and venous anastomoses are complete. Patient recovered well without complication and was disease free 2 years later when succumbed to unrelated myocardial infarction. Photos illustrating multidisciplinary surgical care are courtesy of Drs. Chrys Schmults and Don Annino, Brigham and Women's Hosptial, Boston, MA, USA

metastasis [34, 40]. The lip and the eyelid are two anatomic locations in which radiotherapy has been shown to have good to excellent cure rates and cosmetic outcomes exceeding or comparable to surgery (85 % for the lip and 96.38 % for the eyelid) [12, 73]. In the absence of a randomized trial, it is difficult to know whether reports of low cure rates are due to inferior results of radiation therapy as compared to surgery, or to severe inoperable cases being more commonly referred for primary radiation therapy. At least some of the difference in reported cure rates is likely attributable to the latter.

There are several advantages to radiation therapy, including its noninvasive nature, the lack of requirement for anesthesia, and the preservation of cosmetically or functionally critical structures. However, radiation treatment does pose some barriers to widespread use, including the high cost, inability to histologically confirm clear margins, the intensive treatment schedule of multiple days per week for a period of weeks, and delayed scarring and increased skin cancer formation years

after radiation [52]. It is contraindicated in patients with photosensitivity disorders and/or genodermatoses who are susceptible to cutaneous malignancy formation [34]. Given the advances in surgical options and very high cure rates with Mohs surgery, even for high-risk CSCC, the use of radiation therapy is currently generally limited in the U.S. to cases in which the patient is a poor surgical candidate, surgery is not available to the patient, the tumor is inoperable, or when surgery and reconstruction may result in significant cosmetic disfigurement or functional limitation. However, radiation is commonly used as a primary treatment modality for CSCC in Australia [74].

Adjuvant Therapy Options for High-Risk CSCC Primary Tumors

Given the elevated risk of recurrence, metastasis, and death with high-risk CSCC, adjuvant treatment may be advisable in certain cases in an attempt to lower these risks. However, there is minimal consensus even among expert surgeons regarding the best adjuvant management of high-risk tumors after surgery [27]. This is due to lack of clinical trials of adjuvant therapy of high-risk CSCC. Though some such trials are currently in progress, data are not yet available so decisions regarding the utility and advisability of adjuvant therapy are made on a case by case basis, and generally predicated on the judgment of individual practitioners. Below we will discuss the possible options for adjuvant therapy in conjunction with surgery and present one possible algorithm for its use. Our current approach is based on BWH T staging as it is the only system available that has prognostic estimates associated with each T stage. These estimates have helped us to define management parameters summarized in Table 6.3 below.

Adjuvant Radiation Therapy

Postoperative radiation therapy is utilized to prevent local recurrence when there is a likelihood of residual disease present after surgery. Some indications for its use include positive surgical margins (in which case radiation is salvage therapy rather than adjuvant therapy), perineural invasion (of clinically symptomatic, named, or large caliber ≥0.1 mm nerves), lymphovascular invasion, multiple prior local recurrences, and bone invasion (see Fig. 6.5) [44]. There is little specific data or consensus among micrographic surgeons regarding which CSCC patients should receive adjuvant radiation therapy [27].

Patients with perineural invasion and clear surgical margins who were given radiation therapy postoperatively (adjuvant therapy) fared better than those without clear margins treated with radiation therapy (salvage therapy) which stands to

Table 6.3 Proposed primary and adjuvant treatment parameters by BWH tumor (T) stage

Tumor stage	Treatment
Tis (in situ disease)	Topical therapy with 5 % 5-fluorouracil BID × 4 weeks, MMS if recurrent
T1 (0 risk factors[a])	MMS vs. standard surgical excision
T2a (1 risk factor)	MMS
T2b (2–3 risk factors)	MMS
	CT or PET-CT
	Consider SLNB if imaging is negative and patient is a candidate for lymphadenectomy
	Consider ART if large-caliber (≥0.1 mm) nerve or lymphovascular invasion is present, or if surgical margins are uncertain
	Consider adjuvant EGFR antagonist or chemoradiation case by case for patients felt to be at particularly high risk of recurrence including but not limited to in-transit metastasis, large caliber perineural or lymphovascular invasion, parotid, cartilaginous or bone invasion, close (≤1 mm) or positive surgical margins, or lymph node involvement (see Chap. 8)
T3 (4 risk factors or bone invasion)	As per T2b with MMS plus addition of multidisciplinary surgical approach as needed to achieve clear margins whenever possible

[a]BWH risk factors include tumor diameter ≥ 2 cm, depth beyond subcutaneous fat (excluding bone invasion which upgrades tumor to BWH stage T3), poor differentiation, or invasion of nerve(s) ≥ 0.1 mm in caliber [1]
Other important risk factors to consider in decision-making may include desmoplasia and single-cell spread, lymphovascular invasion, and the immune status of the patient
ART adjuvant radiation therapy, *BWH* Brigham and Women's Hospital, *MMS* Mohs micrographic surgery, *SLNB* sentinel lymph node biopsy

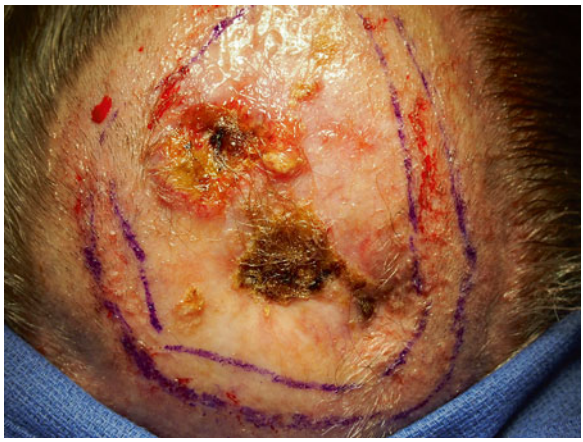


Fig. 6.5 Patient with multiple locally advanced high-risk CSCCs with biopsy proven large-caliber nerve invasion who underwent Mohs Micrographic Surgery and adjuvant radiation

reason and has been shown in many cancer types [5, 34, 44, 57]. This underscores the importance of clear surgical margins above all when considering treatment options and outcomes. Adjuvant radiation therapy is thus not routinely recommended when MMS or surgery with complete circumferential and deep margin assessment is successful and clear margins have been obtained. However, surgical margins can be somewhat equivocal, even with Mohs surgery, when extensive or large-caliber perineural invasion or lymphovascular invasion is present, or when the tumor is highly infiltrative with single-cell spread. No randomized trials evaluating adjuvant radiation vs. surgical monotherapy therapy have been performed for high risk CSCC. However we do recommend, as does the NCCN, considering adjuvant radiation therapy in patients with symptomatic or large caliber (≥0.1 mm) nerve invasion [46]. We also recommend adjuvant radiation in highly infiltrative or recurrent tumors in which tumor clearance is uncertain as well as for tumors with bone or lymphovascular invasion. Salvage radiation therapy is recommended for tumors with positive surgical margins that cannot be cleared with further surgery.

Adjuvant Use of Targeted Molecular Therapies

Epidermal growth factor receptor (EGFR) over-expression has been noted to exert significant effects upon cellular proliferation, progression, and survival in in vitro models of CSCC [63, 71]. EGFR has therefore become a target of significant interest for cutaneous oncologists. There are several EGFR antagonist drugs available, all of which are antibodies to EGFR which block its activity. These include afatinib, cetuximab, erlotinib, and gefitinib. In 2006 the Food and Drug Administration approved cetuximab for the treatment of certain locally and regionally advanced, recurrent, or metastatic oronasopharyngeal mucosal SCCs. Since then, cetuximab has been used in an off-label fashion for the treatment of advanced CSCC. Cetuximab blocks EGFR from binding with epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α) thereby preventing the dimerization and activation of EGFR [41].

In 2008, cetuximab given along with platinum-based chemotherapy and 5-flurouracil was shown to improve overall survival and progression free survival in patients with oronasopharyngeal SCC over patients not given cetuximab [75]. Subsequently, a prospective phase II clinical trial in patients with advanced or metastatic CSCC treated with cetuximab showed disease control response in 69 % of patients (complete response, partial response, or no progression of disease) [42]. Additional case reports have also utilized cetuximab in patients with advanced or unresectable CSCC [19, 32, 54].

There is one report of high-risk CSCC patients benefiting from the use of cetuximab in the adjuvant setting in conjunction with surgery as compared to patients receiving surgery and radiation or chemotherapy [51]. In this series, patients were qualified as very high risk CSCC if tumors displayed lymphovascular, perineural, parotid, periorbital, cartilaginous, or bony invasion; in-transit metastasis; or regional or distant metastasis. 22 patients with very high risk CSCC were identified of whom 4 were treated with surgery alone and 11 were treated with surgery and adjuvant

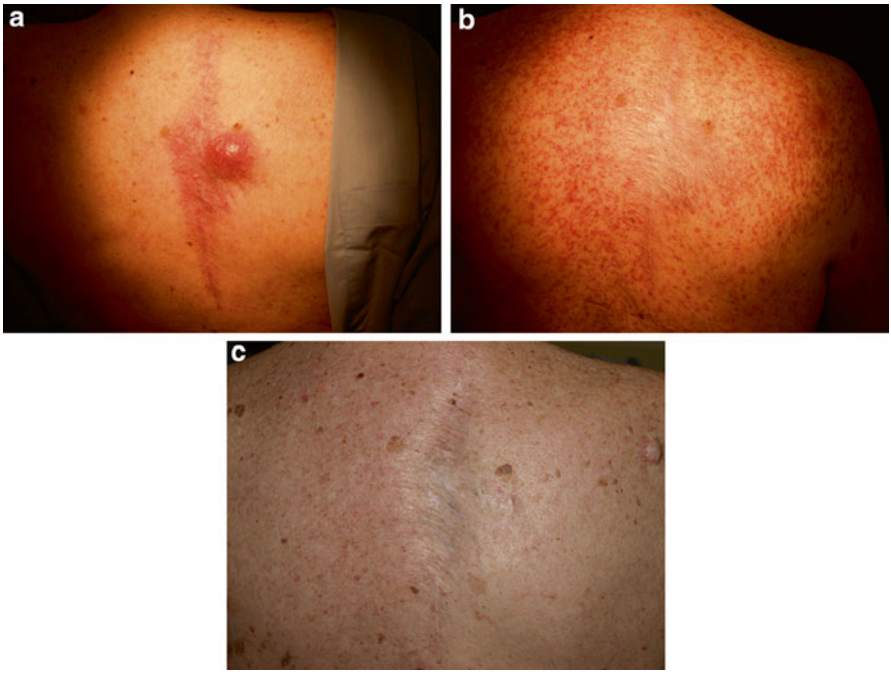


Fig. 6.6 Patient 2 months post excision via MMS of high-risk CSCC on the mid back subsequently (**a**) developing a large in-transit metastasis, (**b**) developing an acneiform eruption following 4 infusions of cetuximab therapy. Infusions were repeated every 6 months for a total of 4 treatment cycles , and (**c**) following therapy with resolution of disease which was maintained at last follow-up 26 months post treatment (Reprinted from Miller K, Sherman W, Ratner D. Complete Clinical Response to Cetuximab in a Patient with Metastatic Cutaneous Squamous Cell Carcinoma. Dermatologic Surgery. 2010 Dec;36(12):2069–74, with permission from Wiley.)

radiation. Of these 15 patients, 10 had disease progression within 1 year. Seven patients with very high risk CSCC were treated with surgery and adjuvant cetuximab, however five of these patients had distant or in-transit metastasis and regional disease. Only two patients had locally advanced very high risk CSCC and were treated with surgical clearance of disease and adjuvant cetuximab therapy following surgery. Both patients obtained complete remission at 2-year follow-up. These authors concluded that cetuximab might prove to be a useful adjuvant agent in tumors with a high risk of recurrence or metastasis that have been cleared with MMS or where clearance is uncertain. Further studies comparing its utility to radiation in the adjuvant setting are needed before concrete recommendations can be made.

Cetuximab dosing is via intravenous infusion and follows a standard protocol of 400 mg/m^2 as an initial dose followed by weekly maintenance doses of 250 mg/m^2 for a total of 6 weeks. Cycles can be repeated as per multidisciplinary oncology recommendation. Of note, patients treated with cetuximab who experience an acne-like rash have been noted to have a better response and increased progression free survival than those without rash (see Fig. 6.6) [42].

Adjuvant Chemotherapy and Chemoradiation

Non-targeted chemotherapy (which generally includes cisplatin in combination with 5-fluorouracil, methotrexate, bleomycin, or doxorubicin) is generally reserved as salvage therapy for locally advanced or metastatic CSCC and is discussed in Chap. 9. However, one study of adjuvant therapy after resection of primary high-risk CSCC (usually with nodal disease) reported a benefit of combined chemoradiation in an adjuvant fashion after surgery [68]. In this study of 61 patients with high risk CSCC of the head and neck region (defined as having at least 1 high-risk pathological feature which includes either involvement of at least 2 lymph nodes (including intraparotid node), positive surgical margins (including those with close, <1 mm margins), or extracapsular invasion), 27 patients (44 %) underwent adjuvant radiation and 34 patients (56 %) underwent adjuvant chemoradiation following surgery. All chemoradiation patients received a platinum agent: 24 patients (70 %) received cisplatin and 10 patients (30 %) received carboplatin. Radiation treatments began 4–8 weeks after surgery and included the primary site with 2-cm margins whenever anatomically feasible. While the median recurrence-free survival was 23.5 months for the entire cohort (95 % CI, 7.4–39.5), recurrence free survival for the adjuvant radiation group was 15.4 months compared to 40.3 months for the adjuvant chemoradiation group. This large improvement in survival with chemoradiation was despite the chemoradiation group consisting of more unfavorable patients (more stage IV, poorly differentiated, and perineurally invasive tumors) although these differences in baseline characteristics were not statistically significant (Tanvetyanon et al. 2014). This may indicate that adjuvant treatment is useful in some subset of high-risk CSCC patients but this subset needs to be better classified and additional clinical trials are sorely needed.

Special Considerations in the Management of High-Risk CSCC Patients

The coexistence of CSCC and immune dysfunction requires further attention to optimize patient management. As detailed in Chaps. 1, 2 and 10, patients with immune dysfunction are at high risk for CSCC development and poor outcomes [6, 17, 22, 43, 64]. Specific management strategies should be undertaken in immunosuppressed subgroups. Within the organ transplant recipient population, reduction of immunosuppression has been shown to reduce the incidence and aggressiveness of CSCC [50]. Certain immunosuppressive medications such as azathioprine and cyclosporine or the antifungal medication voriconazole have been associated with higher rates of CSCC development [79, 80]. Providers should work closely with transplant physicians to optimize immunosuppressive regimens. Specifically, transitioning from calcineurin inhibitors to a sirolimus based immunosuppressive regimen has been associated with decreased formation of CSCC and even improvement

in preexisting lesions [16, 36]. Thus, providers should urge transplant physicians to take such steps to minimize the risk of developing more numerous and more aggressive CSCC without compromising graft function.

Patients with underlying hematologic/immunologic disorders should be monitored closely, especially during surgery, as MMS margins can be more difficult to interpret in patients with atypical lymphocytic infiltrates [4]. Development of high-risk or multiple CSCC may be a sign of worsening hematologic disease or blast crisis [53]. Dermatologists and other skin cancer care providers should therefore notify hematologists of numerous or aggressive CSCC formation in patients with underlying hematologic disease. Similarly, worsening CLL may portend aggressive CSCC formation. In fact, patients with a history of high-stage CLL, even once in remission, have a 12 % risk of death from CSCC which is equivalent to the risk of dying from CLL [72]. Changes in the frequency or aggressiveness of CSCC development in HIV patients may suggest worsening CD4 levels or increased viral loads [64]. HIV physicians may consider checking CD4 and viral load levels or changing antiviral regimens. Good communication with other specialists is key to the management of immunosuppressed patients. A full discussion of CSCC in the immunosuppressed is the topic of Chap. 10.

Patients with extensive photodamage may present with multiple dermally invasive CSCCs in a diffuse field of superficial epidermal actinic damage. These patients pose a special clinical dilemma and their management is covered in Chap. 5. It can be difficult to obtain clear margins in the setting of a field of precancerous lesions surrounding the primary tumor, even using MMS. While surgery may effectively clear the primary tumor, a non-surgical treatment plan may be necessary as well, both to clear adjacent in situ disease or extensive actinic keratoses, and to allow invasive lesions to be detected as early as possible [79, 80]. Initial evaluation of a patient with extensive in situ field disease should first focus on clearing all clinically obvious dermally invasive CSCCs. MMS is recommended as the treatment of choice in this situation since obtaining clear tumor margins in areas with significant surrounding actinic damage may be difficult and requires clinical judgment as well as histologic evaluation of the degree of disease (see Fig. 6.5). It is important that the micrographic surgeon only remove tissue that histologically resembles the primary tumor so as not to unnecessarily remove areas of actinic damage or inflammation. A conservative approach is recommended to prevent enlarging the Mohs surgical defect beyond the need for clear margins.

Once all invasive disease has been surgically removed, multiple treatment modalities can be used to treat the surrounding actinically damaged skin. Clearance of this background damage can be a great aid in clarifying the physical exam. More subtle dermally invasive CSCCs can be detected more easily by dermatologists when they are not camouflaged in a field of actinic dysplasia. Care should be taken to avoid biopsy of lesions which are likely to be epidermal in nature (have no clinical dermal component). These can be treated topically and only biopsied if they fail to respond to this non-invasive approach. Such a strategy allows patients to gain good control of their skin disease without multiple unnecessary biopsies and excisions.

Follow Up

As discussed above, patients who develop high-risk CSCC are at increased risk of recurrence, lymph node metastasis, distant metastasis, and additional high-risk tumors [29]. 65 % of local recurrences occur within the first year and 65 % of local recurrences occur in patients with poorly differentiated tumors [9]. Furthermore, 30–50 % of CSCC patients will go on to develop a second skin cancer within 5 years [45]. Thus, it is critical to follow high-risk CSCC patients closely after treatment. The NCCN recommends that patients undergo a full skin examination and lymph node examination every 3–6 months for the first 2 years, and every 6–12 months for the next 3 years. After 5 years without evidence of recurrence or new disease, an annual exam is recommended [46]. If the patient already has regional disease, more aggressive follow up every 1–3 months is recommended for the 1st year, every 2–4 months for the 2nd year, and 4–6 months until the 5th year. After that, examinations every 6–12 months for the patient's lifetime are recommended [46]. We have incorporated these recommendations into our own algorithm stratified by patient disease stage using the BWH staging system (see Table 6.4). Pre-cancerous actinic keratoses and in situ CSCC should be managed early to decrease the risk of development of high-risk invasive CSCC (see Chap. 5). There is no current data supporting the use of routine radiological examination of lymph nodes to monitor for regional disease recurrence. However, some physicians support the use of radiological examinations every 6 months in patients with extensive perineural invasion or other significant risk factors for aggressive disease (e.g. high level of immunosuppression, history of multiple recurrences of the primary tumor, lymphovascular invasion, or locally advanced disease including very deep infiltration or in-transit metastases) [37]. Lastly, a multidisciplinary team approach composed of cutaneous and medical oncologists, dermatopathologists, Mohs and oncologic surgeons, and radiation oncologists may be of benefit for very high-risk patients to optimize their follow up.

Summary of Management Recommendations for Primary High-Risk CSCC Tumors

High-risk CSCC continues to be a serious and growing problem for which the management strategies are complex and sometimes require a multidisciplinary approach. Prognostic uncertainty has led to inconsistent definitions and treatment recommendations for high-risk CSCC. Clear and precise tumor staging and risk stratification are necessary to effectively manage these patients. Recent advances in prognostic stratification await validation in larger population-based cohorts. Clinical trials are sorely needed to define optimal staging and treatment protocols for different patient subsets but these have not been possible until recently, given the absence of accurate prognostic models that define inclusion criteria in clinical trials.

Table 6.4 Recommended follow up algorithm for patients with high-risk CSCC

BWH T stage	Follow up recommendations
Stage T1 or T2a	Full skin exam and lymph node exam every 6 months for first 2 years
	Then every 6–12 months for next 3 years
	Annually after 5 years
Stage T2a with other non-validated risk factors including immunosuppression	Full skin exam and lymph node exam every 3–6 months for first 2 years
	Then every 6–12 months for next 3 years
	Annually after 5 years
Stage T2b	Full skin exam and lymph node exam every 3 months for first 2 years
	Then every 6 months for next 3 years
	Annually after 5 years
	Consider semiannual radiological evaluation of regional lymph nodes
BWH Stage 3 or AJCC Stage 4	Full skin exam and lymph node exam every 1–3 months for first year
	Then every 2–4 months for next year
	Then every 4–6 months for next 3 years
	Then every 6–12 months for patient lifetime
	Consider semiannual radiological evaluation of regional lymph nodes

Recently, algorithms have been proposed to help guide clinicians in managing high-risk CSCC [51]. We have attempted to synthesize current recommendations and data to provide an up-to-date approach to help clinicians follow a standardized protocol in treating high-risk CSCC (See Table 6.3). The clinical community has not yet have arrived at a general consensus regarding management of high-risk CSCC so some may disagree with elements of this approach and choose not to implement them. However, we have found this framework to be helpful.

Disease stratification and staging are the key initial steps in determining a treatment plan for patients with high-risk CSCC. Since the Brigham and Women's Hospital (BWH) staging system supplies prognostic estimates for each tumor (T) stage, it can be used to prognostically categorize patients. CSCC can be identified as low-risk (BWH stage T1 or T2a) or high-risk (BWH stage T2b or higher). All lesions that fall into the BWH T2b or higher category should be treated with MMS whenever feasible to ensure clear margins. Furthermore, given recent evidence that patients who fall into this category have a 20 % or higher risk of lymph node metastasis, nodal staging should be performed via SLN biopsy (discussed above) and/or CT. PET CT may be used when in transit or distant metastases are of concern [61]. If nodal or metastatic disease is detected, a multidisciplinary approach should be undertaken with tumor board discussion of further surgery, radiation, and possible adjuvant chemotherapy or targeted molecular therapy. If SLN biopsy or PET CT evaluation are negative, there may be a subset of patients who would benefit from adjuvant radiation therapy. Discussion with a tumor board that has experience

managing SCC, such as high risk skin cancer or head and neck groups, can help define treatment plans case by case.

Given that the risk of poor outcomes associated with high-risk features outside the BWH staging system have yet to be well-quantified in multivariate modeling, it is difficult to determine which additional factors, in themselves or in combination, assuredly require further work up or treatment. However, given the significant literature of the poor outcome associated with factors such as desmoplasia, lymphovascular invasion, and pronounced immunosuppression due to kidney, heart or lung transplantation or chronic lymphocytic leukemia, clinicians, with help of tumor boards as needed, should consider such additional factors in determining whether further treatment is necessary. Lastly, whenever negative margins cannot be obtained either via WLE or MMS, the patient should be deemed at high risk for lymph node or metastatic disease and SLN biopsy and PET CT may be considered. Regardless of the outcome of this evaluation, the patient should generally receive some form of adjuvant therapy to eradicate persistent tumor, either via immunotherapy, chemotherapy, and/or radiation therapy.

Conclusions

We have attempted to present the most up-to-date expert opinions regarding comprehensive CSCC management options. However, long-term multicenter and population-based studies are needed to more precisely quantify the exact influence of different risk factors on risks of nodal metastasis and death, and the effectiveness of surgical treatment, nodal staging, adjuvant radiation, and chemotherapy. For now, surgical clearance with complete margin assessment or MMS is the standard of care for most high-risk CSCC primary tumors. Radiological imaging, nodal staging, and adjuvant radiation or chemo/immunotherapy may be appropriate for certain patients as well, especially in patients with certain very high-risk features. Work is underway in these areas to better define which patients may benefit from treatment beyond surgical clearance. Meanwhile, presentation of such patients at multidisciplinary tumor boards to determine course of action is appropriate. Close follow up and early detection of CSCC recurrence and new primaries is an important means of enhancing long-term survival. Future clinical studies should address the questions posed within this chapter to provide clinicians with a complete understanding of the high-risk CSCC disease process and how best to manage it.

References

1. Adam JE. The technic of curettage surgery. J Am Acad Dermatol. 1986;15:697–702.
2. Ahmed MM, Moore BA, Schmalbach CE. Otolaryngol Head Neck Surg. 2014;150(2):180–7.
3. Akoğlu E, Dutipek M, Bekiş R, Değirmenci B, Ada E, Güneri A. Assessment of cervical lymph node metastasis with different imaging methods in patients with head and neck squamous cell carcinoma. J Otolaryngol. 2005;34(6):384–94.

4. Albregts T, Orengo I, Salasche S, Duncan L, Sillman J, Hassoun H. Squamous cell carcinoma in a patient with chronic lymphocytic leukemia. An intraoperative diagnostic challenge for the Mohs surgeon. Dermatol Surg. 1998;24(2):269–72.
5. Al-Othman MO, Mendenhall WM, Amdur RJ. Radiotherapy alone for clinical T4 skin carcinoma of the head and neck with surgery reserved for salvage. Am J Otolaryngol. 2001; 22(6):387–90.
6. Baskaynak G, Kreuzer KA, Schwarz M, Zuber J, Audring H, Riess H, Dörken B, le Coutre P. Squamous cutaneous epithelial cell carcinoma in two CML patients with progressive disease under imatinib treatment. Eur J Haematol. 2003;70(4):231–4.
7. Belkin D, Carucci JA. Mohs surgery for SCC. Dermatol Clin. 2011;29(2):161–74. doi:10.1016/j.det.2011.02.006. vii.
8. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47(1):1–17.
9. Brantsch KD, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, Breuinger H. Analysis of risk factors determining prognosis of cutaneous SCC: a prospective study. Lancet Oncol. 2008;9:713–20.
10. Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992–2003. Br J Dermatol. 2007; 156(6):1295–300.
11. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous SCC. J Am Acad Dermatol. 1992;27:241–8.
12. Caccialanza M, Piccinno R, Gaiani F, Contini D. Relevance of dermatologic radiotherapy in the therapeutic strategy of skin epithelial neoplasms: excellent results in the treatment of lesions localized on eyelids and skin overlying the cartilage of the nose. G Ital Dermatol Venereol. 2013;148(1):83–8.
13. Connolly SM, 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. J Am Acad Dermatol. 2012;67(4):531–50.
14. Dinehart SM, Pollack SV. Metastases from SCC of the skin and lip. An analysis of twenty-seven cases. J Am Acad Dermatol. 1989;21:241–8.
15. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A III, editors. AJCC cancer staging manual. 7th ed. 2010. New York: Springer.
16. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, Broeders N, del Marmol V, Chatelet V, Dompmartin A, Kessler M, Serra AL, Hofbauer GF, Pouteil-Noble C, Campistol JM, Kanitakis J, Roux AS, Decullier E, Dantal J, TUMORAPA Study Group. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367(4): 329–39.
17. Frierson Jr HF, Deutsch BD, Levine PA. Clinicopathologic features of cutaneous SCC of the head and neck in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Hum Pathol. 1988;19:1397–402.
18. Gershenwald JE, Tseng CH, Thompson JW, et al. Surgery. 1998;124:203–10.
19. Giacchero D, Barrière J, Benezery K, Guillot B, Dutriaux C, Mortier L, Lacour JP, Thyss A, Peyrade F. Efficacy of cetuximab for unresectable or advanced cutaneous SCC--a report of eight cases. Clin Oncol (R Coll Radiol). 2011;23(10):716–8.
20. Gore SM et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2015. doi:10.1002/hed.24120.
21. Hao SP, Ng SH. Magnetic resonance imaging versus clinical palpation in evaluating cervical metastasis from head and neck cancer. Otolaryngol Head Neck Surg. 2000;123(3):324–7.
22. Hausauer AK, Maurer T, Leslie KS, Parvataneni R, Stuart SE, Chren MM. Recurrence after treatment of cutaneous basal cell and SCC in patients infected with human immunodeficiency virus. JAMA Dermatol. 2013;149(2):239–41.
23. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous SCC in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989–2008. Eur J Cancer. 2012;48(13):2046–53.

24. Holterhues C, Vries E, Louwman MW, Koljenović S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989–2005. J Invest Dermatol. 2010;130(7):1807–12.
25. Hoey SE, Devereux CE, Murray L, Catney D, Gavin A, Kumar S, Donnelly D, Dolan OM. Skin cancer trends in Northern Ireland and consequences for provision of dermatology services. Br J Dermatol. 2007;156(6):1301–7.
26. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang WT, Gelfand JM, Whalen FM, Elenitsas R, Xu X, Schmults CD. Evaluation of AJCC tumor staging for cutaneous SCC and a proposed alternative tumor staging system. JAMA Dermatol. 2013;149(4):402–10.
27. Jambusaria-Pahlajani A, Hess SD, Katz KA, Berg D, Schmults CD. Uncertainty in the perioperative management of high-risk cutaneous SCC among Mohs surgeons. Arch Dermatol. 2010;146(11):1225–31.
28. Jambusaria-Pahlajani A, Miller CJ, Quon H, et al. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous SCC: *a systematic review of outcomes*. Dermatol Surg. 2009;35:574–85.
29. Johnson TM, Rowe DE, Nelson BR, Swanson NA. SCC of the skin (excluding lip and oral mucosa). J Am Acad Dermatol. 1992;26:467–84.
30. Karia PS, Han J, Schmults CD. Cutaneous SCC: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States. J Am Acad Dermatol. 2012;68(6):957–66.
31. Karia PS, Harrington DP, Jambusaria-Pahlajani A, Murphy G, Qureshi AA, Schmults CD. Evaluation of AJCC and UICC tumor staging for cutaneous squamous cell carcinoma and validation of an alternative system based on 10 year cohort outcome data. J Clin Oncol. 2014 Feb 1;32(4):327-34.
32. Kalapurakal SJ, Malone J, Robbins KT, Buescher L, Godwin J, Rao K. Cetuximab in refractory skin cancer treatment. J Cancer. 2012;3:257–61.
33. Klode J, Poeppel T, Boy C, Mueller S, Schadendorf D, Körber A, Stoffels I, Dissemond J. Advantages of preoperative hybrid SPECT/CT in detection of sentinel lymph nodes in cutaneous head and neck malignancies. J Eur Acad Dermatol Venereol. 2011;25(10):1213–21.
34. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and SCC of the skin. Int J Radiat Oncol Biol Phys. 2004;60:406–11.
35. Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. CA Cancer J Clin. 1999;49:8–31.
36. Leblanc Jr KG, Hughes MP, Sheehan DJ. The role of sirolimus in the prevention of cutaneous squamous cell carcinoma in organ transplant recipients. Dermatol Surg. 2011;37(6):744–9.
37. LeBoeuf NR, Schmults CD. Update on the management of high-risk SCC. Semin Cutan Med Surg. 2011;30:26–34.
38. Leibovitch I, Huilgol SC, Selva D, et al. Cutaneous SCC treated with Mohs micrographic surgery in Australia I. Experience over 10 years. J Am Acad Dermatol. 2005;53:253–60.
39. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):748–55.
40. Lovett RD, Perez CA, Shapiro DL, Garcia DM. External irradiation of epithelial skin cancer. Int J Radiat Oncol Biol Phys. 1990;19:235–42.
41. Liu LS, Colegio OR. Molecularly targeted therapies for nonmelanoma skin cancers. Int J Dermatol. 2013;52(6):654–65.
42. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable SCC of the skin. J Clin Oncol. 2011;29:3419–26.
43. Mehrany K, Weenig RH, Lee KK, et al. Increased metastasis and mortality from cutaneous SCC in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005;53:1067–71.
44. Mendenhall WM, Amdur RJ, Hinerman RW, Cognetta AB, Mendenhall NP. Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. Laryngoscope. 2009;119(10):1994–9.
45. Miller SJ. Defining, treating, and studying very high-risk cutaneous SCC. Arch Dermatol. 2010;146(11):1292–5.

46. Miller S, Alam M, Andersen J, et al. Basal cell and squamous cell skin cancers. J Natl Compr Canc Netw. 2010;8:836–64.
47. Mohs FE, Sevringhaus EL, Schmidt ER. Conservative amputation of gangrenous parts by chemosurgery. Ann Surg. 1941;114(2):274–82.
48. Mohs FE. Chemosurgery: a method for the microscopically controlled excision of cancer of the skin and lips. Geriatrics. 1959;14(2):78–88.
49. Moore BA, Weber RS, Prieto V, El-Naggar A, Holsinger FC, Zhou X, Lee JJ, Lippman S, Clayman GL. Lymph node metastases from cutaneous SCC of the head and neck. Laryngoscope. 2005;115(9):1561–7.
50. Neuburg M. Transplant-associated skin cancer: role of reducing immunosuppression. J Natl Compr Canc Netw. 2007;5(5):541–9.
51. O'Bryan K, Sherman W, Niedt GW, Taback B, Manolidis S, Wang A, Ratner D. An evolving paradigm for the workup and management of high-risk cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2013;69(4):595–602.
52. Pack GT, Davis J. Radiation of the skin. Radiology. 1965;84:436–42.
53. Padgett JK, Parlette 3rd HL, English 3rd JC. A diagnosis of chronic lymphocytic leukemia prompted by cutaneous lymphocytic infiltrates present in Mohs micrographic surgery frozen sections. Dermatol Surg. 2003;29(7):769–71.
54. Preneau S, Rio E, Brocard A, Peuvrel L, Nguyen JM, Quéreux G, Dreno B. Efficacy of cetuximab in the treatment of SCC. J Dermatolog Treat. 2013;25:424–7.
55. Pugliano-Mauro M, Goldman G. Mohs surgery is effective for high-risk cutaneous SCC. Dermatol Surg. 2010;36:1544–53.
56. Ross AS, Schmults CD. Dermatol Surg. 2006;32:1309–21.
57. Ross AS, Whalen FM, Elenitsas R, Xu X, Troxel AB, Schmults CD. Diameter of involved nerves predicts outcomes in cutaneous SCC with perineural invasion: an investigator-blinded retrospective cohort study. Dermatol Surg. 2009;35:1859–66.
58. Rogers HW, Coldiron BM. A relative value unit-based cost comparison of treatment modalities for nonmelanoma skin cancer: effect of the loss of the Mohs multiple surgery reduction exemption. J Am Acad Dermatol. 2009;61(1):96–103.
59. Rowe DE, Carroll RJ, Day Jr CL. Prognostic factors for local recurrence, metastasis, and survival rates in SCC of the skin, ear and lip. J Am Acad Dermatol. 1992;26:976–90.
60. Schmalbach CE, Nussenbaum B, Rees RS, Schwartz J, Johnson TM, Bradford CR. Arch Otolaryngol Head Neck Surg. 2003;129:61–5.
61. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. Staging for cutaneous squamous cell carcinoma as a predictor of sentinel lymph node biopsy results: meta-analysis of American Joint Committee on Cancer criteria and a proposed alternative system. JAMA Dermatol. 2014;150(1):19–24.
62. Scholten AN, Griep C, Davelaar J, Chin A, Leer JW. Electron beam irradiation is effective in the treatment of skin carcinomas; a comparison with superficial roentgen therapy. Ned Tijdschr Geneeskd. 1996;140(8):428–31.
63. Shimizu T, Izumi H, Oga A, et al. Epidermal growth factor receptor overexpression and genetic aberrations in metastatic squamous-cell carcinoma of the skin. Dermatology. 2001;202:203–6.
64. Silverberg MJ, Leyden W, Warton EM, Quesenberry Jr CP, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. J Natl Cancer Inst. 2013;105(5):350–60.
65. Sober A. Cutaneous SCC and other cutaneous carcinomas. In: Edge SB et al., editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
66. Swanson NA. Mohs surgery. Technique, indications, applications, and the future. Arch Dermatol. 1983;119(9):761–73. Review.
67. Talmi YP, Horowitz Z, Wolf M, et al. Delayed metastases in skin cancer of the head and neck: the case of the "known primary". Ann Plast Surg. 1999;42:289–92.
68. Tanvetyanon T, et al. Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2015;37(6):840–5.

69. Tromovitch TA, Beirne G, Beirne C. Mohs' technique (cancer chemosurgery). Treatment of recurrent cutaneous carcinomas. Cancer. 1966;19:867–8.
70. Tromovitch TA, Stegeman SJ. Microscopically controlled excision of skin tumors. Arch Dermatol. 1974;110(2):231–2.
71. Uribe P, Gonzalez S. Epidermal growth factor receptor (EGFR) and SCC of the skin: molecular bases for EGFR-targeted therapy. Pathol Res Pract. 2011;207(6):337–42.
72. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Neel VA, Davids MS, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150:280–7.
73. Veness MJ, Ong C, Cakir B, Morgan G. SCC of the lip. Patterns of relapse and outcome: reporting the Westmead Hospital experience, 1980–1997. Australas Radiol. 2001;45(2): 195–9.
74. Veness M, Richards S. Role of modern radiotherapy in treating skin cancer. Australas J Dermatol. 2003;44:159–66. quiz: 67–68.
75. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116–27.
76. Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. Int J Radiat Oncol Biol Phys. 2001;49:1061–9.
77. Yoon DY, et al. CT, MR, US,18F-FDG PET/CT, and their combined use for the assessment of cervical lymph node metastases in squamous cell carcinoma of the head and neck. Eur Radiol. 2009;19(3):634–42.
78. Zachary CB, Rest EB, Furlong SM, Arcedo PN, McGeorge BC, Kist DA. Rapid cytokeratin stains enhance the sensitivity of Mohs micrographic surgery for SCC. J Dermatol Surg Oncol. 1994;20(8):530–5.
79. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):253–61.
80. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):263–79.

Chapter 7
Management of Local Recurrence and In-Transit Metastasis

Vitaly Terushkin and John A. Carucci

A major risk factor for cutaneous squamous cell carcinoma (CSCC) metastasis is locally recurrent disease, defined as the development of SCC at the site of previously treated tumor. Local recurrence is usually due to inadequate lateral or deep clearance during initial treatment. It may also occur in sites with extensive superficial field disease. Metastasis from recurrent disease ranges from 30 to 50 %, significantly higher than reported with primary SCC [1, 2]. Given the high rate of metastasis and resulting death from local recurrence, timely diagnosis and management of recurrence is critical to preventing mortality from SCC. Depending on extent of disease, management options include surgical and non-surgical options, and/or a combination of treatment strategies. In some cases, a multi-disciplinary setting involving specialists from Mohs surgery, medical oncology, head and neck surgery or surgical oncology, and radiation oncology may be required to give the best chance for cure.

Risk factors for recurrence are covered in Chaps. 1 and 2. This chapter will focus on diagnosis, and management of locally recurrent SCC. An additional section on a recently described and related entity known as in-transit metastases is also included.

Diagnosis and Staging of Recurrent Disease

While recurrent SCC may develop after any duration following treatment of the initial neoplasm, most recurrences occur within 5 years. Rowe et al. [1] found that 58, 75, 83, 91, and 95 % of recurrences are diagnosed by 1, 2, 3, 4, and 5 years after initial therapy. Brantsch et al. [3] followed 615 patients treated for SCC for a median 43 months and found that most patients (13 of 20) developed recurrences within

V. Terushkin, MD (✉) • J.A. Carucci, MD, PhD (✉)
Ronald O. Perelman Department of Dermatology, New York University Langone Medical Center, New York, NY, USA
e-mail: vitaly.terushkin@gmail.com; john.carucci@nyumc.org

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_7

1 year after the primary tumor was diagnosed. In a study of recurrences from treated SCC originating in burn and radiation therapy patients, the median time to recurrence was 15 months [4].

Clinical presentation varies but most lesions arise within or near the original excision site as keratotic and/or ulcerated, erythematous papules, plaques, or nodules. Some lesions may lack surface change if they have little or no epidermal connection and are largely intradermal or subcutaneous. Thus a careful clinical exam including palpation of skin within 10–15 cm of the surgical site is useful during follow-up exams, particularly if the primary tumor met the high risk criteria described in Chaps. 1 and 2. The spectrum of clinical presentations is variable and some cases can be quite disfiguring (Fig. 7.1). However, others can be deceptively subtle in their clinical presentation (Fig. 7.2). A deep shave biopsy is often sufficient to secure a diagnosis, but a punch or incisional/excisional biopsy may be preferred if subcutaneous nodules are present or if there is substantial scarring from prior excision. Histopathology is similar to that of primary cutaneous squamous cell carcinoma, with the possible additional features of vertical compressed blood vessels and horizontal collagen bundles signifying the presence of a scar. A connection to the epidermis may not always be present if the tumor is below the scar.

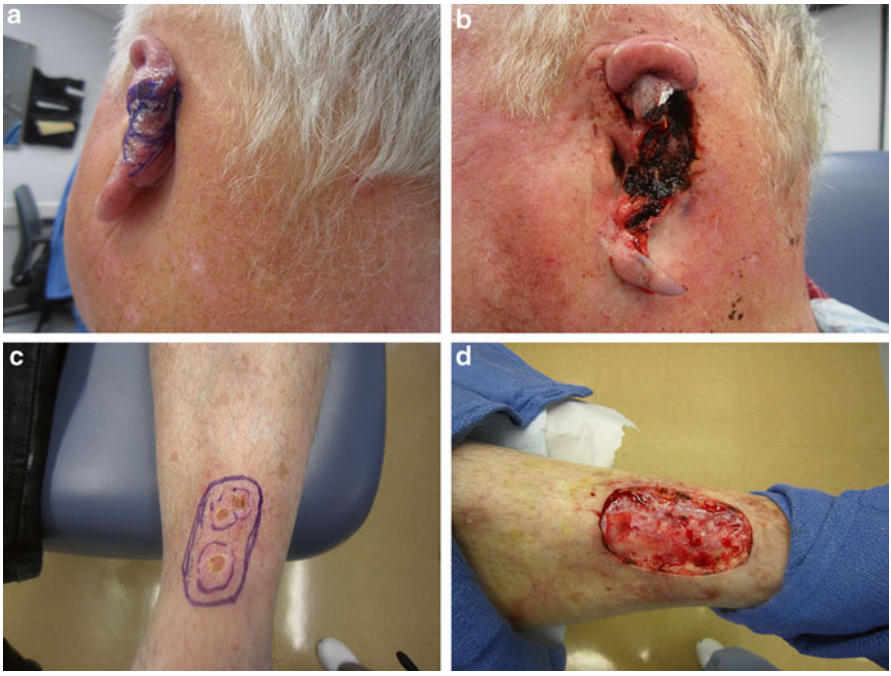


Fig. 7.1 Recurrent SCC. (**a**) Multiply recurrent SCC on the ear; (**b**) Patient s/p Mohs. Remaining area of extensive perineural invasion into the ear canal and positive area of temporal bone were resected in a second procedure via a head and neck surgeon under general anesthesia; (**c**) recurrent SCC on the leg; (**d**) Recurrent SCC after clear margins were obtained via Mohs excision

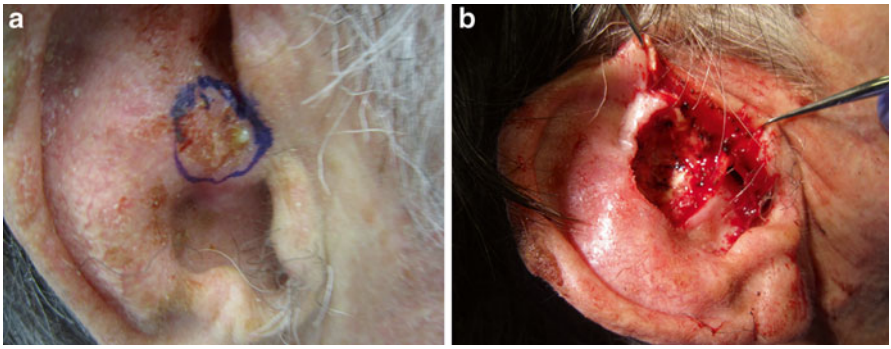


Fig. 7.2 SCC with Perineural invasion. (**a**) Recurrent SCC on the ear of a solid organ transplant recipient; (**b**) Intraoperative view during removal of SCC with extensive perineural invasion. Patient subsequently underwent adjunctive radiation therapy

In addition to evaluating the original excision site, physical examination should also include a thorough neurologic assessment of sensory and motor function in the region. Focal neurologic signs may indicate significant perineural infiltration from recurrent disease. Radiologic evaluation may include magnetic resonance (MR) imaging to assess soft tissue extension and may confirm extensive perineural disease if large nerves are involved. Lesser nerve involvement is often not detectable radiologically.

It is also important to thoroughly palpate the draining lymph nodes as patients with recurrent disease may have progression of disease to involve lymph nodes. Radiological options for nodal staging include MR, CT, PET-CT, ultrasound, and sentinel lymph node biopsy (SLNB). The latter is often not feasible in recurrent cases due to scar and/or tissue rearrangement from prior surgery which impedes sentinel node localization. The authors prefer PET-CT in most cases; however, we suggest discussion with radiologists to determine which might be most appropriate for a given circumstance.

Therapeutic Options for Recurrent Disease

As described above, recurrent SCC is an aggressive entity with potential for significant morbidity and mortality. Treatments which may be used for primary in situ or superficially invasive low-risk SCC, such as liquid nitrogen, electrodessication and curettage, topical chemotherapy, photodynamic therapy, are inadequate and therefore not appropriate for recurrent disease. We strongly recommend surgical management where margins can be examined by histopathology, such as Mohs micrographic surgery (MMS) or surgical excision, to ensure that margins are free of disease. Less frequently, there are instances where radiation therapy, either alone or more commonly in combination with surgery, may be utilized.

Surgery

To date, no randomized studies have compared the efficacy of standard surgical excision versus MMS for either primary or recurrent SCC. However, multiple studies have shown that standard excision which commonly employs 4 mm margins may be inadequate for management of high-risk SCC [5–7].

Tan et al. [7] prospectively studied 10 cases of primary SCC excised with positive margins and 27 recurrent SCCs treated with excision. Of the ten incompletely excised lesions that were referred for re-excision, six (60.0 %) were again incompletely excised. Of the 27 recurrent lesions that were sent for re-excision, 3 (11.1 %) were incompletely excised. More recently, Khan et al. [6] studied 37 recurrent SCCs treated with re-excision with 6 mm margins. The incomplete excision rate for recurrent tumors was double that for primary SCCs (16 vs. 7 %, respectively).

Inadequate tumor clearance by standard excision, as demonstrated by the data above, can lead to high rates of incomplete excision, particularly for locally recurrent SCC that has already failed standard excision. These studies underscore the importance of margin control, both lateral and deep, when treating high-risk and locally recurrent SCC. Locally recurrent SCC and SCC excised with positive margins via standard excision may have histologic features which make margin interpretation prone to error via standard sectioning including infiltrative growth and perineural invasion. Unlike standard excision which examines a small (approximately 1 %) proportion of the margin, MMS allows the examination of nearly 100 % of the lateral and deep margins and is therefore more appropriate for high-risk and locally recurrent SCC, particularly those with the challenging histologic features above. At our center we therefore utilize MMS for such cases, a practice supported by American Academy of Dermatology and National Comprehensive Cancer Network (NCCN) guidelines [8, 9]. Several studies have described the advantages of using the Mohs technique in the treatment of recurrent SCC [1, 10–12]. We will review several large studies and/or systemic reviews and then focus on a number of smaller studies for special sites (i.e. MMS for ear).

In the 1992 systematic review by Rowe et al. [1] of available SCC outcome data, 5-year cure rates with MMS versus excision were 92 vs. 77 %. Overall 5-year recurrence rates for SCCs were lower with MMS versus excision: primary CSCCs (3.1 % of 2065 cases versus 8.1 % of 124 cases) and recurrent SCC (10.0 % of 151 cases versus 23.3 % of 34 cases). The recurrence rates of SCC with PNI was also lower with MMS (0 % of 17 cases) compared to excision (47.3 % of 72 cases).

One of the earliest and largest studies describing the benefits of MMS in the treatment of SCC was performed by Dzubow et al. [13] who characterized the outcomes of 414 primary SCC treated between the years 1966 and 1980. Their group found a 5-year recurrence rate of 6.7 %.

Pugliano-Mauro and Goldman [11] performed a large retrospective review of 215 patients with 260 SCCs they considered high-risk, mostly based on head and neck location (84.6 %), treated with MMS in 2010. Of these 260 tumors, 231 (88.8 %) were primary and 29 (11.2 %) were recurrent (previously treated). Large perineural

nerve involvement was present in only 2 % of primary tumors but over a quarter (27 %, n = 8) of recurrent tumors. During a mean follow-up of 3.9 years, local recurrence rates for primary and previously treated SCC were similar at 1.3 % (n = 3) and 0 % (n = 0), respectively. Metastasis occurred in 4 (1.7 %) primary and 2 (6.9 %) recurrent tumors. Since both primary and recurrent SCCs did well in this series, the authors concluded that MMS should be used for high risk SCC, including locally recurrent tumors, as defined by NCCN criteria (see Chap. 2).

Leibovitch et al. [12] performed a large, prospective, multicenter case series of 1263 patients with SCC treated with MMS in Australia between 1993 and 2002. Of the 1263 cases, 61.1 % (772) of the cases were primary and 38.9 % (491) of the cases were recurrent; of the 491 recurrences, 265 (54.0 %) were previously treated with an excision. The authors found that recurrent tumors were larger than primary tumors, had larger post excision defects, required more levels of excision, and had more cases of subclinical extension. At 5 years of follow-up, 381 (30.2 %) patients were still enrolled in the study. In this group, the recurrence rates for primary and previously treated SCC were 2.6 and 5.9 %, respectively.

Silapunt et al. [14] evaluated the efficacy of MMS for 117 patients with 144 SCC of the auricle. After MMS, patients were followed for 7–67 months (average 34.6 months). Local recurrence developed in 5 of 144 tumors. These tumors were treated again with MMS with no further recurrences.

Multi-Specialty Approach for Large, Recurrent SCC

Despite the high cure rates of MMS, very large or deep recurrent tumors may not be amenable to removal under local anesthesia in an outpatient setting. Such cases include invasion of the parotid gland, bone, and/or extension along nerves within the cranium. In these unfortunate situations, MMS may still be employed for optimal visualization of the entire marginal surface. In fact, MMS may be particularly useful for recurrent disease where tissue planes may be altered from prior surgery and tumor may track within scar, between tissue planes, or within nerves and be easily missed on standard histologic sectioning.

In such cases, it may be important to collaborate with other surgical specialists including head and neck surgeons, neurosurgeons/skull-base surgeons, plastics/craniofacial, or surgical oncologists as needed to obtain optimal surgical outcomes. MMS can be used to clear the lateral margins under local anesthesia while the deep margin can be pursued under general anesthesia in the operating room, thereby eliminating wait time for intra-operative frozen sections, speeding the procedure, and minimizing general anesthesia exposure. Alternatively Mohs can be performed under general anesthesia and tissue processed and read while other surgeons perform nodal biopsy, lymphadenectomy, parotidectomy and/or large flap preparation as needed. Closure may then commence quickly once clear margins have been confirmed.

Radiation Therapy

Not all patients with recurrent SCC are candidates for surgery. Those who cannot tolerate excision due to significant comorbidities, and/or patients who have extensive disease not amenable to surgery due to involvement of vital structures may elect to be treated with radiation either for curative or palliative goals. It is important to recognize that radiation, despite being a reasonable option in select cases, is more time consuming and costly than surgery, can lead to carcinogenesis years later, does not provide margin evaluation for tumor clearance, and may cause delayed healing on lower extremities given poor vascularization. Radiation can also limit treatment options in the future as surgery and re-radiation are often not feasible in a previously radiated field. Studies have also shown that recurrence rates with radiation as monotherapy are generally higher than those of surgically treated patients in most scenarios [1]. However, in the absence of rigorous and validated tumor staging systems, a direct comparison is difficult to make between these modalities because cases treated with primary radiation may be more advanced on average than those treated with primary surgery.

We will briefly review select publications that have evaluated recurrence rates of primary versus recurrent SCC treated with radiation as monotherapy. Kwan et al. [15] evaluated the efficacy of radiation therapy for 121 patients with advanced SCC, defined as T2 or above via UICC 1997 staging (>2 cm or deeply invasive or node positive disease based on clinical or radiologic exam). Thirty-one percent of patients had positive nodes at time of study. Forty-five percent of cases were primary tumors and 55 % were recurrences. Sixty-five percent (30/46) of patients with locoregional recurrences succumbed to their disease. When examining factors associated with poor prognosis, a worse outcome was found on multivariate analysis for recurrent versus primary disease treated with radiation ($p=0.04$). It should be noted that better outcomes for nodal disease have more recently been reported with combined lymphadenectomy and radiation. Management of nodal metastases is covered in detail in Chap. 8.

Another study evaluated the outcomes of 142 SCC treated with radiotherapy [16]. Fifty-five percent (79/142) were primary untreated SCCs and 44.4 % (63/142) were recurrent tumors. Fifteen percent of cases had nodal metastases at enrollment. Patients were followed for a median of 5.8 years, ranging from 2 to 24 years. The authors reported 80 % (113 of 142 cases) of patients were relapse-free. Primary untreated SCC had a better relapse-free rate (89 %) than previously treated (i.e. recurrent SCC) lesions (68 %). The authors also provided data on complication rates and cosmesis. In 13 (9 %) of 142 cases, patients developed soft-tissue necrosis, a potential complication. Overall, cosmesis was adequate, with recurrent and larger lesions resulting in poorer cosmetic outcomes.

Systemic Therapy

Data is limited on the role systemic therapy for locally advanced SCC, including recurrent cases. Systemic treatment for metastatic and unresectable SCC is discussed more fully in Chap. 9 but major studies including patients with extensive

local recurrence are discussed below. Treatment of extensive local recurrence is an important topic in CSCC since most patients die from uncontrolled local and/or nodal disease rather than distant metastases, in contrast to many other forms of cancer. However, no studies have focused on SCC patients with locally recurrent disease only; rather, reports group patients with locally recurrent disease and together with patients having nodal or distal metastases. Results have unfortunately not been separated by disease stage. Thus quantifying the potential benefits of systemic therapy for locally recurrent disease as a unique entity is difficult.

A variety of agents have been used, including cytotoxic chemotherapy, retinoids, interferon-α2a, and more recently epidermal growth factor receptor inhibitors [17]. Sadek et al. [18] evaluated the efficacy of cisplatin, 5-fluorouracil (5-FU), and bleomycin in the treatment of 14 patients with locally advanced SCC, 9 of which were previously treated (five with surgery, four with surgery and radiation, and one with chemotherapy). Information differentiating previously treated patients who had recurrent disease from those who had progression of incompletely treated disease was not available. Overall, four patients obtained a complete response while seven patients achieved a partial response. In seven patients, the regression of the tumor allowed more definitive treatment with either radiation or surgery. After 1 year of follow-up, six patients died from their disease. Cartei et al. [19] treated 14 elderly patients with advanced SCC using oral 5-FU. Four patients had recurrent disease, 10 were primary cases. Measurable improvement was appreciated in nine cases: two partial remissions, three minimal remissions, and four cases of stable disease for a median duration of 30 months. The authors concluded that this single agent could be a reasonable option for inoperable cases of SCC, especially given the ease of administration. Another group performed a phase II study to evaluate the antitumor activity and toxicity of a regimen consisting of paclitaxel and capecitabine, an oral 5-FU pro-drug, in 50 patients with loco-regionally recurrent or disseminated SCC [20]. In this series, 30 (60.0 %) patients had local recurrences or inadequate treatment of primary disease prior to starting therapy. Overall, the response rate was 42 % with 2 patients showing complete responses and 19 with partial responses. The median survival time was 8 months. Retinoids, though effective for preventing the development of new SCC (discussed in Chap. 5) [21, 22], have provided minimal benefits when used for treatment of locally advanced SCC [23–25]. Brewster et al. [24] conducted a 6 month randomized trial where 66 patients with advanced SCC were treated with and without adjuvant 13-*cis*-retinoic acid plus interferon alpha after surgery. After a median follow-up time of 21.5 months, the group found no improvement in time to tumor recurrence in the treatment compared to the control arm. Shin et al. [25] characterized response rates of 39 patients with advanced SCC, 12 (31 %) of which had locally advanced and recurrent disease, to combination therapy of interferon alpha, retinoic acid, and cisplatin. The response rate for patients with locally advanced disease specifically was 67 % compared to a response rate of 17 % for patients with metastatic disease. The median survival time of all patients was 14.6 months. The relatively high response rate may have been due to cisplatin more than retinoids given the results of Brewster et al. [24] above, but this combination may deserve further study.

Cetuximab, a monoclonal antibody which blocks the extracellular domain of the epidermal growth factor receptor (EGFR) and inhibits cell growth and survival, is

currently FDA approved to treat metastatic colon cancer and head and neck carcinomas. Because EGFR is expressed in the basal layer of the epidermis [26] and may be over-expressed in metastatic CSCC [27], some investigators have attempted to use this agent off label to treat aggressive SCC [28–32]. Bauman et al. [28] published one of the first case reports describing durable responses in two patients with extensive SCC recurrences; at the time the case report was written, one patient had a sustained response of 3 months and the other of 5 months. Recently, a phase II trial was performed to evaluate the efficacy and safety of cetuximab as a single agent in patients with advanced SCC [31]. Thirty-six patients were enrolled in the trial; 17 (47.2 %) had local disease, 16 (44.4 %) had lymph node disease, and 3 (8.3 %) had distant metastases. Over half (58.3 %) were previously treated with either surgery, radiation, or a combination therapy. At 6 weeks, the overall disease control rate was 69.4 %: 8 partial responders, 2 complete responders, and 15 patients with stable disease. The mean duration of control was 5 months. Responses were not separated by initial disease stage.

Similar to cetuximab, gefitinib is an EGFR blocker, but this agent works by inhibiting the ATP-binding site of EGFR and preventing it from autophosphorylation and activation. This agent also has been used in a recent study for advanced SCC [33]. In a Phase II study, Lewis et al. [33] evaluated the efficacy of neoadjuvant gefitinib given prior to surgery and/or radiation in 23 patients, most (78 %) of which had regional metastases at the time of enrollment. Seven (30.4 %) patients had a new diagnosis of SCC, 7 (30.4 %) had persistent disease, and 9 (39.1 %) had recurrent disease. Thirteen (56.5 %) patients were previously treated. Overall, complete responses were achieved in 18.2 % of patients and partial responses in 27.3 % of the cases. After induction therapy, 11.8 % underwent surgery, 17.6 % were treated with radiation, 11.8 % were treated with continuation of gefitinib in addition to radiation, and 47 % were treated with continuation of gefitinib in addition to surgery and radiation. At 2 years, the overall survival rate was 72.1 %. Again, responses were not separated by disease stage.

Use of erlotinib, which works similarly to gefitinib, has also been described [32, 34]. For example, a recent report in the ophthalmology literature showed an impressive clinical response of a 90-year-old woman with a recurrent SCC in the periorbital region with a probable parotid metastasis [32]. At the time the report was written, the patient had been on erlotinib for 11 months and doing well.

In-Transit Metastases and Their Management

The concept of in-transit CSCC metastases, a distinct entity from local recurrence, was first proposed by Berg and Otley [35]. In a subset of organ transplant recipients (OTRs), they noticed the development of multiple nondescript, pink gray, 2- to 8-mm papules that, on histopathology, showed non-contiguous foci of metastatic SCC (Fig. 7.3). Martinez et al. [36] studied the clinical course of metastatic SCC in

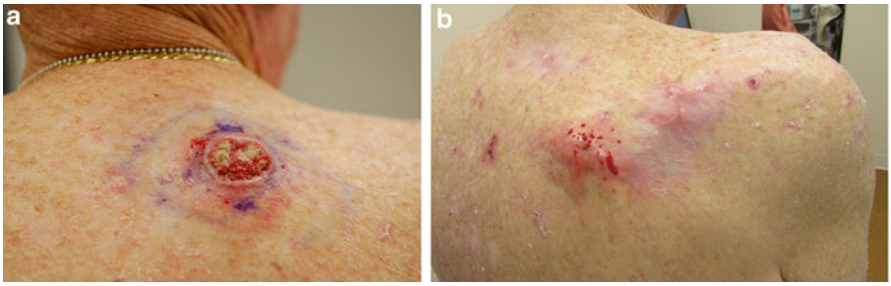


Fig. 7.3 In transit metastases from primary CSCC. (**a**) Transplant recipient with poorly differentiated SCC prior to removal. This SCC was removed with clear margins. The deep margin of excision extended to fascia. (**b**) In transit metastatic SCC developed subsequently near but not contiguous to the primary excision site

68 OTRs, of which 26 % [17] developed in-transit metastasis. Patients with in-transit metastases had a better prognosis than those with distant metastases, 89 vs. 39 % disease-specific survival at 1 year, respectively.

The largest study to date on the clinical outcomes of patients with in-transit metastasis was conducted by Carucci et al. [37] who surveyed members of the International Transplant Skin Cancer Collaborative group on their experience with this entity. Twenty two cases of in-transit metastases occurring in 21 patients were identified, of which 15 were OTRs. Their group defined in-transit metastases as "foci of CSCC originating within dermal or subcutaneous tissue clinically distinct from the primary tumor and occurring before the first echelon of regional lymph nodes." Most in-transit metastases were less than 0.8 cm in size, located at a mean distance of 2.5 cm from the primary tumor or scar, and diagnosed at a mean 10 weeks (range 1–56 weeks) after treatment of primary (30 % of cases) or recurrent (70 % of cases) SCC. Ten patients (50 %) presented with multiple (mean 3.5) in-transit metastases. Most (15 of 21) primary tumors were located on the head and neck region and PNI was found in 28 % of the primary lesions. The average size of primary tumors was 1.7 cm (range 0.4–3.6). In the OTR group, in-transit metastases occurred on an average of 11.5 years (4–31 years) after starting immunosuppression.

Of the 20 patients who agreed to treatment, 15 were treated with surgery and radiation, 4 with radiation alone, and 1 had an amputation. Intralesional or systemic chemotherapy was used in 2 patients, oral retinoids in 3 patients, and immunosuppression was reduced or discontinued in 7 of 15 transplant patients. Patients were followed for a mean 24 months (range 1–108). Non-transplant patients had better overall outcomes than OTRs. Specifically, at 24 months of follow-up, 33 % of OTRs had no evidence of disease, 33 % were alive with disease, and 33 % died from disease. In contrast, 80 % of non-transplant patients had no evidence of disease and 20 % were alive with disease. There were no deaths in the immunocompetent group, resulting in a disease specific mortality of 0 % at 24 months. Interestingly, of the five OTRs who were alive, all were treated with combination surgery and radiation;

three of five were indirectly treated with decreases in immunosuppression medications.

Several important points were made by the authors in their study. First, in-transit metastases are associated with high-risk SCC, including cases with large diameter, nerve invasion, or local recurrence after clear–margin surgery. Second, in-transit metastases in OTRs occur years after transplantation after patients have received a high cumulative dose of immunosuppressive therapy and they carry a dismal prognosis compared to those found in immunocompetent individuals. Third, the authors promote the use of radiation therapy to treat a 1–5 cm field surrounding the metastasis after surgical excision. Fourth, it may be important to consider decreasing the amount of immunosuppressive agents patients with in-transit metastasis are receiving. The benefits of immunosuppression reduction are discussed more fully in Chaps. 5 and 9. Fifth, it is important to examine patients with a history of high-risk SCC closely for in-transit metastases at all follow up exams. Finally, it is crucial to manage patients with in-transit disease in collaboration with medical oncology, radiation oncology, and/or head and neck surgeons.

We attempt to remove in transit metastases by Mohs where feasible. Wider initial margins are obtained as compared to Mohs resections of less aggressive primary skin cancers. Mohs is particularly useful in cases where determination of deep marginal recurrence versus in transit metastasis is difficult. In either case, every effort is made to obtain a tumor free plane. Repairs are chosen based on potential for rapid healing allowing for beginning of adjuvant RT within 6–8 weeks after surgery. In our personal experience, we have utilized Mohs surgery followed by RT with success in cases of in-transit metastases without adenopathy. Patients with possible perineural disease should be evaluated with MR imaging. Patients with extensive macroscopic perineural disease may benefit from referral to an appropriate oncologic surgeon for resection of the involved nerve(s) as far as tumor extends along them, to be followed by evaluation for adjunctive RT.

During initial or follow-up examination, palpation of the draining nodal basin and neurologic exam are essential. Patients with palpable nodes need referral for FNA, core or excisional biopsy and appropriate imaging. The authors prefer PET CT for imaging patients with in transit metastatic SCC. SCC patients with biopsy proven adenopathy should be referred to an appropriate oncologic surgeon for excision and lymph node dissection and to a radiation oncologist for evaluation for adjunctive RT.

Follow-Up

After treating a patient with recurrent SCC either with surgery or combination of surgery and radiation, close follow-up is necessary. Patients should be evaluated every 3 months for the first year, every 4–6 months for years 2–3, and then every 6 months afterwards with a total body skin and complete lymph node exam. Specifically, it is important to inspect the surgical site for any recurrences and

palpate the site and at least 10 cm of surrounding skin for any subcutaneous nodules as in-transit metastases, described above, may present as subtle skin colored subcutaneous nodules. Because in-transit metastases were found at a median 10 weeks after surgery in the Carucci et al. [37] study, patients should be advised to not only perform monthly skin self-examinations but to also consider palpating around the surgical site a month following excision of a high-risk or locally recurrent SCC. If any findings are concerning, they should return to their provider immediately. At our center, we follow patients as frequently as every 6–8 weeks for the first 12 months, particularly organ transplant and chronic lymphocytic leukemia patients who have an elevated risk of recurrence from high-risk and locally recurrent SCC. After a 1 year period, patients are evaluated every 3 months.

Conclusions

Recurrent SCC can behave in an aggressive fashion and lead to significant mortality and morbidity. Early diagnosis and removal of recurrent disease with clear surgical margins is critical to providing optimal patient outcomes. In cases of advanced locally recurrent SCC or when recurrences manifest as in-transit metastasis, systemic agents and radiation therapy may be used in combination with surgery when feasible or alone when surgery is not feasible. Close follow-up should be provided after treatment. In the organ transplant recipient population, it is important to collaborate with our transplant medicine colleagues to consider modifying immunosuppressive regimens. Similarly, hematology-oncology physicians should be made aware of the mortality risk of aggressive SCC in patients with chronic lymphocytic leukemia. The value of multi-disciplinary care cannot be overemphasized when caring for these patients. Please refer to Chaps. 1 and 2 for comprehensive listings of patient subsets at elevated risk of recurrence post definitive treatment of SCC.

References

1. Rowe DE, Carroll RJ, Day Jr CL. 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(6):976–90.
2. Tavin E, Persky M. Metastatic cutaneous squamous cell carcinoma of the head and neck region. Laryngoscope. 1996;106(2 Pt 1):156–8.
3. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713–20.
4. Eroglu A, Camlibel S. Risk factors for locoregional recurrence of scar carcinoma. Br J Surg. 1997;84(12):1744–6.
5. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;27(2 Pt 1):241–8.

6. Khan AA, Potter M, Cubitt JJ, Khoda BJ, Smith J, Wright EH, et al. Guidelines for the excision of cutaneous squamous cell cancers in the United Kingdom: the best cut is the deepest. J Plast Reconstr Aesthet Surg. 2013;66(4):467–71.
7. Tan PY, Ek E, Su S, Giorlando F, Dieu T. Incomplete excision of squamous cell carcinoma of the skin: a prospective observational study. Plast Reconstr Surg. 2007;120(4):910–6.
8. Connolly SM, Baker DR, Coldiron BM, Fazio MJ, Storrs PA, Vidimos AT, 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. J Am Acad Dermatol. 2012;67(4):531–50.
9. Miller SJ, Alam M, Andersen J, Berg D, Bichakjian CK, Bowen G, et al. Basal cell and squamous cell skin cancers. J Natl Compr Canc Netw. 2010;8(8):836–64.
10. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia II. Perineural invasion. J Am Acad Dermatol. 2005;53(2):261–6.
11. Pugliano-Mauro M, Goldman G. Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. Dermatol Surg. 2010;36(10):1544–53.
12. 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(2):253–60.
13. Dzubow LM, Rigel DS, Robins P. Risk factors for local recurrence of primary cutaneous squamous cell carcinomas. Treatment by microscopically controlled excision. Arch Dermatol. 1982;118(11):900–2.
14. Silapunt S, Peterson SR, Goldberg LH. Squamous cell carcinoma of the auricle and Mohs micrographic surgery. Dermatol Surg. 2005;31(11 Pt 1):1423–7.
15. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. Int J Radiat Oncol Biol Phys. 2004;60(2):406–11.
16. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):748–55.
17. Cranmer LD, Engelhardt C, Morgan SS. Treatment of unresectable and metastatic cutaneous squamous cell carcinoma. Oncologist. 2010;15(12):1320–8.
18. Sadek H, Azli N, Wendling JL, Cvitkovic E, Rahal M, Mamelle G, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer. 1990;66(8):1692–6.
19. Cartei G, Cartei F, Interlandi G, Meneghini G, Jop A, Zingone G, et al. Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged. Am J Clin Oncol. 2000;23(2):181–4.
20. Bentzen JD, Hansen HS. Phase II analysis of paclitaxel and capecitabine in the treatment of recurrent or disseminated squamous cell carcinoma of the head and neck region. Head Neck. 2007;29(1):47–51.
21. Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. Arch Dermatol. 2005;141(4):456–64.
22. Wright TI, Spencer JM, Flowers FP. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol. 2006;54(6):933–46. quiz 47–50.
23. Lippman SM, Parkinson DR, Itri LM, Weber RS, Schantz SP, Ota DM, et al. 13-Cis-retinoic acid and interferon alpha-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. J Natl Cancer Inst. 1992;84(4):235–41.
24. Brewster AM, Lee JJ, Clayman GL, Clifford JL, Reyes MJ, Zhou X, et al. Randomized trial of adjuvant 13-cis-retinoic acid and interferon alfa for patients with aggressive skin squamous cell carcinoma. J Clin Oncol. 2007;25(15):1974–8.
25. Shin DM, Glisson BS, Khuri FR, Clifford JL, Clayman G, Benner SE, et al. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. J Clin Oncol. 2002;20(2):364–70.

26. Nanney LB, Magid M, Stoscheck CM, King Jr LE. Comparison of epidermal growth factor binding and receptor distribution in normal human epidermis and epidermal appendages. J Invest Dermatol. 1984;83(5):385–93.
27. Shimizu T, Izumi H, Oga A, Furumoto H, Murakami T, Ofuji R, et al. Epidermal growth factor receptor overexpression and genetic aberrations in metastatic squamous-cell carcinoma of the skin. Dermatology. 2001;202(3):203–6.
28. Bauman JE, Eaton KD, Martins RG. Treatment of recurrent squamous cell carcinoma of the skin with cetuximab. Arch Dermatol. 2007;143(7):889–92.
29. Suen JK, Bressler L, Shord SS, Warso M, Villano JL. Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab. Anticancer Drugs. 2007;18(7):827–9.
30. Arnold AW, Bruckner-Tuderman L, Zuger C, Itin PH. Cetuximab therapy of metastasizing cutaneous squamous cell carcinoma in a patient with severe recessive dystrophic epidermolysis bullosa. Dermatology. 2009;219(1):80–3.
31. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011;29(25):3419–26.
32. El-Sawy T, Sabichi AL, Myers JN, Kies MS, William WN, Glisson BS, et al. Epidermal growth factor receptor inhibitors for treatment of orbital squamous cell carcinoma. Arch Ophthalmol. 2012;130(12):1608–11.
33. Lewis CM, Glisson BS, Feng L, Wan F, Tang X, Wistuba II, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. Clin Cancer Res. 2012;18(5):1435–46.
34. Yin VT, Pfeiffer ML, Esmaeli B. Targeted therapy for orbital and periocular basal cell carcinoma and squamous cell carcinoma. Ophthal Plast Reconstr Surg. 2013;29(2):87–92.
35. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47(1):1–17. quiz 8–20.
36. Martinez JC, Otley CC, Stasko T, Euvrard S, Brown C, Schanbacher CF, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermatol. 2003;139(3):301–6.
37. Carucci JA, Martinez JC, Zeitouni NC, Christenson L, Coldiron B, Zweibel S, et al. In-transit metastasis from primary cutaneous squamous cell carcinoma in organ transplant recipients and nonimmunosuppressed patients: clinical characteristics, management, and outcome in a series of 21 patients. Dermatol Surg. 2004;30(4 Pt 2):651–5.

Chapter 8
Management of Nodal Metastases

Michael Veness and Julie Howle

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second commonest malignancy in the world, after basal cell carcinoma. Despite this, the number of patients developing metastatic CSCC is relatively low with incidence rates of 2–3 % documented [1], but is increased (10–30 %) in a subset of what is often referred to as 'high-risk' patients [2, 3]. There are well-documented clinic-pathological features defining a high-risk patient and this topic is discussed in depth in other chapters of this book. The aim of this current chapter is to discuss the management of a patient presenting with nodal metastases.

The first site of metastatic CSCC is nearly always to regional lymph nodes within the lymphatic drainage of the primary (or index) CSCC. Patients developing non-nodal metastatic CSCC as a first site of disease are very rare and generally incurable. Consideration should also be given to excluding other primary sources for metastatic SCC such as lung cancer in smokers. Although nodal metastases are also relatively rare in CSCC patients, the absolute number of patients developing nodal metastases from CSCC is not inconsequential. For example, an estimated 5600–12,500 persons develop nodally metastatic CSCC annually in the U.S. [4]. The development of nodal metastases can have catastrophic consequences for the patient with a minority dying of their disease despite treatment. Death is usually a result of uncontrolled regional recurrence (86 %) and to a lesser extent the development of

M. Veness, MB, BS, MD (USyd), FRANZCR (✉)
Westmead Cancer Care Center, Westmead Hospital,
Hawkesbury Road, Sydney, NSW 2145, Australia
e-mail: michael.veness@health.nsw.gov.au

J. Howle, BSc, MBBS, MS, FRACS, FACS
Department of Surgery, Westmead Hospital,
Hawkesbury Road, Sydney, NSW 2145, Australia

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_8

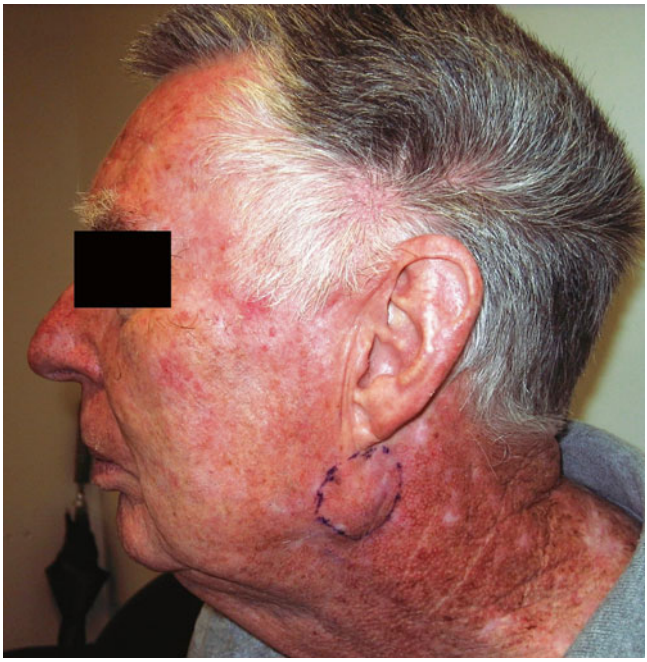


Fig. 8.1 Sixty-three year old male with a 3 cm mobile metastatic lymph node containing CSCC located in his left parotid tail. The patient did not have an identifiable index lesion within the draining ipsilateral head and neck but had previous ablative treatment over the years for superficial actinic lesions

distant metastases (14 %) [5]. Thus any strategies aimed at improving regional control are almost certainly going to positively impact a patient's chance of cure.

The head and neck (HN) is overwhelmingly the site of preference for the development of CSCC nodal metastases, reflecting the higher incidence of primary CSCC in this sun-exposed region. Caucasian males aged >60 years old are typically the most frequently afflicted (Fig. 8.1), although younger men and females also can develop nodal metastases. In most institutional series ~10 to 15 % of patients with metastases are immunosuppressed, either secondary to organ transplantation or haematological malignancy (e.g. chronic lymphocytic leukemia) [2, 5]. Most patients developing metastatic disease do so within a year following treatment of the primary lesion, but can present up to 3–4 years post treatment [6]. Patients may also present with metastatic nodal disease with no known (or suspected) primary site [7], although invariably these patients have a past history of treated skin cancer.

The parotid gland and its associated lymph nodes, is the commonest site for the development of metastatic nodes and has been previously termed "the metastatic basin" for metastatic CSCC [8]. Parotid gland involvement occurs in approximately two thirds of patients with metastatic CSCC of the HN, with the remaining one third developing cervical (levels I–IV) nodal metastases without parotid gland involvement. Because of the visible aspect of enlarging HN nodes most patients will be

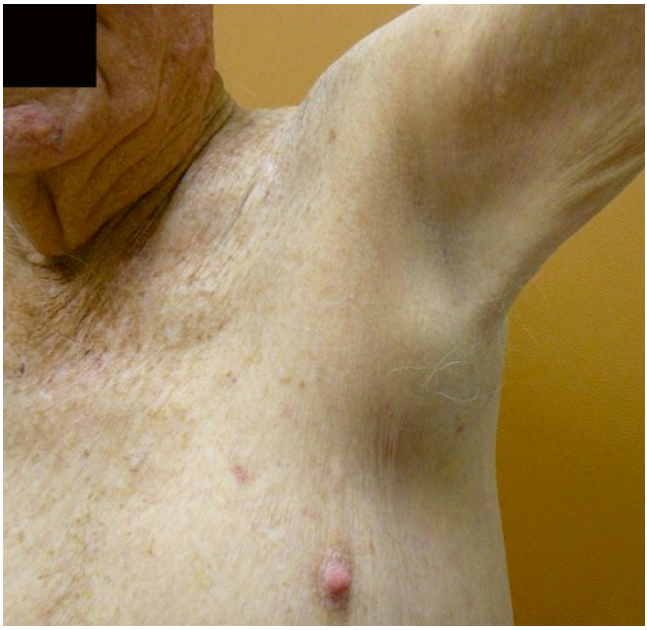


Fig. 8.2 Seventy-five year old male with a large 8 cm mobile metastatic lymph node located in his left inferior axilla. Biopsy confirmed CSCC noting he had previously had a CSCC excised from his left forearm 15 months previously. The patient proceeded to axillary dissection followed by 5 weeks of adjuvant radiotherapy

found at diagnosis to have 1–2 metastatic nodes 20–30 mm in maximum dimension [2]. Metastatic nodes are more often located inferiorly within the parotid tail and clinically may be difficult to distinguish from level II nodes (jugulo-digastric nodes). Less often patients will present with a more superiorly located pre-auricular nodes that may extend superiorly to the level of the zygoma. It should be noted that metastatic nodal SCC involving the parotid almost never arises from a mucosal SCC, excepting in rare retrograde lymphatic spread in patients with already advanced cervical nodal metastases. The axilla and groin are also regional sites for the development of metastatic nodes, often from an extremity or truncal primary (Fig. 8.2).

Patients who develop nodal metastases should be referred and managed within the confines of a multidisciplinary unit experienced in managing patients with this cancer. However, few cancer centers have groups dedicated to managing metastatic CSCC. This plus the rarity of the condition have inhibited development of clinical trials and establishment of clear care standards. Head and neck oncology centers usually have the most experience managing metastatic CSCC but specialist referral for non HN cases is not well-established, even at major cancer centers.

On presentation, patients should undergo a thorough history, examination and relevant investigations often including radiologic imaging prior to any management decision. A history of previous radiotherapy (RT) may impact the ability to deliver

this as an adjuvant treatment. Patients with parotid nodal metastases should have facial nerve function clinically tested to exclude a malignant palsy due to tumor involvement of the facial nerve trunk or one or more of its branches.

Cases occasionally arise of metastatic SCC developing in a cervical node in a patient who is a smoker with a past history of skin cancer but without an obvious mucosal or cutaneous primary. In these patients a positron emission tomography (PET) scan will often aid in detecting a small (<10 mm) mucosal based lesion, with the tonsil and tongue base common sites for detecting an 'unknown' mucosal primary. A nasoendoscopy to visualize the upper aerodigestive tract should also be undertaken. Clinicians ultimately need to decide on the likely origin of the metastatic SCC as the management differs markedly between mucosal and cutaneous primary tumors.

Confirmation of metastatic disease prior to any treatment is mandatory and is usually achieved via a fine needle aspiration biopsy (FNAB). The FNAB should be repeated if the result is equivocal. An open/excisional biopsy is rarely required but may be considered for a small accessible node. High quality contrast enhanced computer assisted tomography (CT) scans of the relevant nodal region are essential and provide valuable information on the extent of macroscopic cancer and its relationship to nearby structures such as the carotid vessels and bones (such as the skull base) (Fig. 8.3). Additional staging investigations could include CT scans of the chest, abdomen and pelvis, although very few patients present with synchronous distant metastases. The addition of other investigations such as magnetic resonance imaging (MRI) scan or a PET scan may be appropriate in select cases but not as

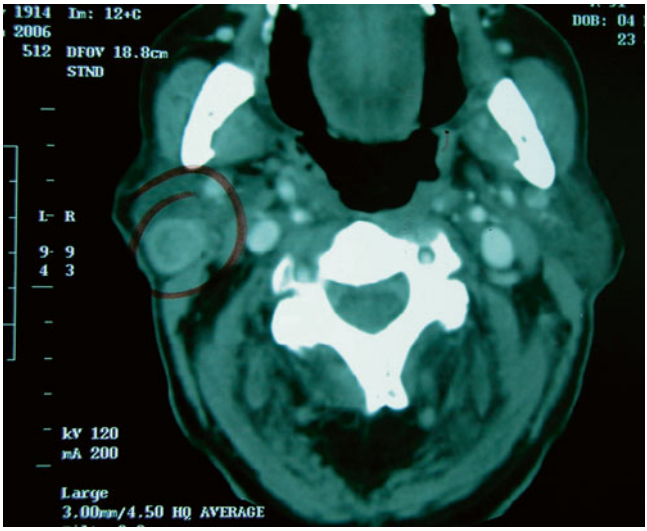


Fig. 8.3 CT scan administered with intravenous contrast highlighting (*black marker pen*) a 2 cm metastatic node located within the posterior aspect of the right inferior parotid gland. Note the contrast enhancement of the circular node with central hypodensity present consistent with necrosis. These are all radiological features typical of a metastatic node containing cutaneous squamous cell carcinoma

routine investigations. A patient's fitness for surgery should also be determined. Medically inoperable patients are often still candidates for high dose RT alone.

The evidence base for recommendations on managing patients with nodal metastases is supported by institutional retrospective/prospective studies [9–11] as there are currently no published randomized control trials comparing treatments. In the majority of patients, the mainstay of treatment is surgery followed by adjuvant RT. Such a combined approach is considered current best practice as supported by published clinical research summarized below. The natural history of relapse in treated patients is dominated by regional relapse in the treated nodal bed, as opposed to distant relapse. It is therefore imperative that appropriate regional treatment is utilized as the best means to cure a patient. Patients that relapse post treatment are rarely candidates for radical salvage treatment and most will succumb to their disease.

There is considerably less published data on CSCC metastasizing to non-HN nodal sites, i.e. the axilla and groin, from CSCC originating on the trunk or extremities. The proportion of non-HN nodal metastatic patients compared to HN metastatic nodal patients is estimated at 1:10 and consistent with the fact that 75–80 % of CSCC are located on the sun exposed HN. While the management of patients with metastatic HN CSCC has become better defined of late, this is not the case with metastatic CSCC to the axilla or groin. It is also unclear if patients with truncal and extremity CSCC have a higher risk of developing nodal metastasis compared with HN CSCC. A German study [12] reported a metastatic rate of 3.9 % for CSCC originating on the trunk and extremities versus 3.3 % for all locations, while an Australian study [13] reported a rate of 4.9 % in 695 patients. Similarly it's unclear if these patients have a worse outcome compared to HN CSCC but limited data would suggest this possibly to be the case. This could be due, in part, to delayed presentation, as unlike in the HN, metastatic disease in the axilla or groin is often difficult to detect until the nodal burden is significant. It may also be that non HN patients are treated with less aggressive surgery and radiation due to concerns regarding lymphedema and thus have a higher risk of relapse.

Role of Surgery in the Head and Neck

Low-Risk Patients

Patients presenting with metastatic nodal CSCC, unless contraindicated, should proceed to an appropriate operation. The majority of these patients will subsequently proceed on to a 6-week course of adjuvant RT to eradicate residual microscopic CSCC. A minority of patients (10–15 %) may avoid adjuvant RT if they are deemed as 'low-risk' for harboring microscopic CSCC and therefore unlikely to benefit markedly from adjuvant RT. In these cases the risk of subsequent regional relapse must be balanced against the acute and potential late side effects of RT and the need for 6 weeks of daily treatment. In a study by Ebrahimi et al., 33 patients with a single involved node <3 cm, with no extracapsular spread (ECS), experienced a 5 year disease specific survival of 97 % when treated with surgery alone

[14]. Such low-risk patients who may avoid radiation must not be immunosuppressed, have undergone elective dissection of the next echelon of lymph nodes and, particularly in the case of parotid metastases, have documented negative excision margins. If all these criteria are met a policy of close observation is feasible but should be discussed with the patient.

Contraindications to Surgery

A minority of patients will present with very advanced nodal metastases that may preclude surgery as an option. Patients with skull base bone invasion and/or carotid artery encroachment may be considered technically inoperable, depending on the clinical situation and surgical opinion and may be offered definitive RT as an alternative. Resecting an involved facial nerve up to the ganglion to achieve a clear resection margin is feasible in select patients treated in skull based units. Such patients nearly always still warrant adjuvant RT [15]. Cutaneous involvement as a result of tumor fungation and associated dermal involvement is not necessarily a contraindication to surgery but will require wide excision or Mohs micrographically controlled clearance of all involved tissues and often large or free-flap reconstruction (Fig. 8.4). Patients with a malignant facial nerve palsy are also still considered operable, assuming no intracranial spread, but will require sacrifice of the facial nerve. These patients should have an MRI pre-operatively to exclude intracranial disease. Patients may also suffer from medical co-morbidity that places them at high risk of perioperative morbidity/mortality, which precludes them from undergoing general anesthesia and surgery (Fig. 8.5). These patients may also be unable to tolerate an extended course of high-dose definitive RT (60–70 Gy) but could still be considered for a shorter course of RT (2–5 weeks). Rarely patients are unsuitable for any RT but if so should be offered best supportive care.

Treatment of the Parotid

In the setting of a functioning facial nerve there is no convincing evidence that outcome is improved by more aggressive surgery in the form of a radical parotidectomy (deep lobe excision and nerve sacrifice), compared to a facial nerve sparing superficial parotidectomy followed by adjuvant RT [16]. Radical parotidectomy is reserved for patients who present pre-operatively with a malignant facial nerve palsy involving multiple branches of the facial nerve or who are found to have facial nerve involvement intra-operatively. In cases where the facial nerve is sacrificed, we recommend that frozen section be performed on the proximal nerve stump to ensure that a clear margin of excision has been obtained. Where possible the divided facial nerve or its branches should be anastomosed primarily or a cable nerve interposition graft utilized. Most patients who undergo nerve grafting have return of facial nerve function within 9 months, but maximal function may take up to 2 years to develop

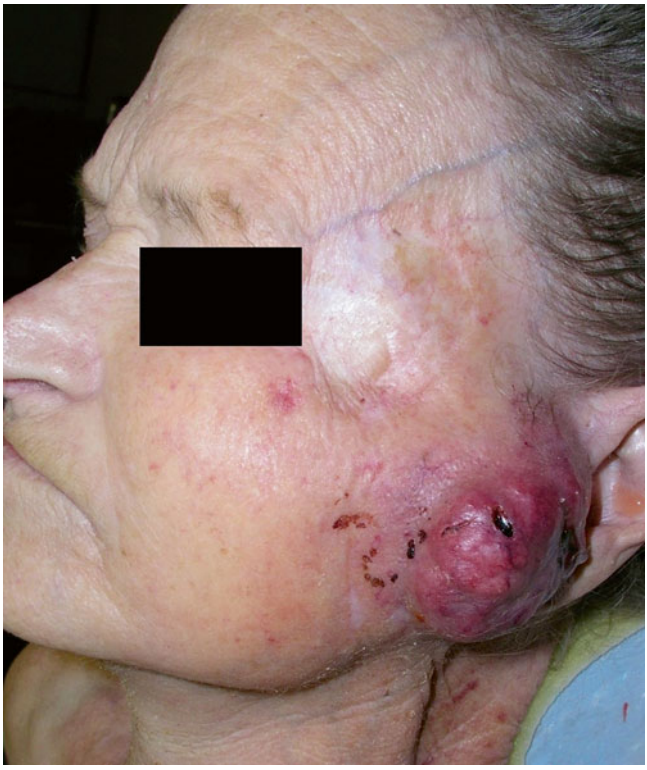


Fig. 8.4 Seventy-nine year old female with a large metastatic lymph node in her left pre-auricular parotid gland. Note the areas of ulceration and surrounding cutaneous erythema indicating dermal infiltration by cancer. The patient had previously undergone excision of a left temple squamous cell carcinoma (note the skin graft). She subsequently required wide excision of the involved tissue, in addition to a parotidectomy and neck dissection, reconstruction with a free flap, and post surgical adjuvant radiotherapy

[17]. Where possible, static re-animation should be performed at the time of grafting/anastomosis in order to provide the patient with immediate form and function before nerve function returns. Despite some concern, the addition of adjuvant RT has been shown not to have a negative impact on facial nerve function following repair [18]. The morbidity of a facial nerve palsy should not be underestimated, even with attempts to graft or re-animate. However interestingly, in at least one study of patients treated for metastatic HN CSCC, facial nerve sacrifice did not appear to adversely impact quality of life [19].

Oncological excision margins (>5 mm) are rarely achieved in patients who undergo nerve-sparing /superficial parotidectomy, especially at the deep plane close to the facial nerve. Studies have documented high rates of close or incomplete excision (40–65 %) following parotidectomy. ECS is also a common pathological finding (30–75 %) and in combination with a close or positive margin adds weight to the importance of adjuvant RT to improve regional control and may explain the high

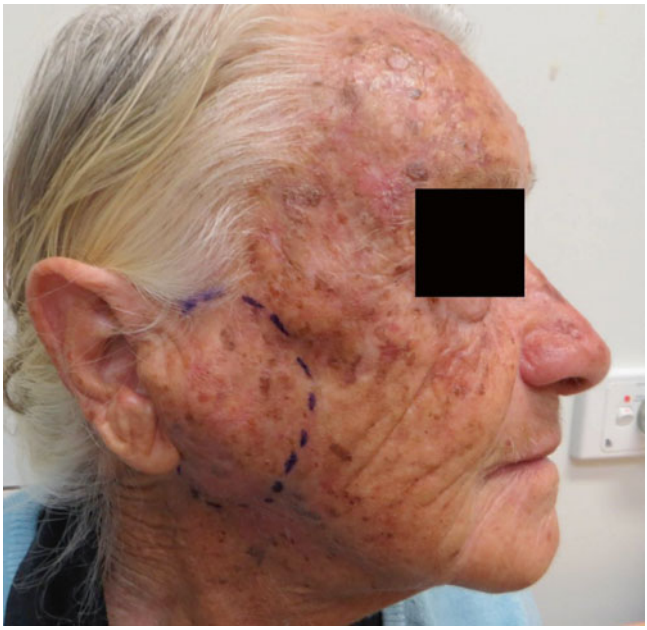


Fig. 8.5 Eighty-eight year old female with a large metastatic lymph node occupying the right parotid gland. Clinically the mass was fixed but the patient's facial nerve was still functioning. Medical co-morbidity precluded her undergoing a total parotidectomy/neck dissection and adjuvant radiotherapy. She was subsequently recommended high palliative radiotherapy utilizing high dose electrons to a total dose of 50 Gy in 20 fractions using a shrinking field technique after 10 fractions and not treating the lower neck. Treatment was well tolerated with a complete clinical response by treatment end

recurrence rate following surgery alone. A study by Iyer et al. demonstrated that in patients who had undergone a nerve-sparing parotidectomy and adjuvant RT, those who had involved margins adjacent to the facial nerve did not have a significant increase in local recurrence and no difference in survival, compared to those with clear margins of excision [16]. We recommend that all these patients undergo adjuvant RT to reduce the risk of regional recurrence.

Neck Dissection

Clinically Node Negative Neck

In patients with parotid metastases and a clinically node negative neck there is a documented incidence of occult cervical nodal metastases in a minority of patients [20] (Table 8.1). We recommend that these patients undergo a parotidectomy and a selective neck dissection (SND) followed by adjuvant RT (if appropriate). The extent of SND will be dictated by site of the primary (or index) lesion: for most

Table 8.1 Surgery according to primary site, parotid involvement, and nodal status

Clinical stage	Primary site	Surgery
P0 N+	Any	CND
P+ N+	Any	Parotidectomy + CND
P+ N0	Anterior/external ear	Parotidectomy + SND (levels I–III)
P+ N0	Posterior scalp/neck	Parotidectomy + SND (levels II–V)

CND comprehensive neck dissection, *N+* clinically evident cervical metastases, *N0* no clinically evident cervical metastases, *P0* no clinically evident parotid metastases, *SND* selective neck dissection

primary sites, a level II–III neck dissection is sufficient, with the addition of level I when the primary is located on the midzone of the face. In the case of a primary located on the posterior scalp or neck, the addition of level IV and V is recommended [21] based on data summarized in the next section.

Clinically Node Positive Neck

Traditionally patients presenting with clinically positive regional metastases in the neck underwent a modified radical neck dissection (MRND) (i.e. resection of levels I–V with preservation of one or more of the following: internal jugular vein, sternocleidomastoid muscle and accessory nerve) rather than a SND. In a study comparing outcome of patients undergoing either a MRND or SND, there was no significant difference reported in 5 year overall survival (61 vs. 57 %; $p=0.86$), noting also that the majority (84 %) of patients also received adjuvant RT [22]. Studies in the setting of mucosal HN SCC also support performing a SND in selected patients in reducing the risk of surgical morbidity compared to a MRND [23].

In a large study of patients undergoing neck dissection for clinically positive neck, involvement of lymph nodes at different levels of the neck were documented and correlated with the site of the primary index CSCC [24]. The authors observed that level I metastases in the absence of level II or level III involvement is observed more commonly in patients with midline facial lesions (Fig. 8.6). In addition, the involvement of levels IV and V was analyzed, which demonstrated that no lesions of the external ear developed nodal metastases to levels IV or V, and only 2.7 % of lesions arising on the face or anterior scalp developed nodal metastasis to levels IV or V. However, the involvement of levels IV and V was higher (15.8 %) in patients who had CSCC located on the posterior scalp and neck. Based on these findings, SND including levels I to III is suggested for patients with primary tumors of midline facial structures, SND including levels II to III for patients with primary tumors of anterior scalp and external ear, and SND including levels II to V for patients with primary tumors of posterior scalp and neck. The external jugular node, which is not assigned to a specific level although often included as a level II node, should be excised in any neck dissection. This node is located superficial to the sternocleidomastoid muscle just inferior to the tail of the parotid adjacent to the external jugular

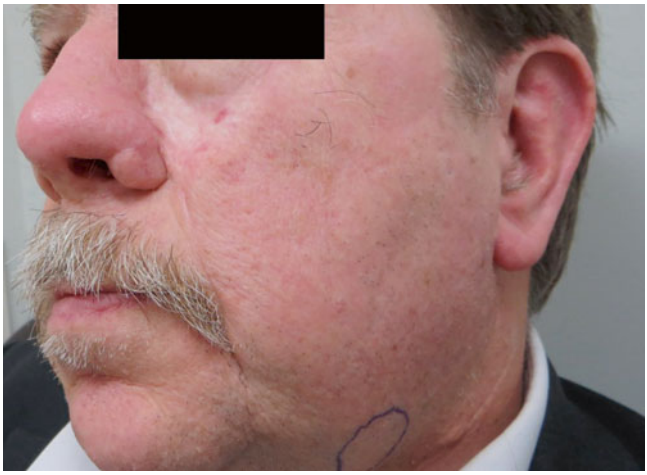


Fig. 8.6 Fifty-six year old male with a 2 cm mobile metastatic node in his left level 1B neck secondary to a previously treated left nasal squamous cell carcinoma (note the local flap and graft reconstructions). The time interval between primary treatment and nodal metastases was 3.5 years. There was no evidence of parotid gland involvement and thus the parotid was not treated

vein. Involvement of this node is pathognomonic for spread from a cutaneous malignancy.

Extended Resections Requiring Reconstruction (Secondary to Skin Involvement)

A minority of patients with HN CSCC nodal metastases present with cutaneous involvement and may require large excisions of skin and subcutaneous tissue as well as parotidectomy and/or neck dissection. When large areas of skin are removed, subsequent treatment must be taken into consideration when planning reconstruction. If the patient is to undergo adjuvant RT, the tissue must be sufficiently robust and the wound healed. Some patients may need reconstruction using a pedicled flap such as pectoralis major flap, or a free flap, particularly if the site has previously been irradiated; radial forearm and latissimus dorsi free flaps are frequently used to reconstruct soft tissue and skin defects in the HN.

Role of Surgery in the Axilla and Groin

The incidence of CSCC metastasis occurring in nodal basins other than the cervical or parotid region is low, with studies reporting rates of ~4 to 5 % [13]. There is a paucity of literature regarding the management and outcome of patients with nodal metastases in these locations. A study of 136 patients with CSCC of the trunk and

extremities developing axillary or groin metastases reported patients having a high risk of recurrence and death [25]. An Australian study of 695 patients with CSCC of the trunk and extremities documented a 4.9 % rate of nodal metastasis, a large number of which were considered inoperable, and with a mortality rate of over 70 % in those developing nodal metastases [13]. Another study of patients with axillary or groin metastases reported a 27 % rate of recurrence following treatment, the majority occurring at distant sites with all patients succumbing following recurrence [26].

Mullen et al. recommended that patients with advanced loco-regional CSCC of the trunk or limbs undergo surgery provided the risk of morbidity and mortality is acceptable [25]. We recommend that patients with operable axillary nodal metastases undergo level I–III axillary lymphadenectomy and those with inguinal disease undergo an inguino-pelvic node dissection, followed by adjuvant RT if indicated. Currently there is no evidence to support the routine use of adjuvant chemotherapy in this setting, with the exception of perianal or anal margin SCC. The etiology of these SCCs is often virally related (Humanpapilloma virus) and the course can be rapidly progressive with a very high risk of metastasis akin to anal carcinoma. Subsequently treatment is along the lines of an anal canal SCC [27].

Of note patients with metastatic CSCC to the inguinal lymph nodes should be assessed for primary SCC of the anogenital region. As with metastases to the HN, a primary or index lesion is not always present or suspected on history.

Role of Adjuvant Radiotherapy

Current evidence supports surgery and adjuvant RT as best practice in operable HN patients with the exception of low-risk patients who may avoid radiation as discussed above. Considering the heterogeneity of patient, tumor and treatment factors across multiple studies, a patient treated with a combined approach overall has a 10–15 % chance of developing regional relapse. The aim of adjuvant (or postoperative) RT is to treat and eradicate residual microscopic CSCC within the operative bed (parotid and/or neck) and also within undissected nearby nodes that may contain (not clinically detectable) occult metastatic CSCC.

Current RT delivers megavoltage energy X-rays (or photons) using machines referred to as linear accelerators. Photons impart lethal double stranded DNA damage to dividing malignant cells as well as normal tissues within an irradiated volume. It is a therapeutic difference in DNA repair between normal and malignant cells that provides the therapeutic ratio of fractionated (i.e. daily) RT. Current technology allows for the conformal delivery of accurately defined RT 3D target volumes that limit many of the toxicities associated with older less conformal, and less accurate, 2D technology.

A typical daily treatment (or fraction of RT) takes 10–15 min to deliver each day Monday to Friday over 6 weeks. Based on analogous data from other tumor sites, adjuvant RT will reduce the relative risk of recurrence by ~50 to 60 % and patients should understand that the aim of adjuvant RT is to reduce, but not eliminate, the risk of relapse.

Recent Evidence

The evidence, albeit institutional and non-randomized and mostly from Australia, supports the addition of adjuvant RT in reducing the risk of regional recurrence and that the majority of patients with nodal disease should be considered for combined treatment. Publications from the Westmead Hospital Group, Sydney, have documented the outcome of a large number of patients treated with a consistent approach since the 1980s, with operable patients undergoing surgery followed by adjuvant RT. The most recent analysis from this group confirmed a significant decrease in regional relapse (23 vs. 55 %) and improved 5 year disease free survival (74 vs. 34 %; $p=0.001$) with the addition of adjuvant RT compared to surgery alone [9]. In a large Australian study Bron et al. reported adjuvant RT as the only factor that significantly improved control in the parotid and recommended it as standard treatment [28]. Similarly, Del Charco et al. documented treatment (surgery/RT vs. RT) as the only factor to predict parotid disease control on multivariate analysis ($p=0.004$) [29] and Jol et al. reported decreased locoregional failure in patients undergoing surgery and adjuvant RT compared with surgery alone (17 vs. 44 %) [30].

In at least one Australian study the finding of soft tissue metastases (STM), defined as free soft tissue deposits lacking continuity with the primary tumor and not associated with nodal tissue, portended to a worse prognosis. After adjusting for other covariates STM was an independent predictor of worse survival. The authors suggested patients with STM be considered for combined treatment, irrespective of other factors. Further studies are still needed to confirm this association but similar to the finding of ECS it would be prudent to recommend adjuvant RT in STM patients also [31].

Elective Treatment

The role of elective treatment, be that RT or surgery, to uninvolved cervical nodes is controversial. Two Australian studies have documented a 35 % rate of subclinical metastases in dissected clinically negative neck nodes in patients with metastatic parotid nodes following elective neck dissection [10, 20]. This compares with a lower incidence (16 %) of occult spread in neck nodes in a Canadian study by Audet et al. [32] while a study from the MD Anderson Cancer Centre, Texas documented a higher 42 % incidence of occult cervical metastases in patients with metastatic parotid SCC [33]. Despite variation these and other studies suggest that a minority of patients will harbor subclinical nodal metastases that left untreated will progress to clinically enlarged nodes in many patients. The risk is therefore of clinical progression and the associated morbidity and mortality as the size and number of metastatic nodes increases. Identifying individual patients at greatest risk is difficult and although close observation may be an option, patients need to be reviewed regularly (every 3–4 months) for 4–5 years.

An accepted practice for patients with parotid metastases, and a clinically negative neck, is to undergo a SND (levels I/II or I/II/III) in conjunction with a parotidectomy. Deleting a neck dissection in the setting of parotid metastases and a clinically N0 neck is an option. However this will commit all patients to receive elective RT (50 Gy) to the hemi-neck. Although it is well accepted that neck control is equivalent in a clinically N0 neck with either surgery or RT the finding of pathologically negative upper level neck nodes may result in a patient avoiding adjuvant RT to the lower neck. Patients with clinically positive cervical nodes should undergo an appropriate neck dissection. Adjuvant RT is delivered to the ipsilateral neck if cancer is identified in multiple nodes ($\geq$2) or extranodal spread is present in a single node.

A scenario occasionally encountered is that of a patient with an index lesion located on the temple/forehead or ear with nodal metastases in the cervical nodes, but without nodes involving the parotid gland. The mechanism of this 'skip' spread is unclear. The question arises in these cases of whether elective treatment to the intervening parotid nodes is warranted. There is no data to guide clinicians but patients undergoing adjuvant RT to the dissected neck may benefit from the extension of fields to also encompass, at a minimum the lower parotid nodes (i.e. tail of parotid). An alternative would be to perform a nerve sparing parotidectomy in conjunction with the neck dissection and thereby potentially avoid the added toxicity of RT to the oropharynx/oral cavity from the exiting RT beams.

Similarly, some clinicians may consider electively treating a presumed index lesion if the development of metastatic nodal CSCC has arisen within a relatively short defined interval from initial treatment to the development of metastatic nodes (e.g. <12 months) and unfavorable features were present such as a close or positive margin. There is however no evidence to support this approach and in the setting of a controlled primary lesion we would not recommend electively treating the primary site with either surgery or RT.

Technical Aspects of Radiotherapy (Dose Fractionation Schedules/Volumes to Treat)

Adjuvant RT is usually delivered to the ipsilateral neck and/or parotid gland and rarely, if ever, requires a comprehensive (i.e. bilateral) approach. The toxicity of RT, while not inconsequential, does not involve the treatment of large areas of mucosa, compared with mucosal based primary HN SCCs (e.g. tongue base SCC). The predominant acute toxicities of comprehensive mucosal HN SCC are painful mucositis (odynophagia) and xerostomia which are not a major concern with ipsilateral parotid RT. The expected acute toxicity of ipsilateral RT that encompasses the parotid bed includes mild xerostomia, alteration in taste, skin erythema/desquamation and fatigue. The addition of hemi-neck RT to the superior parotid fields will add to the extent of skin treated and possibly the degree of fatigue experienced. Late

toxicities include potential hearing impairment if the superior extent of the treatment volume includes the middle ear structures and also a degree of ongoing xerostomia. Patients with poor dentition would benefit from pre-RT dental assessment that may result in extraction of posterior lower molar teeth that may be in the treatment field.

A dose fractionation schedule of 60 Gy in 30 daily fractions is recommended as best practice to post-operative (at risk) volumes. Clinicians may elect to boost smaller volumes with positive margins to 66–70 Gy (from 60 Gy). Undissected necks (or parotid) can be prescribed 50 Gy in 25 fractions when receiving elective treatment. Alternative dose fractionation schedules utilizing 2.5–3 Gy fractions may be considered in select patients to reduce the duration of treatment but most should receive 2 Gy fractions to minimize potential late toxicity. The use of altered fractionation in the adjuvant setting, as a means to improve locoregional control, is not standard but has been reported. The University of Florida Group have used hyperfractionation (74.4 Gy in 1.2 Gy twice daily fractions or similar) for many years in select patients with advanced and metastatic skin cancers and reported good results [34].

The delivery of adjuvant RT should optimally be commenced within 6 weeks of surgery. All patients should be treated with contrast enhanced (if not contraindicated) CT planned conformal RT to accurately define planning target volumes and important organs at risk (e.g. eyes, brainstem, middle ear and spinal cord). The use of highly conformal intensity modulated RT (IMRT), if available, may be considered, especially in cases where perineural invasion (PNI) involving the trunk, or branches of, the facial nerve, as this warrants the consideration of extending RT coverage beyond the skull base to encompass the intracranial extent of the facial nerve, in some cases back to the brainstem. In these circumstances an IMRT approach may provide better coverage and less toxicity to central nervous system structures [35].

The addition of bolus (tissue compensation) to either surgical scars or the irradiated skin of the parotid and/or neck with the aim to increase the dose delivered to the skin is not recommended unless there is known cutaneous involvement. Even in these circumstances the increased skin toxicity (in-field moist desquamation) may result in some circumstances in the requirement of a RT treatment break to allow for healing with at least one Australian study documenting increased cutaneous toxicity and no outcome benefit from this approach [36].

Role of Adjuvant RT in Non-HN Regions

Analogous to recommending adjuvant RT to the parotid and/or neck is treating the axilla or groin after nodal surgery. Although less published data is available to guide the clinician in assessing risk of recurrence associated with unfavorable factors such as ECS, patients with multiple involved nodes or close excision margins are at risk of developing regional relapse and should be recommended adjuvant RT. The aim of RT is to decrease this risk, in keeping with data from the HN setting. A complication of axilla or groin adjuvant RT, in contrast to the HN, is the risk of the development of extremity lymphedema, which is exacerbated post surgery by the addition

of adjuvant RT and in a minority of patients, can be severe. Patients need to be warned of this potential late side effect and we recommend that all patients who undergo an axillary or inguino-pelvic node dissection and/or radiotherapy be referred for lymphedema education and management.

Axillary RT is easily achieved using CT 3D conformal planned opposing AP/PA megavoltage photons and attempting to minimize the amount of underlying lung irradiated, taking into consideration the curvature of the chest wall and the need to cover the often medially located axillary nodes. The supraclavicular fossa should also be included in the treatment fields. This technique is well defined using anatomical landmarks with one study reporting excellent regional control rates and minimal late toxicity [37]. The risk of brachial plexus plexopathy and rib fractures can be minimized by limiting the total dose delivered to 50 Gy in 25 fractions. Other authors have treated to a higher dose of 60 Gy equivalent to the dose recommended in HN regions [38].

The groin is also usually approached with either opposing AP/PA megavoltage photon fields or with a high energy electron field. Various techniques are reported, often depending on whether the hemi-pelvis (to treat deeper pelvic nodes), as well as the groin, are to be treated. With involved nodes often in close proximity to the underlying femoral head, groin RT carries with it a risk (10–15 %) of late femoral neck fracture. Despite this, inadequate deep coverage (5–6 cm) in an attempt to decrease the dose to the femoral head, especially using electrons, may undertreat deeply located nodes and increase the risk of regional relapse [39].

Inoperable Metastases

Radiotherapy Alone

Patients with skull base bone invasion, brain or carotid vessel involvement should be considered inoperable, but still treatable. Such patients usually present with very advanced disease, which is frequently fixed to underlying structures. In the case of metastatic CSCC occurring in nodal basins other than the HN, it is less common to encounter a patient who has unresectable disease. More frequently, the patient is not a candidate for surgery due to co-morbidities.

In patients with operable nodal disease that are treated with high dose (66–70 Gy) RT (medically unfit/patient refusal of surgery) there is a chance of cure although patients with more advanced borderline operable or inoperable disease are unlikely to obtain durable regional control.

Palliative Radiotherapy

Patients who are unsuitable for surgery and/or 5–6 weeks of RT due to poor performance status may still benefit from shorter schedules of palliative RT. Examples of recommended dose fractionation schedules include 20–25 Gy in 5 fractions, 30–35 Gy in 10 fractions or 40–45 Gy in 15 fractions (Fig. 8.7). Clinicians should

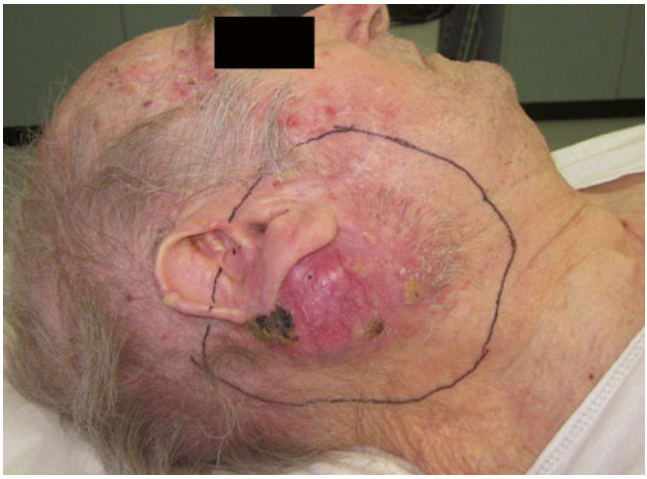


Fig. 8.7 Elderly nursing home patient of poor performance status with an advanced metastatic tail of parotid node treated palliatively with a moderate energy (12 MeV) electron field (as marked) to a dose of 25 Gy in 5 daily fractions to obtain growth restraint and tumor reduction and prevent fungation

consider limiting irradiated volumes to macroscopic disease with 1–2 cm margins using simple techniques such as opposed megavoltage photons fields or a direct electron field. In a Canadian study [40] patients with advanced HN CSCC (median size 5 cm) not suitable for radical treatment received 24 Gy of RT in 3 divided fractions delivered on days 0, 7 and 21 over 3 weeks. A variety of modalities and techniques were utilized and field margins encompassing macroscopic disease were 1–2 cm. The authors reported a complete clinical response rate of 36 % and the alleviation of symptoms in most patients without any marked late toxicity. The choice of which palliative dose fractionation schedule to utilize is dependent on multiple factors but very much dependent on the patient's ability to tolerate prescribed treatment.

Depending on the initial response to palliative RT and the dose delivered, suitable patients may be candidates for further RT to sites of symptomatic disease.

Patients with symptomatic sites of metastases such as skeletal metastases or soft tissue deposits may benefit from a single 6–8 Gy fraction of RT or multiple fractions such as 20 Gy in 5 fractions. Symptoms of pain or bleeding are usually well palliated with local RT. Sites of painful nodal metastases are better treated with a fractionated approach as opposed to a single fraction.

Role of Chemotherapy

Adjuvant Radio-Chemotherapy

Chemotherapy is also discussed in Chap. 9, particularly with regard to palliative therapy in terminal cases. Combined chemoradiation for control of nodal disease is discussed below. Despite the current optimal treatment of nodal disease with surgery

and adjuvant RT a minority of patients develop recurrence, predominantly regional in the treated nodal bed. There are data in mucosal HN SCC that combination concurrent platinum chemotherapy and adjuvant RT can improve regional control and disease free survival postoperatively in high-risk patients (ECS, multiple nodes, positive margins) [41, 42]. Though such studies have not been conducted in CSCC, high-risk pathological features such as multiple nodes, extranodal spread, positive margins, and perineural or vascular invasion, are often present in metastatic HN CSCC patients. The first trial testing chemoradiation in such CSCC patients has recently been conducted in Australia and New Zealand under the auspices of the Trans Tasman Radiation Oncology Group (TROG) with the aim to accrue 265 patients randomized to receive adjuvant RT (60 Gy) or adjuvant RT and weekly carboplatin (Post-Operative Skin Trial; POST 05.01). Carboplatin was chosen on the basis that the patients in this study are unlikely to tolerate cisplatin (renal and ototoxicity) as many are older with pre-existing co-morbidities. As of 2014 the study has closed to accrual and analysis and publication of the results is likely in the near future.

Palliative Chemotherapy

Patients with disseminated disease who are of good performance status may be considered for single or combination palliative chemotherapy. As in patients with mucosal HN SCC the combination of 5FU and platinum has been utilized. This is covered more fully in Chap. 9.

Recurrent Disease Post Treatment

Recurrent nodal metastases in a treated nodal bed are associated with a poor prognosis and often associated with subsequent distant relapse despite successful regional salvage. Prior to recommending radical intent salvage treatment, patients should be appropriately re-staged to exclude the presence of visceral (e.g. lung, liver) metastases. Investigations should include whole body contrast enhanced CT scans, or alternatively a CT/PET scan.

Salvage Surgery

Regional SCC recurrence after a previous dissection and/or RT should be re-operated on where possible. The extent of previous surgery and RT and the site of recurrence will dictate the type and extent of salvage surgery. Generally we would recommend patients have a completion neck dissection. Recurrent SCC in the parotid bed following nerve sparing parotidectomy may require salvage radical parotidectomy with sacrifice of the facial nerve. Surgery is often technically challenging, particularly if the patient has had RT previously, as this increases tissue fibrosis and may delay

wound healing. Recurrences often involve the overlying skin, which should also be re-excised with clear margins whenever possible. Pre-operative peripheral margin Mohs micrographic surgery can sometimes be helpful in such cases to establish the lateral extent of skin and subcutaneous recurrence. This helps surgeons to plan reconstruction pre-operatively (since they know in advance how much skin will be lost) and allows them to focus on clearing the deep margin intraoperatively as peripheral margins have already been determined. Adjuvant RT should be offered to all patients who have not previously been irradiated, and should encompass the surgical bed and uninvolved next echelon nodes. Patients considered not suitable for salvage surgery, or that decline surgery, should be offered definitive RT. Doses of 60–70 Gy using CT planned megavoltage photons offer the patient a chance of cure, or at the very least durable in-field regional control. Patients not suitable for high-dose RT should still be considered for a shorter course of RT.

Regional Re-Irradiation

Regional recurrence after adjuvant RT poses a difficult problem as patients will usually have had a large volume (e.g. ipsilateral parotid bed +/-hemi-neck, groin, axilla) of normal tissue (e.g. mandible, soft tissue, brainstem/spinal cord, nerves, carotid artery, femoral head, ribs) irradiated to 50–60 Gy. Following appropriate re-staging, operable patients should proceed to surgery. For inoperable patients the evidence available for re-irradiation relates predominantly to treating mucosal HN SCC patients. In this analogous setting recent evidence has emerged supporting the use of highly conformal IMRT [43, 44]. Patients retreated with IMRT are likely to have a better outcome (improved regional control and decreased severe late effects) compared with conventional 3D conformal re-irradiation. The best results are achieved with radical re-irradiation doses of ~60 to 70 Gy in 2 Gy daily fractions and re-treatment volumes limited to ~2 cm around gross disease or the resection bed. The spine, brainstem and optic chiasm should receive a limited re-treatment dose (15–25 Gy) if previously irradiated to tolerance. Of note, even when utilizing IMRT, serious late toxicity and treatment related deaths are reported in around 20 % of patients. The addition of concurrent chemotherapy to re-irradiation has also been recommended in select patients with mucosal SCC. The role of re-irradiating after salvage nodal surgery is less well defined but in patients with unfavorable pathology (i.e. close/positive excision margins, ECS) it should be considered.

Prognosis

The older literature often reported a dismal outcome for patients developing metastatic nodal CSCC with only a minority curable. However this should not be considered the case with contemporary treatment. The prognosis of patients with metastatic

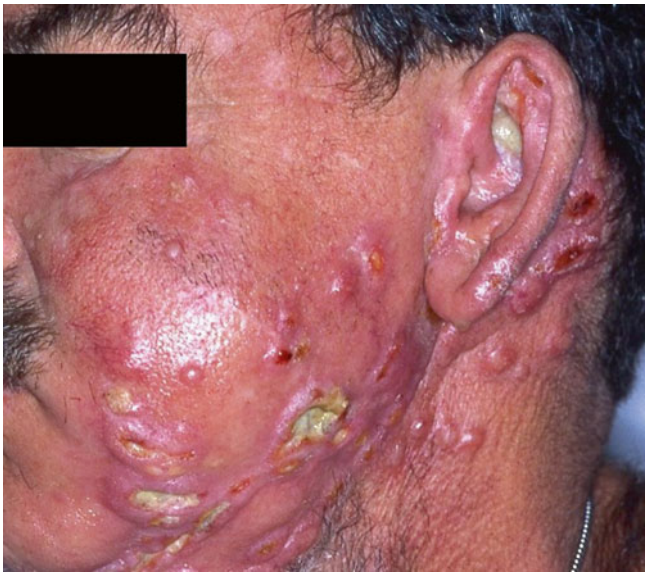


Fig. 8.8 Fifty-two year old male cardiac transplant recipient with widespread dermal based metastases following recent surgery and adjuvant radiotherapy with metastatic cutaneous squamous cell carcinoma to the left parotid. The patient was incurable and after cessation of his immunosuppressive medications was treated palliatively

HN CSCC if treated appropriately is favorable with most cured with the expectation of a 60–75 % 5 year disease free survival [2, 6, 7]. A large study of 250 patients identified 4 independent predictors of prognosis: immunosuppression, type of treatment, extracapsular spread and surgical margin status (ITEM), and subdivided the patients into three risk categories according them an ITEM score with the 5 year risk of dying from disease for patients reported to be 52 %, 24 % and 6 % for high-risk, moderate risk and low risk groups, respectively [41]. Patients who underwent surgery and adjuvant RT had a significantly improved outcome (hazard ratio 0.32, 95 % CI 0.16–0.66; $p=0.002$) compared with surgery alone, and patients with ECS and/or immunosuppression, fared worse [45]. It is well documented that immunosuppressed patients do badly despite appropriate treatment [46] (Fig. 8.8). Thus the level of immunosuppression should be reduced if at all possible [47].

There has been much less published data regarding the outcome of patients with nodal metastases in areas other than the HN, with some series reporting relapse rates of 30–60 % [25, 37], many with distant sites of first relapse. However most series are small and heterogeneous and it is therefore difficult to make definitive comparisons with metastatic HN CSCC.

New Advances/Studies/Follow up Post Treatment

Until recently, adjuvant systemic treatment for nodal metastatic CSCC consisted of traditional chemotherapeutic agents such as cisplatin and carboplatin. There is ongoing research investigating the use of more novel agents including molecular targeted therapies.

Agents such as interferon α, and 13 *cis*-retinoic acid have shown some activity against CSCC. However, a phase III study of the use of retinoic acid and interferon in the adjuvant setting for patients with "aggressive CSCC" including those with nodal metastases showed this treatment did not improve the time to tumor recurrence or prevent second primary tumors [48]. Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase which is expressed in CSCC and often over-expressed in metastatic disease. Recently there has been interest in using agents such as cetuximab, an anti-EGFR monoclonal antibody for the treatment of CSCC. A phase II study of the use of cetuximab in patients with unresectable CSCC demonstrated a 69 % response rate [49]. Cetuximab is a known radiosensitizer and several case reports/series have documented its use in combination with RT. In one study of eight patients with either advanced or unresectable CSCC treated with Cetuximab +/-RT the authors reported 6/8 responding with 3 complete responses and a median overall survival of 22.5 months [50]. However, its use in the adjuvant setting for the treatment of nodal metastases of CSCC has not yet been established and remains investigational in this setting.

Abbreviations

CSCC	Cutaneous squamous cell carcinoma
CT	Computer assisted tomography
DNA	Deoxyribonucleic acid
ECS	Extracapsular spread
EGFR	Epidermal growth factor receptor
FNAB	Fine needle aspiration biopsy
HN	Head and neck
IMRT	Intensity modulated radiotherapy
MRND	Modified radical neck dissection
MRI	Magnetic resonance imaging
PET	Positron emission tomography
RT	Radiotherapy
SCC	Squamous cell carcinoma
SND	Selective neck dissection
STM	Soft tissue metastasis

References

1. Rowe D, Carroll R, Day CL. Prognostic factors for local recurrence, metastasis and survival rates in squamous cell carcinoma of the skin, ear and lip. J Am Acad Dermatol. 1992;26:976–90.
2. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 patients treated with metastatic nodal disease. Cancer. 2006;106:2389–96.
3. Karia PS, Harrington DP, Jambusaria-Pahlajani A, Murphy G, Qureshi AA, Schmults CD. Evaluation of AJCC and UICC tumor staging for cutaneous squamous cell carcinoma and validation of an alternative system based on 10 year cohort outcome data. J Clin Oncol. 2014;32:327–34.
4. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68:957–66.
5. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year single institution cohort study. JAMA Dermatol. 2013;149:541–7.
6. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck. 2007;29:621–31.
7. Hinerman R, Indelicato D, Amdur R, et al. Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes. Laryngoscope. 2008;118:1989–96.
8. O'Brien CJ. The parotid gland as a metastatic basin for cutaneous cancer. Arch Otolaryngol Head Neck Surg. 2005;131:551–5.
9. Wang J, Palme C, Morgan G, et al. Predictors of outcome in patients with metastatic cutaneous head and neck cutaneous squamous cell carcinoma involving cervical lymph nodes: improved survival with the addition of adjuvant radiotherapy. Head Neck. 2012;34:1524–8.
10. Veness MJ, Morgan GJ, Palme C, Gebski V. Cutaneous head and neck squamous cell carcinoma metastatic to cervical lymph nodes: surgery and adjuvant radiotherapy should be considered best practice. Laryngoscope. 2005;44:870–5.
11. Dona E, Veness MJ, Cakir B, Morgan GJ. Metastatic cutaneous squamous cell carcinoma to the parotid: the role of surgery and adjuvant radiotherapy to achieve best outcome. ANZ J Surg. 2003;73:692–6.
12. Breuninger H, Black B, Rassner G. Microstaging of squamous cell carcinomas. Am J Clin Pathol. 1990;94:624–7.
13. Joseph M, Zulueta W, Kennedy P. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. ANZ J Surg. 1992;62:697–701.
14. Ebrahimi A, Clark JR, Lorincz BB, Milross CG, Veness MJ. Metastatic head and neck squamous cell carcinoma: defining a low-risk patient. Head Neck. 2012;34:365–70.
15. Panizza B, Solares CA, Redmond M, Parmar P, O'Rourke P. Surgical resection for clinical perineural invasion from cutaneous squamous cell carcinoma. Head Neck. 2012;34:1622–7.
16. Iyer N, Clark J, Murali R, Gao K, O'Brien C. Outcomes following parotidectomy for metastatic squamous cell carcinoma with microscopic residual disease: implications for facial nerve preservation. Head Neck. 2009;31:21–7.
17. Iseli T, Harris G, Dean N, Iseli C, Rosenthal E. Outcomes of static and dynamic facial nerve repair in head and neck cancer. Laryngoscope. 2010;120:478–83.
18. Gidley P, Herrera S, Hanasono M, Yu P, Skoracki R, Roberts D, Weber R. The impact of radiotherapy on facial nerve repair. Laryngoscope. 2010;120:1985–9.
19. Wang A, Palme C, Wang J, Morgan G, Gebski V, Gilchrist J, Veness M. Quality of life assessment in patients treated for metastatic cutaneous squamous cell carcinoma of the head and neck. J Laryngol Otol. 2013;127(Suppl S2):S39–47.

20. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer C. Incidence of cervical node involvement in metastatic cutaneous malignancy involving the parotid gland. Head Neck. 2001;23:744–8.
21. D'Souza J, Clark J. Management of the neck in metastatic cutaneous squamous cell carcinoma of the head and neck. Curr Opin Otolaryngol Head Neck Surg. 2011;19:99–105.
22. Wang J, Palme C, Morgan G, Gebski V, Veness M. In patients with metastatic head and neck squamous cell carcinoma to cervical lymph nodes, the extent of neck dissection does not influence outcome. J Laryngol Otol. 2013;127(Suppl S1):S2–7.
23. Ambrosch P, Kron M, Pradier O, Steiner W. Efficacy of selective neck dissection: a review of 503 cases of elective and therapeutic treatment of the neck in squamous cell carcinoma of the upper aerodigestive tract. Otolaryngol Head Neck Surg. 2001;124:180–7.
24. Vauterin TJ, Veness MJ, Morgan GJ, Poulsen MG, O'Brien CJ. Patterns of node spread of cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2006;28:785–91.
25. Mullen J, Feng L, Xing Y, et al. Invasive squamous cell carcinoma of the skin: defining a high risk group. Ann Surg Oncol. 2006;13:902–9.
26. Goh A, Howle J, Hughes T, Veness MJ. Managing patients with cutaneous squamous cell carcinoma metastatic to the axilla or groin lymph nodes. Australas J Dermatol. 2010;51:113–7.
27. Jiang Y, Ajani JA. Anal margin cancer: current situation and ongoing trials. Curr Opin Oncol. 2012;24:448–53.
28. Bron LP, Traynor SJ, McNeil EB, O'Brien CJ. Primary and metastatic cancer of the parotid: comparison of clinical behavior in 232 cases. Laryngoscope. 2003;113:1070–5.
29. Del Charco JO, Mendenhall WM, et al. Carcinoma of the skin metastatic to the parotid area lymph nodes. Head Neck. 1998;20:369–73.
30. Jol JAD, van Velthuysen MLF, Hilgers FJM, et al. Treatment results of regional metastasis from cutaneous head and neck squamous cell carcinoma. Eur J Surg Oncol. 2002;29:81–6.
31. Kelder W, Ebrahimi A, Forest VI, et al. Cutaneous head and neck squamous cell carcinoma with regional metastases: the prognostic importance of soft tissue metastases and extranodal spread. Ann Surg Oncol. 2012;19:274–9.
32. Audet N, Palme CE, Gullane PJ, et al. Cutaneous metastatic squamous cell carcinoma to the parotid gland: analysis and outcome. Head Neck. 2004;26:727–32.
33. Moore BA, Weber RS, Prieto V, et al. Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. Laryngoscope. 2005;115:1561–7.
34. Mendenhall WM, Amdur RJ, Hinerman RW, Cognetta AB, Mendenhall NP. Radiotherapy for cutaneous squamous and basal cell carcinoma of the head and neck. Laryngoscope. 2009;119:2366–8.
35. Gluck IG, Ibrahim M, Popovtzer A, et al. Skin cancer of the head and neck with perineural invasion: defining the clinical target volumes based on the pattern of failure. Int J Radiat Oncol Biol Phys. 2009;74:38–46.
36. Prama A, Browne L, Graham P. Metastatic cutaneous squamous cell carcinoma to parotid nodes: the role of bolus with adjuvant radiotherapy. J Med Imaging Radiat Oncol. 2012;56:100–8.
37. Fogarty GB, Cassumbhoy R, Martin JM, Ainsle J. Technique for axillary radiotherapy using computer-assisted planning for high-risk skin cancer. Australas Radiol. 2007;51:267–75.
38. Beydoun N, Graham PH, Browne L. Metastatic cutaneous squamous cell carcinoma to the axilla: a review of patient outcomes and implications for future practice. World J Oncol. 2012;3:217–26.
39. Koh WJ, Chiu M, Stelzer KJ, Greer BE, et al. Femoral vessel depth and the implications for groin node radiation. Int J Radiat Oncol Biol Phys. 1993;27:969–74.
40. Barnes EA, Breen D, Culleton S, et al. Palliative radiotherapy for non-melanoma skin cancer. Clin Oncol. 2010;22:844–9.
41. Cooper JS, Pajak TF, Forestiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. N Engl J Med. 2004;350:1937–44.

42. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350:1945–52.
43. Duprez F, Madani I, Bonte K, et al. Intensity-modulated radiotherapy for recurrent and second primary head and neck cancer in previously irradiated territory. Radiother Oncol. 2009;93:563–9.
44. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer disease control and morbidity outcomes. Int J Radiat Oncol Biol Phys. 2009;73:399–409.
45. Oddone N, Morgan G, Palme C, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck. The immunosuppression, treatment, extranodal spread, and margin status (ITEM) prognostic score to predict outcome and the need to improve survival. Cancer. 2009;115:1883–91.
46. Southwell KE, Chaplin JM, Eisenberg RL, McIvor NP, Morton RP. Effect of immunocompromise on metastatic cutaneous squamous cell carcinoma in the parotid and neck. Head Neck. 2006;28:244–8.
47. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management. Part 2. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65:263–79.
48. Brewster A, Lee J, Clayman G, et al. Randomized trial of adjuvant 13- cis-retinoic acid and interferon alfa for patients with aggressive skin squamous cell carcinoma. J Clin Oncol. 2007;25:1974–8.
49. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011;29:3419–26.
50. Giacchero D, Barriere J, Benezery K, et al. Efficacy of Cetuximab for unresectable or advanced cutaneous squamous cell carcinoma – a report of eight cases. Clin Oncol. 2011;23:716–21.

Chapter 9
Management of Widely Metastatic and Unresectable Cutaneous Squamous Cell Carcinoma

Glenn J. Hanna, Emily Stamell Ruiz, and Jochen H. Lorch

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer and though most cases are easily cured with surgical excision, it is associated with a 3 % metastatic risk [1, 2]. Seventy to 80 % of all non-melanoma skin cancers occur in the sun exposed regions of the head and neck. It is estimated that 2500–8800 patients succumb each year to CSCC in the United States, often a result of uncontrolled loco-regional disease [3, 4]. Distant metastases are less common. This chapter will discuss the management of such patients with unresectable local, regional, or distant disease, particularly with regard to chemotherapy and chemoradiation. Radiation therapy for nodal disease is also discussed in Chap. 8.

G.J. Hanna, MD
Department of Medical Oncology and Hematology, Dana Farber Cancer Institute,
450 Brookline Avenue, Smith 353, Boston, MA 02215, USA

E.S. Ruiz, MD
Department of Dermatology, Brigham and Women's Hospital,
1153 Centre Street, Suite 4349, Boston, MA 02130, USA

J.H. Lorch, MD, MSc (✉)
Department of Medical Oncology, Harvard Medical School, Dana Farber Cancer Institute,
450 Brookline Ave, Boston, MA 02115, USA
e-mail: Jochen_lorch@dfci.harvard.edu

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_9

Clinical Features

Location of Metastatic Spread

Risk factors of primary tumors and patient factors which impact risk of metastasis are covered extensively in earlier chapters of this book. However, it is important to note that up to 27 % of patients with nodal metastases have no identifiable primary lesion on cutaneous skin examination [5]. This may be because most patients with metastatic CSCC have had multiple primary CSCC tumors and determining which primary gave rise to metastases can sometimes prove difficult. Studies to date have relied upon tumors' anatomic proximity to metastatic nodal basins, high-risk features, and timeframe of primary tumor appearance to metastasis to determine which of several primary tumors give rise to nodal disease. However, such information may be imprecise. Genetic profiling of primary tumors and metastases may prove very helpful in future investigations to clarify which tumors result in metastases.

Cervical lymph nodes are the most common site of metastatic spread from CSCC (60 %, often involving the submental or submandibular nodes), followed by the parotid gland (30 %). CSCC of the pinna, given its regional lymphatic drainage pattern and proximity to the parotid gland, most often (60–70 %) results in metastatic disease to the ipsilateral cervical lymph nodes or parotid gland [6]. Ear location may carry a higher risk of metastasis [7]. Fewer than 20 % of patients with metastasis present with distant metastases at the time of initial presentation. Half of patients develop recurrence at the primary cutaneous site prior to the development of metastatic disease [8]. Thus, patients who develop locally recurrent CSCC after clear-margin excision (Mohs or non-Mohs) should be considered at risk for metastasis.

Staging Systems for Metastatic CSCC

Traditionally, TNM staging for CSCC categorized lymph node metastases as either involved or uninvolved; however, the seventh edition of the American Joint Committee on Cancer (AJCC) staging system for CSCC revised the nodal staging system to reflect the number, diameter, and laterality of involved lymph nodes (Table 9.1) [9]. While this is an improvement over the former TNM staging system, contralateral metastases only occurred in 2 % of patients and there was only a 1 % difference in the risk of death at 3 years in the N2 subgroups in one study [10]. Others have proposed alternatives to AJCC nodal staging (Table 9.2). O'Brien et al. developed a staging system for metastatic CSCC of the head and neck that separates parotid and neck disease. The staging system when applied to 87 patients trended toward a significant correlation between survival and P stage ($p=0.07$). Increasing clinical ($p=0.04$) and pathologic ($p=0.006$) N stage was associated with decreased survival. O'Brien's staging system is an improvement over the TNM, but is complex due to the separation of the parotid and neck staging systems and the utility of such separation has not been investigated [12].

Table 9.1 AJCC Regional Lymph Node Staging for CSCC [9]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest diameter
N2a	Metastasis in a single ipsilateral 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

Table 9.2 Proposed alternative staging systems for patients with metastatic cutaneous squamous cell carcinoma

O'Brien et al. (2002) [11]	Forest et al. (2010) (N1S3) [12]
Parotid gland	
P1: Node ≤3 cm	I: Single lymph node measuring ≤3 cm
P2: Node >3 cm but ≤6 cm or multiple nodes	II: Single lymph node measuring ≤3 cm or multiple lymph nodes measuring ≤3 cm
P3: Node >6 cm or facial nerve involvement, skull base invasion	III: Multiple lymph nodes measuring >3 cm
Neck	
N0: Clinically negative neck	
N1: Single node ≤3 cm (ipsilateral)	
N2: Single node >3 cm, multiple or contralateral nodes	

Forest et al. developed the N1S3 staging system, which considers nodes from the parotid and neck together [12]. This system defines three stages based on the number of involved nodes from the parotid and neck and size above or below 3 cm. The N1S3 system was developed based on a 215 patient cohort and then applied to a different 250 patient cohort for validation. This staging system was able to discriminate between the three different groups for locoregional control (log rank $p=0.01$) and disease-specific survival ($p=0.004$) [12].

Treatment and Prognosis

Nodal Metastases

A thorough discussion of management of nodal metastases and recent data in this realm is the subject of Chap. 8. Some have advocated for elective lymph node dissections in patients with high risk lesions greater than 4 cm, cartilage invasion, deep invasion, or high risk lip lesions, but data are limited [13]. There is currently no formal consensus as to the appropriate treatment strategy for patients with nodally metastatic

CSCC, but patients should be treated with the intent of cure. Patients are generally offered either lymphadenectomy or radiation treatment, or a combination of both.

Induction and Definitive Chemotherapy for Advanced CSCC

Due to the rarity of the diagnosis of metastatic CSCC, the literature for chemotherapy is limited to small phase II studies and case series, which are summarized in Table 9.3 [14, 19]. There are no FDA-approved chemotherapy drugs specifically for

Table 9.3 Summary of trials utilizing systemic chemotherapy to treat cutaneous squamous cell carcinoma

Authors	Study design, n	Treatment	Response	Notes
Traditional definitive chemotherapy				
Guthrie et al. (1990) [14]	Cohort, 28 Advanced (BCC and SCC)	Cisplatin and Doxorubicin, Cisplatin (includes both neoadjuvant and definitive cases)	28 % CR 40 % PR	
Sadek et al. (1990) [15]	Phase II, 14 Advanced	Cisplatin, 5-FU, bleomycin and infusional 5-FU	84 % ORR 30 % CR 34 % PR	
Khansur et al. (1991) [16]	Case series, 7 Metastatic or locally advanced	Cisplatin and 5-FU	3 CRs 3 PRs	One patient was alive and disease-free at 2 years
Wollina et al. (2005) [17]	Case series, 4 Advanced	Capecitabine and Interferon	2 CR 2 PR	
Nakamura et al. (2013) [18]	Case series, 8 Metastatic	Cisplatin and Adriamycin, Cisplatin and Epirubicin, Carboplatin and Adriamyycin	2 CR 1 PR 2 SD 3 PD	
Adjuvant and neoadjuvant chemotherapy				
Guthrie et al. (1990) [14]	Cohort, 28 Advanced (BCC and SCC)	Cisplatin and Doxorubicin, Cisplatin (includes both neoadjuvant and definitive cases)	28 % CR 40 % PR	
Denic (1999) [19]	Case series, 5 Advanced (BCC or SCC)	Neoadjuvant Cisplatin and Bleomycin	1 CCR 3 PR 1 PD	
Tanvetyanon et al. (2015) [30]	Retrospective cohort study, 61 Stage III/IV	Surgery + Radiation vs. Surgery + Chemoradiation	Chemo-XRT: 2 DM 8 LR XRT: 1 DM 13 LR	HR of chemo-XRT:XRT = 0.31 (95 % CI, 0.13–0.78) for risk of disease recurrence or death

(continued)

Table 9.3 (continued)

Authors	Study design, n	Treatment	Response	Notes
Targeted therapy (definitive unless otherwise stated)				
Read (2007) [20]	Case series, 3	Erlotinib	2 PR	Tumor recurred on discontinuation in the CR patient
	Metastatic or locally recurrent		1 CR	
Maubec et al. (2010) [21]	Phase II, 36	Cetuximab	69 % ORR	Infusion reactions and acneiform rash notable
	Metastatic		2 CR	
			8 PR	
Giacchero et al. (2011) [22]	Case series, 8	Cetuximab, Cetuximab and Radiotherapy	3 CR	Grade 3 or 4 adverse events in eight patients
	Advanced or unsectable		3 PD	
			1 SD	
			1 PD	
Kalapurakal et al. (2012) [23]	Case series, 4	Cetuximab	3 CR	One CR relapsed within 6 months
	Recurrent SCC		1 PR	
Lewis et al. (2012) [24]	Phase II, 23	Neoadjuvant Gefitinib	18.2 % CR	
	locally advanced		27.3 % PR	
O'Bryan et al. (2013) [25]	Case series, 7 high risk post resection	Six patients received cetuximab + surgery	4 CR	
		One patient received cetuximab + surgery + XRT	2 PD	
			1 UA	
Preneau et al. (2013) [26]	Pilot study, 19	Five patients received cetuximab + XRT	9 PR	
	Inoperable	Nine patients received cetuximab + carboplatin	6 SD	
			4 PD	
		Five patients received cetuximab monotherapy	47 % ORR	
			78 % overall disease control	
Heath et al. (2013) [27]	Phase I, 15 locally advanced or lymph node involvement	Erlotinib + XRT	65 % OS (2 years)	
			60 % DFS	
			26.7 % recurrence	

CR complete remission, *PR* partial remission, *CCR* complete clinical remission, *ORR* overall response rate, *OS* overall survival, *SD* stable disease, *PD* progression of disease, *PFS* progression free survival, *DM* distant metastasis, *LR* local recurrence, *UA* unable to access response, *DFS* disease free survival

CSCC and no well-established treatment regimens. Thus the information below is for off-label uses. Most regimens have been based on mucosal head and neck SCC treatment protocols.

Advanced CSCC, defined as loco-regional disease that has failed surgery and radiation or is widely metastatic, is generally treated with systemic chemotherapy.

Previously chemotherapy was used primarily as a palliative treatment, but current regimens are implemented with curative intent for loco-regional disease. Conversely, treatment of distant organ metastases and intracranial extension remains mostly palliative. It is important to recognize that many chemotherapeutic regimens are associated with significant toxicity.

Induction chemotherapy is the administration of chemotherapy prior to definitive loco-regional control. It is beneficial for unresectable tumors (that may be resectable after induction therapy) or for early treatment of subclinical metastases. Induction chemotherapy is generally used in conjunction with radiation. The most frequently used induction chemotherapy regimens are 5-fluorouracil (5-FU)/cisplatin combinations [28].

Definitive chemotherapy, in contrast to induction therapy, is aimed at cure or best possible control of disease not amenable to surgical clearance. It is usually combined with radiation and is most often used for organ preservation or for patients unable to tolerate surgery. The most common definitive chemotherapy regimens include cisplatin, 5-FU/cisplatin combinations, 5-FU/carboplatin combinations, and paclitaxel/carboplatin combinations [28]. Most studies evaluating these regimens have been performed in mucosal head and neck SCCs (originating from the oral cavity, oropharynx, hypopharynx, and larynx). Pignon et al. [29] published a large meta-analysis of 87 randomized trials of mostly mucosal (non-cutaneous) head and neck SCCs, which included 16,485 patients. Their analyses found greater benefit of chemotherapy administered concurrent with radiation (HR 0.81, 95 % CI 0.79–0.86) as compared to induction chemotherapy administered prior to radiation and/or surgery which did not show a survival advantage (HR 0.96, 95 % CI 0.9–1.02) [29].

Studies specific to CSCC are limited and much work remains to define optimal systemic therapy. Though most patients will have an initial clinical response, sustained remissions are rare and the large majority of patients ultimately succumb to disease. Studies of traditional chemotherapy have focused on definitive rather than induction regimens. Khansur et al. [16] reported a case series of seven patients with advanced locoregional or metastatic CSCC treated with cisplatin and 5-FU. This series noted three partial responses, three complete responses, and one stable disease. Sadek et al. [15] reported an 84 % objective response to a combination regimen of cisplatin, 5-FU, and bleomycin in 13 patients with CSCC. Complete response was seen in 30 % of patients. Nakamura et al. [18] more recently reported a complete response in two out of eight patients receiving a combination of platinum and anthracycline chemotherapy with progression of disease in three patients.

There are a few case series that evaluate alternatives to platinum based chemotherapy. Wollina et al. [17] performed a prospective case series of four patients with advanced CSCC treated with oral capecitabine plus subcutaneous interferon alpha, of which two patients had complete response and two a partial response. Of note, the patients had only mild side effects.

Adjuvant Chemotherapy

Adjuvant chemotherapy is generally used in conjunction with adjuvant radiation postoperatively after clear surgical margins have been obtained for patients with high-risk pathologic features or history of recurrence for whom concern for further recurrence and metastasis is high. Identification of patients eligible for adjuvant chemotherapy is made case by case since no established standards are in place to guide patient selection.

Similar to the definitive chemotherapy regimens, utilization of adjuvant chemotherapy following definitive surgical excision is primarily extrapolated from the head and neck literature. To our knowledge, there is one study in the literature that specifically evaluates adjuvant chemoradiation for CSCCs. Tanvetyanon et al. [30] retrospectively compared 61 patients who underwent definitive surgical excision followed by adjuvant radiation or chemoradiation. This series noted a decreased risk of recurrence and death on multivariate analysis in patients who received chemoradiation compared to those who only underwent adjuvant radiation (HR 0.31, 95 % CI 0.13–0.78). These results indicate that treating high-risk patients post surgery with adjuvant chemoradiation, prior to the occurrence of clinical metastases, may result in a higher cure rates and prevention of mortality. However, defining which patients are candidates for adjuvant chemoradiation requires further study.

A significant amount of research has investigated the use of retinoids in the management of CSCC lesions, but while they offer some prophylactic benefit, they do not alter the progression of the existing tumor [31]. Their prophylactic use is covered more extensively in Chap. 5.

Molecular Targeted Therapies

Currently there are no available molecular markers to identify high-risk CSCC patients or to aid treatment selection for those with metastatic disease. However, since CSCC is among the most heavily mutated of all cancers [32], it is likely that therapies targeting specific genetic and molecular alterations within a given CSCC will play a pivotal role in future therapeutic approaches. As the mutational landscape of CSCC appears to be highly variable from one tumor to the next without a predominating defect (in contrast to the hedgehog pathway in basal cell carcinoma or bRAF in melanoma), optimal molecular therapy for CSCC may need to be highly individualized [33]. The epidermal growth factor receptor (EGFR)-Ras-Raf-MEK-ERK signaling pathway has been implicated in head and neck SCCs [34]. Therapeutics that specifically target this pathway have recently been studied in patients with CSCC.

Cetuximab (Erbitux) is a human-mouse chimeric monoclonal antibody that competitively binds to the external domain of the EGFR, thereby inhibiting dimerization and overall tumor growth. It is currently approved as adjuvant therapy with concomitant radiation for use in patients with metastatic mucosal head and neck

SCC. A recent phase II trial investigated the use of cetuximab in metastatic CSCC. After 6-weeks of treatment, there was a 69 % disease response rate in the 31 patients in the study. Mean progression-free and overall survival were 121 and 246 days, respectively [21]. Interestingly, the development of an acneiform drug rash with treatment was associated with better outcomes, as noted in prior studies in head and neck cancer patients. In a small case series, cetuximab alone or in combination with radiation was shown to be efficacious with a treatment response in six out of eight patients [22]. A phase II study of neoadjuvant gefitinib which inhibits the ATP-binding site of EGFR showed an 18 % complete response and 27 % partial response in 22 subjects [24]. Two-year overall, disease-specific, and progression-free survival rates were 72.1 %, 72.1 %, and 63.6 %, respectively. Some data have demonstrated similar benefits with erlotinib, currently approved for use in non-small cell lung cancer [20, 27]. Additional studies of EGFR antagonists alone or in combination with radiation and as adjuvant and neoadjuvant treatment for locally extensive and metastatic CSCCs are needed given the current dearth of literature.

The hedgehog (Hh) pathway is a developmental signaling pathway involved in numerous cellular processes, affecting cell survival and differentiation. Mutations via ligand-independent mechanisms of constitutive activation have been noted in cancers such as basal cell carcinoma. Preliminary reports in murine models have demonstrated that overexpression of PTCH-1 (a regulatory tumor suppressor acting through the Hh pathway) in transgenic mice synergizes with Hras mutations to promote SCC development [35]. These findings could have implications with regards to treatment utilizing novel Hh signaling inhibitors. However, anecdotally, cutaneous basosquamous carcinomas (a histologic mix of basal and squamous cell carcinoma) treated with Hh inhibitors do not do well. Though the basaloid component regresses, the squamous portion appears resistant and subsequently predominates. Thus, Hh inhibitor monotherapy may have a limited role in CSCC therapy.

Conclusion

Metastatic CSCC presents a management challenge due to lack of prognostic estimates and clinical trials. Combined surgical resection followed by adjuvant radiation is the current standard treatment for nodal disease. Chemotherapy is generally reserved for patients with recurrent local and/or nodal disease after such treatment, or for those with rare distant organ metastases. There are no clearly defined protocols for systemic therapy of CSCC. Though various regimens have been tried, no treatment has been reported to be highly effective. Early treatment with adjuvant chemoradiation immediately after surgical clearance shows promise but defining an appropriate patient population for adjuvant therapy and defining optimal regimens requires additional investigation. Targeted chemotherapy and immuno therapy are likely to play a major role in the future, but further studies are necessary to elucidate molecular markers for prognostication and to individualize therapy in this heavily mutated and genetically heterogeneous disease.

References

1. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. JAMA Dermatol. 2013;149:541–7.
2. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20.
3. Silverberg E, Boring CC, Squires TS. Cancer statistics, 1990. CA Cancer J Clin. 1990;40:9–26.
4. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68:957–66.
5. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. Cancer. 2006; 106:2389–96.
6. O'Brien CJ. The parotid gland as a metastatic basin for cutaneous cancer. Arch Otolaryngol Head Neck Surg. 2005;131:551–5.
7. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. Am J Surg. 1984;148:542–7.
8. Tavin E, Persky M. Metastatic cutaneous squamous cell carcinoma of the head and neck region. Laryngoscope. 1996;106:156–8.
9. Sommer S, Merchant WJ, Sheehan-Dare R. Severe predominantly acral variant of angiokeratoma of Mibelli: response to long-pulse Nd:YAG (1064 nm) laser treatment. J Am Acad Dermatol. 2001;45:764–6.
10. Brunner M, Ng BC, Veness MJ, Clark JR. Assessment of the new nodal classification for cutaneous squamous cell carcinoma and its effect on patient stratification. Head Neck. 2015;37:336–9.
11. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. Head Neck. 2002;24:417–22.
12. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers. Cancer. 2010;116:1298–304.
13. Afzelius LE, Gunnarsson M, Nordgren H. Guidelines for prophylactic radical lymph node dissection in cases of carcinoma of the external ear. Head Neck Surg. 1980;2:361–5.
14. Guthrie Jr TH, Porubsky ES, Luxenberg MN, Shah KJ, Wurtz KL, Watson PR. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. J Clin Oncol. 1990;8:342–6.
15. Sadek H, Azli N, Wendling JL, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer. 1990;66:1692–6.
16. Khansur T, Kennedy A. Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. Cancer. 1991;67:2030–2.
17. Wollina U, Hansel G, Koch A, Kostler E. Oral capecitabine plus subcutaneous interferon alpha in advanced squamous cell carcinoma of the skin. J Cancer Res Clin Oncol. 2005;131:300–4.
18. Nakamura K, Okuyama R, Saida T, Uhara H. Platinum and anthracycline therapy for advanced cutaneous squamous cell carcinoma. Int J Clin Oncol. 2013;18:506–9.
19. Denic S. Preoperative treatment of advanced skin carcinoma with cisplatin and bleomycin. Am J Clin Oncol. 1999;22:32–4.
20. Benson JM, Sachs CW, Treacy G, et al. Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab. Nat Biotechnol. 2011;29:615–24.
21. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: part II. Treatment options. J Am Acad Dermatol. 2011;65:15–22. quiz 3–4.
22. Giacchero D, Barriere J, Benezery K, et al. Efficacy of cetuximab for unresectable or advanced cutaneous squamous cell carcinoma--a report of eight cases. Clin Oncol. 2011;23:716–8.

23. Kalapurakal SJ, Malone J, Robbins KT, Buescher L, Godwin J, Rao K. Cetuximab in refractory skin cancer treatment. J Cancer. 2012;3:257–61.
24. Lewis CM, Glisson BS, Feng L, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. Clin Cancer Res. 2012;18:1435–46.
25. O'Bryan K, Sherman W, Niedt GW, et al. An evolving paradigm for the workup and management of high-risk cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2013;69:595–602. e1.
26. Preneau S, Rio E, Brocard A, et al. Efficacy of cetuximab in the treatment of squamous cell carcinoma. J Dermatolog Treat. 2014;25:424–7.
27. Heath CH, Deep NL, Nabell L, et al. Phase 1 study of erlotinib plus radiation therapy in patients with advanced cutaneous squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2013;85:1275–81.
28. Martinez JC, Otley CC, Okuno SH, Foote RL, Kasperbauer JL. Chemotherapy in the management of advanced cutaneous squamous cell carcinoma in organ transplant recipients: theoretical and practical considerations. Dermatol Surg. 2004;30:679–86.
29. Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4–14.
30. Tanvetyanon T, Padhya T, McCaffrey J, et al. Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2015;37:840–5.
31. Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. Arch Dermatol. 2005;141:456–64.
32. Watt SA, Pourreyron C, Purdie K, et al. Integrative mRNA profiling comparing cultured primary cells with clinical samples reveals PLK1 and C20orf20 as therapeutic targets in cutaneous squamous cell carcinoma. Oncogene. 2011;30:4666–77.
33. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015;517:576–82.
34. Cohen EE. Role of epidermal growth factor receptor pathway-targeted therapy in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol. 2006;24:2659–65.
35. Kang HC, Wakabayashi Y, Jen KY, et al. Ptch1 overexpression drives skin carcinogenesis and developmental defects in K14Ptch(FVB) mice. J Invest Dermatol. 2013;133:1311–20.

Chapter 10
Immune Dysfunction and Immunosuppression: Impacts on SCC Incidence, Prognosis, and Management

Travis W. Blalock and Thomas Stasko

Introduction

There is now a basic understanding of the damaging impact of ultraviolet (UV) light on the immunologic response to cutaneous tissue. As detailed in Chapters 3 and 4, progress continues to be made in the pursuit of a more comprehensive understanding of the biologic and molecular impact of these changes on the initiation and evolution of cutaneous squamous cell carcinoma (CSCC). We have also observed the increased incidence and aggressiveness of SCC seen with systemic immunosuppressive medications and in diseases that induce immunosuppression. Overall immunoresponsiveness is now seen as a spectrum, involving local and systemic factors, in which there are alterations in tumor behavior biologically, cinically, and epidemiologically. This is perhaps most clearly demonstrated by observing solid organ transplant medicine and the continuous balancing act required to keep patients adequately immunosuppressed to assure organ survival while minimizing the risk of development of CSCC and other malignancies. In this chapter, we will address how immune suppression, whether originated by disease, iatrogenically induced, or simply age related, affects incidence, prognosis, and management of CSCC.

T.W. Blalock, MD (✉)
Department of Dermatology, Oklahoma University Health Sciences Center, 619 NE 13th Street, Oklahoma City, OK 73104, USA

Department of Dermatology, Emory University School of Medicine, 1525 Clifton Road, Atlanta, GA 30306, USA
e-mail: travis.w.blalock@emory.edu

T. Stasko, MD
Department of Dermatology, Oklahoma University Health Sciences Center, 619 NE 13th Street, Oklahoma City, OK 73104, USA

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7_10

Localized Immunosuppression

While the crux of this chapter will discuss how generalized immunosuppression promotes SCC formation, CSCC tumorigenesis results, at least in part, from localized immunosuppression due to UV light exposure. UV light, both acutely and chronically, induces a breakdown of the localized interplay of the innate and adaptive immune systems [1]. In elderly patients, a decline in innate and adaptive immunity results in a relative immune deterioration, most notably in sun exposed areas where there is an exacerbation of local immune suppression. There is epidermal atrophy and a decrease in the number of Langerhans cells. The generalized immune senescence that progresses with advancing age also decreases the T-cell response to tumor related antigens [2]. With aging, SCCs are more likely to extend to subcutaneous fat and deeper soft tissue structures despite being less than 2 mm from the skin surface due to fat loss, while at the same time, they are less likely to be detected by the immune system. In solid organ transplant patients, who are globally immunosuppressed, the most at risk sites by far are those that are antecedently immunosuppressed by years of UV light exposure. Though some of this risk is due to genetic defects induced by UV light on keratinocytes (Chapter 3), UV-induced immunologic alterations play a crucial role as well. Localized immunosuppression and immune dysfunction, including the impairment of immune surveillance against tumor or tumor susceptible keratinocytes (HPV infected, genetically altered, etc.) put tumor growth in motion.

With a competent immune system, UV induced genetic damage and molecular alterations including thymidine dimmers, reactive oxygen species, 6–4 photoproducts, and others, are reversed through mechanisms such as p53 tumor suppressor gene products as well as DNA repair mechanisms, before they become clinically relevant. UV radiation over time can induce mutations in p53 which limit keratinocytes' ability to repair genetic alterations, most notably further UV-induced DNA damage. With the addition of immunosuppression, these natural internal regulators, like the p53 gene, become further overwhelmed, and the tumor has no checkpoint. Recent work has begun to shed light on precisely how the immune system eradicates SCC or allows it to grow. Please see Chapters 3 and 4 for discussions of work in this area.

A more generalized concept of localized immune suppression arises from the context of SCC induction. While there is a continued debate regarding the exact keratinocytic origin of CSCC, the concepts of localized immunosuppression to induce tumor formation are clearly at the center of each position [3]. We believe that each position summarized below is not only reasonable, but likely represents a diverse spectrum of CSCC origins, thereby explaining tumoral diversity in clinical morphology, development, and response to treatment.

White et al. argue that Ras/p53 mutated SCCs are more likely to develop within follicular stem cells as opposed to interfollicular epithelium [4]. This concept, along with the recognition that the bulge area of the hair follicle and the associated stem

cells have a relative immune privilege, places the follicular unit at particular risk for induction of SCC [5]. The immunosuppressed follicular cytokine environment (increased interleukin-10, transforming growth factor-b1, and alpha-melanocyte stimulating hormone) may allow more aggressive tumor subtypes to form [5, 6]. From a clinical standpoint, this may explain why follicularly based actinic keratoses are believed to be more aggressive and it may also explain why certain keratoses or SCCs that have follicular extensions (or origins) recur following treatment with electrodessication and curettage (ED&C) [7].

While the concept of SCC induction from the follicular unit has gained momentum, others stand by the clinical reality that many SCCs do not arise in hair bearing areas. For example, SCC is common on bald scalps and can in fact be particularly aggressive in this location. Some have proposed that interfollicular epithelial stem cells can be progenitors to SCC. In this scenario, UV bombardment is the likely culprit of both immunosuppression and genetic damage leading to SCC formation as UVB and UVA are able to penetrate to the level of interfollicular stem cells (but not follicular stem cells) [3, 8].

Marjolin ulcers are classically understood as SCCs that occur in a chronic wound, burn, or scar, which are locally immunosuppressed areas. One can understand the localized immunosuppressive effects of a Marjolin ulcer by evaluating the immunosuppressed setting of a slowly or non-healing wound, usually resulting from chronic venous stasis, a non-healing burn injury, a pressure sore, a draining sinus tract, or an abscess. While there is constant inhibition of adequate healing, there is an abundance of pro-proliferation cytokines which are failing to repair the damaged tissues, not to mention an epidermal opening for viral infection (see HPV below). Together, these set the stage for tumorigenesis. Chronic scarring alters the native lymphatic drainage, restructures the local vascular supply, alters cellular makeup, and induces an abnormal cytokine milieu. Thus, with other potential factors, like UV light or constant trauma, exacerbating the already immunosuppressed area by depleting the area of Langerhans cells and altering the cytokine milieu even more, an already immunosuppressed area is further suppressed. It is not surprising that somewhere along this path of poor healing a tumor may arise. In fact, Marjolin tumors are more aggressive than typical SCCs and have a higher metastatic capability [9]. The ultimate clinical example is recessive dystrophic epidermolysis bullosa (RDEB), a disorder which involves chronic blistering and scarring of the skin. Patients with RDEB begin developing aggressive SCCs in their teens and most die before age 30 from locally advanced or metastatic SCC [10].

In summary, localized immunosuppression sets the stage for discussion of generalized immunosuppression when considering SCC. It is within these locally immunosuppressed areas where introduced generalized immunosuppression makes the largest clinical impact.

Disease Induced Immunosuppression

HIV

Patients infected with the human immunodeficiency virus (HIV) have been shown to have an increased incidence of CSCC. Most studies were performed early in the epidemic and show only a modestly increased risk [11–13]. A recent study from Northern California cited a relative risk of 2.6 for the development of SCC in HIV infected patients ($p<0.001$) [14]. The study also showed a strong correlation between SCC and immunosuppression as gauged by recent CD4 counts. Nguyen et al. presented a series of HIV patients with SCC suggesting earlier age of onset, rapid lesion growth, and possibly a higher chance of recurrence and metastasis in these patients [15]. In a more recent study, Hausauer et al. report a 13.8 % 5-year tumor CSCC recurrence rate in well-controlled HIV patients, while only a 2.9 % 5-year tumor recurrence rate in HIV negative patients [16]. It has been speculated that HIV patients with undetectable viral load may be able to mitigate the increased risk of SCC. However, if the data from the above studies is accurate, well-controlled HIV alone may not be enough to prevent aggressive SCC formation. Nguyen et al. found no correlation between the CD4 count or opportunistic infections and the aggressiveness of the tumor [15].

HIV patients should undergo increased surveillance for skin cancer due to the increased incidence, frequent abnormal tumor presentations, the propensity for multiple and abnormal HPV subtypes, and the more aggressive nature of the tumors themselves. While the controversy of HPV as a causative role for all SCC may be unresolved, the transformation of anogenital keratinocytes to in situ and invasive disease is well accepted and anal SCC is a cause of significant morbidity in HIV patients [17]. From an epidemiologic standpoint, the prevalence of anal squamous intraepithelial dysplasia in HIV positive men who have sex with men (MSM) and HIV positive women is correlated with low CD4 counts and high risk HPV [18–20]. As highly active antiretroviral therapy (HAART) therapy becomes more effective, easier to tolerate, and more accessible, the incidence of anogenital disease may decline. Meanwhile, HIV positive MSMs and women with a history of cervical dysplasia or genital warts should undergo anoscopy at least annually.

Chronic Lymphocytic Leukemia

Patients with chronic lymphocytic leukemia (CLL) are also known to have an increased risk of SCC as well as more aggressive tumors. The majority of information regarding SCC in these patients refers to the B cell subtype of CLL which predominates (>95 %), but probably applies to all CLL subtypes. It is generally believed that CLL induces a diverse and progressive immune system down regulation including down regulation of the ability of T cells to interact with antigen

presenting cells as well as up-regulation of B cell induced immunosuppressive factors. These activities result in an inability to monitor and respond to intraepithelial neoplasia, an increased development of SCC, and likelihood for aggressive tumor behavior [21].

Mehrany et al. report a 19 % 5-year recurrence rate for CSCC after treatment with Mohs micrographic surgery for patients with CLL. In this group, neither histologic grade nor tumor diameter predicted tumor recurrence [21]. In a different case–control study of SCC outcomes, Mehrany et al. compared CLL to non-CLL patients with head or neck SCC [22]. Patients with CLL had an 18 % risk of metastatic SCC by 5 years after their first procedure for the primary tumor as compared to zero metastases in the non-CLL control group. This difference was statistically significant. Mehrany's group also found that histologically aggressive SCCs are more commonly found in the setting of CLL [23]. Toro et al. showed that a history of SCC prior to the diagnosis of CLL increased all-cause mortality by a factor of 1.86 ($p<0.0001$) as compared to CLL patients with no history of SCC, suggesting that prior sun damage and predisposition to skin cancer may impact outcomes in a complex manner in combination with the immune suppression of CLL [24]. In a relatively large cohort of CLL patients, Velez et al. found that CLL disease stage (Rai stage) predicted outcomes and that patients with high Rai-stage CLL had as high a chance of dying from skin cancer as they did from CLL (approximately 12 %) [25]. These studies suggest strongly that CLL is associated with an increased incidence of aggressive SCC which can cause death. Thus, heightened suspicion and increased cancer surveillance is of paramount importance in patients with CLL.

Strategy for Skin Cancer Prevention in the Immunosuppressed

While much of the discussion regarding management of high-risk SCC patients has derived from solid organ transplant patients, the principles of management can be somewhat extrapolated to all immunosuppressed patients whether the cause be a disease or iatrogenic. As multiple physicians are often involved in the care of immunosuppressed patients, the importance of establishing a good relationship and open communication between all providers must be emphasized. By having direct access and communication between dermatologists, transplant physicians, hematologists, oncologists, infectious disease physicians, and other providers, clinicians and immunosuppressed patients can have a concerted and unified understanding of the patient's situation and plan to treat. A collaborative environment educates all parties and equates to better patient care and likely improved outcomes.

One of the most important aspects of management regarding the immunosuppressed is to strive for good skin health prior to or immediately after the development of immunosuppression. Education regarding the effects of UV light and a thorough discussion about how to recognize skin changes that are premalignant or

malignant is the most prudent preventative care. With the progressive immunosuppression of simple aging, good skin care, and limiting ongoing UV damage (including localized UV-induced immunosuppression of the skin discussed above) is a constant strategy to be advocated to all patients. While time consuming, the education regarding avoiding intense sun exposure, use of UV protective clothing and sunscreens with an effective sun protection factor (SPF 30 or higher), and avoidance of tanning beds will be a valuable exercise for all patients, especially those facing immunosuppression. We must also challenge our patients to eliminate tobacco intake, as the evidence seems to be insinuating accelerated clinical and histologic aging of the skin with tobacco use [26].

A formal pre-immunosuppression evaluation is probably most practical for solid organ transplant patients, who could have a skin cancer oriented evaluation while awaiting transplant. This may be done for severely actinically-damaged patients or those with a prior history of skin cancer. However, as patients are often very ill prior to and immediately after transplantation, many transplant centers defer skin counseling until approximately 6 months post transplantation when patients are well enough to consider sun protective behavior changes and other prevention strategies. An effective relationship built with the patient prior to having problems will increase the likelihood of patient self-skin exam, sun protective behaviors, and compliance with routine skin surveillance exams. A patient history focusing on predisposing factors should be noted, as high-risk factors may become more consequential when the immunosuppressed state sets in. These factors include:

1. Advanced Age
2. Light Skin Type (Fitzpatrick I–II)
3. Personal history of skin cancer/actinic keratosis (AK)
4. Personal history of extensive UV exposure (sun, tanning beds. therapeutic)
5. Personal history of HPV infection
6. History of scars from trauma, illness, radiation, etc.
7. Cigarette or tobacco use
8. Personal history of immunosuppressive conditions
9. Personal history of immunosuppressive or photosensitizing medications.

Interestingly, most of these factors predispose any individual to SCC but the risk is compounded with immunosuppression. Physical examination should focus on the presence of actinic damage or actinic keratoses, any indication of HPV infection, and the presence of any skin malignancies in sun exposed or non-exposed areas. Evaluation of mucosal areas, genital and perianal regions, and periungual skin is important as these sites are known to have more aggressive tumors and are often overlooked by healthcare providers.

Early recognition and modification of risk factors prior to the initiation of immunosuppression may be helpful. By reducing the burden of modifiable risk factors prior to immunosuppression, including preexisting neoplasms, viral infections, or early intraepithelial neoplasms, it may be possible to prevent progression to invasive disease. Thompson et al. suggest that sunscreen use may have a significant impact on the regression of solar keratoses [27]. In the study of 588 Australians over 40

years old, a dose–response relation was found with more clinical remission and fewer new actinic keratoses (AKs) in those patients who used sunscreen. A study in German transplant recipients demonstrated that guided intense use of sunscreen decreases the development of SCCs, Basal cell carcinomas, and AKs while reducing the number of existing AKs [28].

When a patient presents for pre-transplant evaluation, all existing AKs should be treated to decrease likelihood of developing invasive disease. It is unclear whether physicians also address viral factors by utilizing HPV vaccinations. The Center for Disease Control and Prevention recommends the quadrivalant HPV vaccine to HIV infected children [29]. Studies are needed to determine if vaccination of adults against the types of HPV implicated in cervical cancer would decrease the incidence of skin cancer in immunosuppressed patients. Similarly, would prophylactic field therapy (photodynamic therapy, topical immunomodulators, etc.) for actinic damage prior to or after immunosuppression decrease SCC formation? In the absence of studies addressing these issues, logic dictates that curtailing intraepithelial disease may lessen progression to SCC in these patients.

Solid Organ Transplant Patients

The balancing act needed to achieve adequate immunosuppression in organ transplant recipients has shed a great deal of light on the consequences of immunosuppression and its effect on the development of SCC. While iatrogenic immunosuppression serves to minimize organ rejection, too much immunosuppression results in an increased susceptibility to infection and malignancies as well as other side effects with significant morbidity and mortality. Regarding cutaneous malignancies, the goal is to maximize transplant survival while minimizing the morbidity and mortality of cutaneous carcinoma. Christenson et al. showed that renal transplant patients who developed a non-melanoma skin cancer (NMSC) after their transplant had a better 5-year allograft and patient survival than kidney patients who did not develop a NMSC [30, 31]. Liver and heart transplant patients who developed NMSC after the transplant had a better 5-year overall survival as compared to their counterparts that did not develop NMSC. This association may indicate that NMSC is a surrogate marker for more profound immunosuppression which may be beneficial in the early years after transplantation. However, the increased incidence of NMSC coupled with metastatic rates of 5–8 % may play a significant role in transplant morbidity and mortality in later years [32]. This association reinforces the need for primary prevention, such as sun protection, which does not rely on a reduction in immunosuppression.

It is too simplistic to simply say someone is immunosuppressed or not-immunosuppressed. A transplant patient's immune system fluctuates and spans a range that is followed by clinical performance as well as laboratory values. Although new tests are available which seek to quantify a patient's level of immune suppression, the only clear measure of under-suppression, at this point, is organ rejection.

Pinpointing exactly where transplant patients are on the spectrum of immunosuppression is currently impossible, making it extremely difficult to interpret study data. Nevertheless, organ transplant patients, on their respective immunosuppressive regimens, have up to a 100-fold chance of developing cutaneous malignancies as compared to the general population [33]. Of these malignancies, SCC has been estimated at 65 times the rate for the general population when matched for age and sex in a Norwegian population [34].

When assessing the degree of immunosuppression and its correlation to the development of SCC, solid organ transplant patients highlight the parallel. Heart transplant patients, who are generally on the highest doses of immune suppressive therapy, have a threefold higher risk for the development of SCC than renal-transplant patients [34]. Liver transplant patients, who typically require low dose or even no immunosuppression, have a lower risk of developing CSCCs than their more immunocompromised heart and renal transplant cohorts [32].

In a recent retrospective analysis, Wisgerhof et al. reviewed 1800 kidney transplant patients performed in their hospital over a 40-year period [35]. In their review, 9.8 % of kidney transplant patients developed CSCCs and 7.9 % developed an internal malignancy. The internal malignancies identified in the study included breast cancer, aero-digestive tract cancers, prostate cancer, hematologic cancers, and one unclassifiable cancer. In patients who developed CSCC post transplant, there was a threefold increased adjusted risk of developing internal malignancies. While the study could not analyze the impact of changing immunosuppressive regimens over a 40-year period, the increased internal malignancies in organ transplant patients who have had SCC indicates that higher immunosuppression may protect grafts well but may lead to higher risks of both internal malignancies and SCC.

Strategy for Skin Cancer Management in Immunosuppressed Patients

Few management guidelines have been published for SCC patients who are immunosuppressed. One set of guidelines based on literature review and expert consensus was published by the International Transplant–Skin Cancer Collaborative (ITSCC) and the European Skin Care in Organ Transplant Patients Network (SCOPE) in 2004 [33]. While other types of immunosuppressed patients with a risk/history of SCC may need specific appraisal, management of these different groups may follow the ITSCC organ transplant guidelines which are part of the discussion below.

As noted above, pre-immunosuppression evaluation and treatment is the optimal starting point for preventing and managing SCC. Each time a patient presents, it is imperative to review all of the risk factors, as well as review the status and changes in the person's overall immune system. An evaluation of medication lists, emphasizing changes in medications and including an estimation of compliance is needed. At each visit, it is important to repeat education about self-conducted skin examinations and remind patients to use continuous sun protection. Thomas et al. recently reported that recall of sun protective education and the actual practice of sun protec-

tion in liver transplant patients is, at best, modest and reinforces the need for constant education [36].

The physical examination of high-risk immunosuppressed patients requires a full body skin examination of sun and non-sun exposed areas. The skin examination of immunosuppressed patients is best performed with the patient in a hospital gown without other clothing to achieve optimal detection of suspicious lesions. Placing a patient in a gown also facilitates the effective evaluation of regional lymphatic chains that might be difficult to palpate or even missed through clothing.

Evaluation and Intervention in Immunosuppressed Patients

During the physical examination, any lesions that may have an increased propensity to become neoplastic in the immunosuppressed should have a thorough evaluation and appropriate treatment. Lesions that may have an increased predilection for developing into SCCs include actinic keratoses, verrucae, porokeratoses, previously radiated skin, or chronic non-healing scars. Previously radiated skin and non-healing scars may necessitate wound care, monitoring for clinical changes, and active non-intervention. However, actinic keratoses, verrucae, and porokeratoses can be effectively treated by a variety of methods summarized in the chapter on field cancerization management. An adaptation from the ITSCC guidelines for evaluation and treatment of lesions with potentially neoplastic potential is in Fig. 10.1.

None of the topical medications are specifically approved by the FDA for immunosuppressed patients, though physicians have clearly used them successfully in such patients for mild to moderately aggressive lesions [37–39]. Topical immunomodulators have been effective in field therapy and also provide an additional modality to treat multiple discrete lesions in the same area. Transplant patients can present with diffuse actinic damage and multiple hyperkeratotic lesions (Fig. 10.2). The concept of field therapy and treatment options for field cancerization are

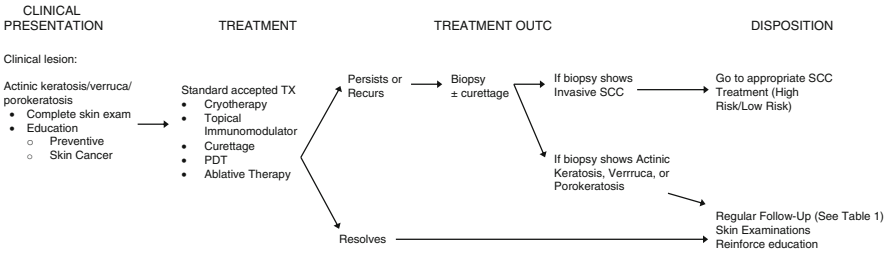


Fig. 10.1 Management of Lesions with Neoplastic Potential in the Immunosuppressed (adapted from the 2004 ITSCC Guidelines for the Management of Squamous Cell Carcinoma in Organ Transplant Patients)

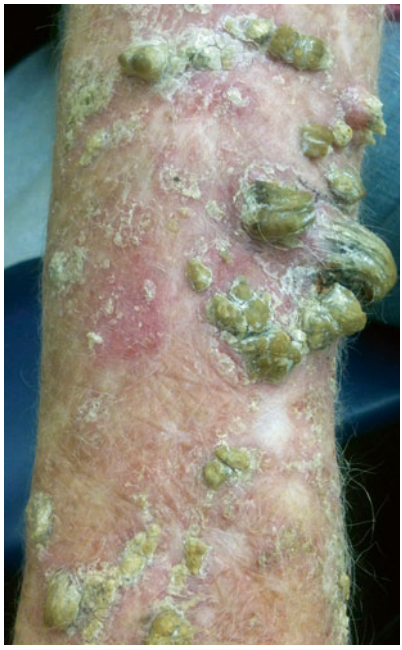


Fig. 10.2 Field cancerization is common in the immunosuppressed, highlighting the concept that sun-exposed skin has areas of squamous cell carcinoma surrounded by additional potentially malignant intraepithelial neoplasms

detailed in Chapter 5. If such treatment of pre-cancerous or in situ lesions fails, biopsy and/or alternative treatment should ensue. Many dermatologists with large transplant populations provide a cyclical approach of evaluation and field therapy to treat epithelial dysplasia that is constantly cultivated by the immunosuppressed state [40]. While the number of studies regarding actinic keratoses treatment in the immunocompromised is small, available data indicate topical treatments are useful. Data specific to immune suppressed patients is summarized below.

Ulrich et al. provided evidence that, imiquimod may effectively treat actinic keratoses in heart, liver, and kidney transplant patients, and that the efficacy may correlate with the level of immunosuppression of the patient. In an imiquimod versus vehicle randomized study with application three times a week for 16 weeks over a 100 cm^2 area, this study found a 62.1 % complete clearance (CC) rate and a 79.3 % partial clearance (PC) rate for actinic keratoses [41]. When separated by organ groups, heart transplant patients who are typically on higher-dose immunosuppressive regimens, cleared less actinic keratoses (PC 71 %/CC 42 %) than the kidney (PC 80 %/CC 65 %) or liver (PC 100 %/CC 100%) patients (who are on the least immunosuppressive medication). Of note, 0 % of the vehicle arm of the study had regression of actinic keratoses. The same group performed a similar study with 3 % diclofenac in 2.5 % hyaluronic acid applied twice daily over a 50 cm^2 area for 16 weeks. At the conclusion of the study, 41 % had a CC as opposed to 0 % in the vehicle arm of the study. Unlike the imiquimod study, there was no correlation with the level of immunosuppression and the efficacy of diclofenac.

Combination treatments have been attempted with multiple different topical treatments and techniques. Ritchie et al. present an inclusive approach combining sunscreen, 5-florouracil, diclofenac, and imiquimod [31]. 'Chemowraps', where 5 % 5-fluorouracil cream is used under occlusion and extremities are wrapped with a nonabsorbent material (zinc unna wraps) to enhance cutaneous penetration of the medication, have been found to be very effective for refractory areas in the immunosuppressed, though controlled studies are lacking [40].

Topical therapy for verrucae in immunosuppressed patients has been used with varying success. Saiag et al. evaluated efficacy of 5 % imiquimod on perianal and genital verrucae in well-controlled HIV patients on highly active antiretroviral therapy (HAART) [42]. Fifty patients applied imiquimod three times weekly for 16 weeks. At the end of the 16 weeks, 32 % of patients had total wart clearance. Beyond the clinical response, it was found that the HPV DNA load decreased or was undetectable in 40 % of the treated patients. Many other topical or intralesional therapies for verrucae in the immunosuppressed have been described including cidofivir for organ transplant recipients and HIV patients, imiquimod for common warts in HIV patients, intralesional bleomycin in HIV patients, and intralesional *candida* in HIV patients [43–47].

Oral and topical retinoids have gained widespread usage in organ transplant dermatology as a modality for primary prevention of actinic keratoses and SCC. While some have reported a decrease in size of pre-existing SCCs, most believe that oral retinoids are better at suppressing the development of new SCCs as opposed to treating existing ones [48, 49]. The exact mechanism of tumor prevention is still unresolved, but is usually attributed to retinoid induced alterations in keratinization; however, Rook et al. reported an increase in Langerhans cells after treatment with tretinoin and etretinate. This study suggests that at least one mechanism may involve induction of localized immune surveillance [50]. One of the more convincing clinical studies performed in renal allograft recipients, despite the small number, was performed by George et al. over a 2-year period [51]. In the study, 23 patients with a history of a non-melanoma skin cancer were randomly enrolled into two groups—an acitretin group and a non-drug group. After 1 year, each group crossed over to the opposite treatment regimen. They found a 42 % increase in the number of SCCs that developed while patients were not on acitretin. While this suggests a positive reduction in development of SCC, there was a 36 % drop out rate from the side effects of acitretin.

The use of oral retinoids has been refined over the past few years with many physicians starting at very low doses and increasing as per the patient's tolerability. This minimizes side-effects and maximizes the ability of the patient to continue the medication and enjoy the benefits of improved skin appearance and fewer biopsies and surgeries. This approach also allows physicians to carefully monitor potential side effects with small incremental dosage increases, including liver function test abnormalities, hypertriglyceridemia, hypercholesterolemia, arthralgias, headaches, and dryness [52].

The role of retinoids has recently been touted to potentially assist in the treatment of CLL. Bruno et al. published a study showing how N-(4-hydroxyphenyl)

retinamide, a synthetic retinoid, promotes apoptosis of resting and proliferating B-cell CLL cells [53]. In a similar study assessing N-(4-hydroxyphenyl) retinamide and acitretin on CLL and multiple myeloma cells, Sayeed et al. showed that each drug had the ability to decrease cell viability as well as cellular migration capabilities [54]. If these studies equate to retinoids having a clinical role in the treatment of CLL, it may concomitantly prevent the progression of actinic damage and SCC formation. Randomized trials in this area would be important, but empirically, retinoids have been used successfully in CLL patients as well as in HIV patients to reduce progression of precancerous keratinocytic proliferations [52].

Photodynamic therapy (PDT) has long been utilized for treatment of actinic keratosis. While sometimes uncomfortable during and immediately after the treatment, many patients prefer this brief treatment to the 4–6 week application of topical medications. Recent publications indicate it may be effective for organ transplant patients. In a study of 165 patients, Hasson et al. reported the treatment of facial actinic keratoses utilizing topical methylaminolaevulinate (MAL) followed by PDT utilizing a 635-nm non-coherent red light source [55]. Patients received one to two treatments depending on clinical response. In 100 % of patients, it was noted to have a complete and lasting clinical response of their actinic keratoses at 12 and 24 weeks following the treatment. Using a photodamage scale, many patients had a significant decrease in the amount of photodamage, though this finding was not statistically significant ($p = 0.21$). There is also some evidence that PDT reduces the number of invasive CSCCs organ transplant patients develop. Willey et al. demonstrated that PDT treatment performed cyclically, in 4–8 week intervals, on solid organ transplant patients may reduce the incidence of new SCC formation [56]. Evaluated for 2 years following treatment, the reduction of new SCCs at 12 and 24 months post-treatment was 79 % and 95 %, respectively. Interestingly, all patients were treated on forearms, hands, and shins which tend to be refractory areas indicating potential high efficacy with cyclic PDT regimens.

Some lesions are biologically responsive to one therapeutic modality and not to others. Thus, some researchers have compared various modalities head to head while others note a multipronged approach is sometimes needed to effectively treat. Perrett et al. evaluated treatment of actinic keratoses in organ transplant patients with 5-flourouracil (twice daily for a 3 week application) and compared outcomes to those treated with topical MAL followed by PDT utilizing a 635 nm non-coherent red light source (two treatments 1 week apart) [57]. In their study, they found an 89 % complete response rate in those patients treated with PDT with only an 11 % complete response rate with 5-flororuacil. Helsing et al. reported a 73 % clearance rate of actinic keratoses with one treatment of ablative fractional CO2 and concomitant PDT in organ transplant patients, while ablative fractional CO2 alone had a 31 % clearance rate [58]. As clearance can be partial and many patients will have some recurrence of actinic lesions within 6–24 months, physicians may have to try several approaches to find effective treatment for each individual and treatments often have to be repeated over time.

Regardless of the treatment entertained, a biopsy should be performed if there is any question as to the diagnosis or if a lesion grows or becomes clinically concerning

Table 10.1 Follow up intervals for immunosuppressed patients[a]

Patient Risk Factors	Frequency of Skin Examination
No risk factors except immunosuppression	Initial exam + exam every 12–24 months
Risk factors but no history of malignant/ premalignant lesions	Initial exam + exam every 6–12 months
Actinic keratoses or warts	Initial exam + treatment + exam every 3–6 months
One SCC	Initial exam + treatment + exam every 3–6 months
High-risk SCC	Initial exam + treatment + exam every 3 months
Metastatic SCC	Initial exam + treatment + exam every 1–3 months

[a]Adapted from ITSCC Guidelines for Follow-Up Intervals for Organ Transplant Recipients

post treatment. The threshold for biopsy should be reasonably low compared to non immunosuppressed patients due to non-classic morphology, which occurs commonly in immunosuppressed patients, non-responsive lesions, which occur at an increased rate in organ transplant recipients, and lesions with a tendency for subclinical spread, which occur in CLL patients [23]. SCC in the immunosuppressed tends to occur more rapidly, more aggressively, and sometimes more subtly, so it is essential to be attentive to the potential need for biopsy.

While evaluation and intervention are the mainstays of transplant dermatology, the necessity for planned and intentional follow-up evaluations is critical and must be stressed to patients. The appropriate time interval to evaluate immunosuppressed patients is a product of their immunosuppressed status as well as their clinical state in reference to their risk for squamous cell carcinoma. The intervals suggested by the ITSCC and Otley et al. are reasonable guidelines [33, 59]. An adaptation from the ITSCC management guidelines is found in Table 10.1.

Management of Squamous Cell Carcinoma in the Immunosuppressed

While the prevention and treatment of premalignant or potentially malignant lesions is an admirable goal, the eventual diagnosis of a concerning and histologically confirmed SCC is likely with immunosuppressed patients, particularly those with a history of sun exposure and actinic damage. Before commencing with a treatment plan, it is important to initiate a pre-treatment workup and evaluation, which should include not only a full body skin examination, but an assessment of any particular tumor(s) with potential for aggressive behavior. Tumor specific factors should be considered, including:

1. Tumor location
2. Tumor diameter (taking into account induration and surrounding erythema)
3. Rate of lesion growth
4. Tumor duration
5. Previous treatment
6. Presence of local parasthesias, pain, or compromised motor function

Evaluation for loco-regional lymphadenopathy by direct palpation as well as assessment for evidence of cutaneous satellite lesions is essential to appraise disease extent. By taking into account the physical examination along with the histologic parameters provided by the pathology of the tumor, the clinician can assess and determine the plan for treatment. If the clinician decides to perform treatment at the time of the biopsy, the histologic evaluation must be reviewed retrospectively to determine if adequate treatment was achieved.

Once all information is gathered, the appropriate management is determined by patient risk stratification. Please see Chapters 2, 5 and 6 for discussions of CSCC staging/risk stratification, management of diffuse epidermal damage, and management of dermally-invasive CSCC tumors, respectively. In this section we will discuss management within the specific context of immunosuppression. In Figs. 10.3 and 10.4 we have included adaptations from the ITSCC management guidelines for the management of SCCs of low-risk and high-risk types as per NCCN definitions which are summarized in Table 10.2. While surely not a consensus algorithm for all immunosuppressed patients, it is a starting point that concurs with existing guidelines [33, 61].

Treatment of low-risk tumors can include surgical excision utilizing standard excision or excision with margin control including Mohs micrographic surgery or intraoperative frozen sections. Mohs micrographic surgery allows the additional advantage of evaluating the entire excised margins with higher cure rates and maximum tissue conservation. Mohs also maximizes the treatment of the invasive

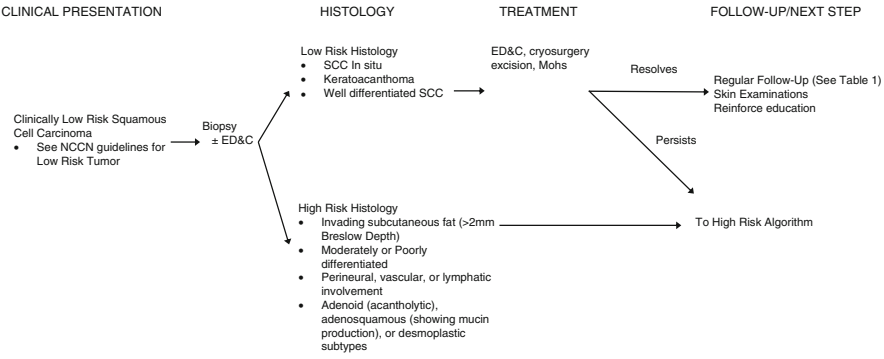


Fig. 10.3 Management of Low risk/less aggressive Squamous Cell Carcinoma in the Immunosuppressed (adapted from the 2004 ITSCC Guidelines for the Management of Squamous Cell Carcinoma in Organ Transplant Patients)

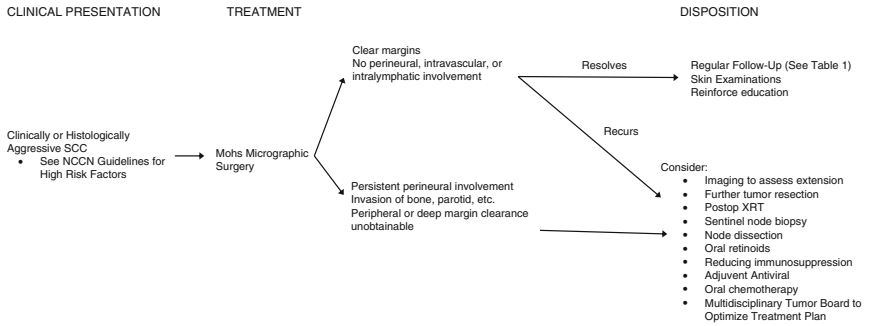


Fig. 10.4 Management of High risk/more aggressive Squamous Cell Carcinoma with Neoplastic Potential in the Immunosuppressed (adapted from the 2004 ITSCC Guidelines for the Management of Squamous Cell Carcinoma in Organ Transplant Patients)

components of the SCC within the area of field cancerization, allowing the physician to treat surrounding intraepidermal (in situ) dysplasia with other non-surgical field therapies.

Standard excision with histopathologic confirmation of clear margins is typically performed with clinical margins of 4–6 mm of skin without clinical evidence of invasive disease. These typical margins ascribed to immunocompetent patients may not be adequate due to the propensity for subclinical extension in immunosuppressed patients; however, no adequate margin comparison has been completed between the immunosuppressed and the immunocompetent. The appropriate use criteria for Mohs surgery set forth in 2014 include Mohs as an option for all dermally-invasive SCCs occurring in immunosuppressed patients [62].

Destructive techniques including electrodessication and curettage (ED&C), cryosurgery, or ablative laser techniques should be utilized with caution as margin evaluation is based solely on clinical evaluation, and in organ transplant patients and CLL patients, subclinical extension may be extensive (Fig. 10.5) [23]. This is not to say that ED&C or other destructive methods cannot be effective. de Graff et al. reported an overall recurrence rate of only 6 % in 211 low-risk squamous cell carcinomas treated with ED&C in organ transplant patients (n = 48) [63]. Higher recurrence rates were noted for lesions treated on the head and neck (11 %) as well as the dorsal hands and fingers (7 %). While histologic margin evaluation may be optimal, in cases where multiple squamous cell carcinomas may be present, destructive methods like ED&C can be fast, practical, and effective for low risk tumors.

Treatment of high-risk tumors (Table 10.2/Fig. 10.4) confined to skin and soft tissue typically is best managed with excision with margin control, most commonly Mohs micrographic surgery. Standard wide local excision with 6 mm margins with intra or postoperative margin evaluation may be utilized if Mohs surgery is not available. One relevant aspect of the tumor margin assessment is that dense lymphocytic infiltrates (commonly found in CLL) can obscure tumor margins and may be indicators of tumor aggressiveness (Fig. 10.6). Smoller et al. suggest for CLL that

Table 10.2 National Comprehensive Cancer Network® (NCCN®) high risk factors for cutaneous squamous cell carcinoma

	Risk factors for recurrence	
H&P	Low risk	High risk
Location/size[a]	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm	Area M ≥10 mm
	Area H <6 mm[b]	Area H ≥6 mm[b]
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[c] or Clark level	<2 mm or I, II, III	≥2 mm or IV, V
Perineural or vascular involvement	(−)	(+)

Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Basal and Squamous Cell Skin Cancers V.2.2013. © 2013 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc

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

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

Area L = trunk and extremities (excluding pretibial, hands, feet, nail units, and ankles)

Connolly et al. [60]

[a]Must include peripheral rim of erythema

[b]Location independent of size may constitute high risk in certain clinical settings

[c]A modified Breslow measurement should exclude parakeratosis or scale/crust, and should be made from base of ulcer if present

this could be a lymphocytic response to tumor specific antigens or may simply be secondary to the sheer presence of a proliferative lymphocytic disease [64]. Regardless, if performing Mohs or reviewing permanent sections, the presence of an associated lymphocytic infiltrate may highlight a tumor with more aggressive biology, the presence of untreated tumor, or, if undiagnosed, the presence of a systemic immunosuppression [65].

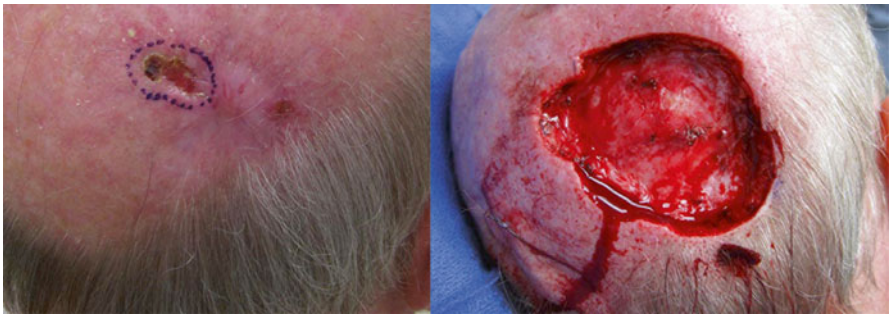


Fig. 10.5 In this patient, who received Mohs micrographic surgery, the preoperative clinical tumor grossly underestimated the actual tumor size and the resultant defect size

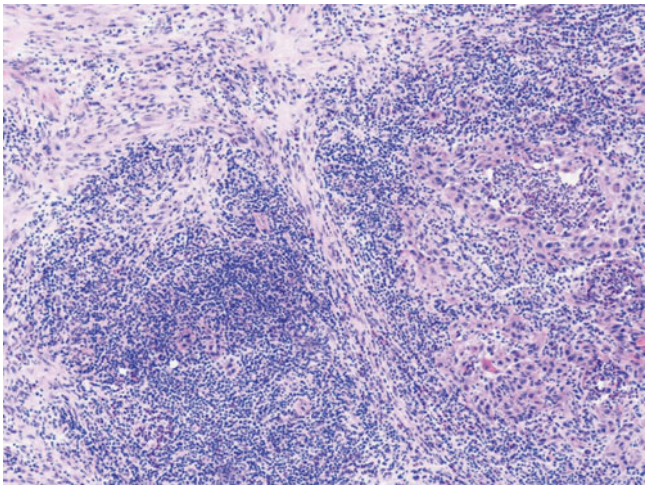


Fig. 10.6 Dense lymphocytic infiltrates, like those found in this frozen section (H&E, 20×), may obscure the histopathologic features of SCC or it may indicate the possibility of residual tumor

When high-risk disease has moved from local to loco-regional, a discussion with the patient's team of physicians should ensue. Conversation should include the possibility of altering immune status including reduction of immunosuppression in transplant patients or augmenting antiretrovirals in HIV patients, as well as the possible need for further resection, radiation, and chemotherapy in light of their other health issues.

Secondary Prevention in the Immunosuppressed

Secondary prevention involves proactive measures and interventions to decrease the morbidity or mortality of a disease that is already present. For example, after the development of skin cancer, UV light avoidance and constant skin examinations have elements of secondary prevention. Some treatment modalities, such as PDT and topical imiquimod or 5-fluorouracil, may be considered secondary prevention although reports of their efficacy in prevention are varied.

While the benefit of preventing progression of potentially malignant lesions is clear, many immunosuppressed patients of diverse etiologies (HIV, CLL, organ transplant patients, genodermatoses, etc.) are only placed on oral retinoids when they have numerous or significantly aggressive SCCs. Acitretin is the most commonly studied and used, though isotretinoin and etretinate have also been used successfully [66, 67]. Oral retinoids for prophylaxis are covered in Chapter 5 and their use is generally equivalent in immunosuppressed and non-immunosuppressed patients. However, discussion with the patient's other care providers should be done before initiating therapy as immunosuppressed patients often have complex medical regimens. Collaboration is necessary to minimize unanticipated effects of adding a retinoid.

As an alternative to retinoids, chemotherapeutic treatments have been advocated to reduce the non-melanoma skin cancer burden in solid organ transplant patients. Endrizzi et al. described a low dose oral capecitabine (5-florouracil prodrug) regimen (0.5–1.5 g/m^2) in 3-week cycles with a marked reduction in clinical incidence of SCC [68]. This reduction was statistically significant at 12 months with a 68.1 ± 29.8 % mean reduction in new SCC. Epidermal growth factor receptor (EGFR) antibodies that block the extracellular domain of the receptor, like cetuximab, have also been shown to inhibit the proliferative signaling in metastatic SCC. O'Bryan et al. have suggested, based on positive responses with various modalities of radiation, surgery, cetuximab, and other chemotherapeutic agents, an algorithm that includes consideration of cetuximab in patients who exhibit "very high risk tumors." [69] These tumors include those that display lymphovascular, perineural, parotid, periorbital, cartilaginous, or bony invasion, tumors that have in-transit metastasic lesions, and tumors that exhibit regional or distant metastasis. While EGFR inhibitors have been advocated for already advanced loco-regional disease and have been used successfully to decrease disease burden in a small number of patients, further studies are needed to define how EGFR inhibitors will fit into the SCC treatment algorithm. EGRF inhibitors must be used with extreme caution in lung transplant recipients, if at all, as there have been reports of fatal diffuse alveolar damage [70]. Our personal experience in this regard includes two single-lung transplant patients with metastatic CSCC who failed surgical resection, radiation, or chemoradiation therapy and were ultimately treated with the EGFR inhibitor cetuximab. Both patients died shortly after initiation of cetuximab due to diffuse alveolar damage, reinforcing that EGFR inhibitors should be used with extreme caution in lung transplant recipients.

In the organ transplant population, epidemiologic and clinical information has provided insight to the management of the immunosuppression after SCCs have occurred. While the history behind immunosuppression in organ transplant patients is beyond the scope of this chapter, the understanding of how certain medications work, their effects on the immune system, and their effect on development of SCC is necessary as patients are on multiple different regimens (Table 10.3) [71–73].

Reduction of immunosuppression may also reduce the development of malignancies. Dantal, et al., found a reduction in the development of skin cancer in patients on low dose (75–125 ng/ml) than those on normal dose (150–250 ng/ml) cyclosporine with similar graft and patient survival [74]. In renal transplant recipients who had developed multiple NMSC and subsequently lost their graft, cessation of immunosuppression resulted in marked improvement regarding the development of new lesions in four of six patients [75]. Moloney, et al. reported on an uncontrolled series of nine patients with deeply invasive or metastatic SCC. Of five patients with no change in immunosuppression, all died from SCC with functioning grafts. Of four patients with immunosuppression stopped or reduced, one died from metastatic disease with a functioning graft, two showed no evidence of recurrence with functioning grafts, and one had no recurrence, but lost his graft [76].

The evolution towards medications that are less likely to induce tumorigenesis [i.e. mammalian target of rapamycin (mTOR) inhibitors] has provided significant reductions in the incidence of invasive SCC. These medications still provide lymphocytic inhibition, which is necessary for graft survival. A study from Hoogendijk-van den Akker et al. evaluated whether a conversion to sirolimus based immunosuppression for stable kidney transplant patients would decrease the incidence of new CSCCs as compared to kidney transplant patients who continued on their traditional immunotherapy [77]. Each patient included in the study was stable on a standard chemotherapy regimen and had a history of at least one SCC. In this 2-year randomized controlled prospective trial, there was a 24 % risk reduction in SCC after 2 years for those switched to a sirolimus based regimen, but this was not statistically significant ($p = 0.055$, adjusted for sex and number of squamous cell carcinomas before inclusion). However, after 1 year, a 50 % reduction was found and it was significantly significant ($p = 0.006$, adjusted). Similar improvement was found by Euvrard, et al., but serious adverse reactions in the sirolimus group resulted in a 23 % drop out rate. This group has found that more gradual conversion to mTOR inhibition leads to better tolerability. Adverse effects were twice as likely in patients who underwent rapid conversion than those on a more progressive protocol [78].

Some transplant physicians are reluctant to switch completely to alternative medications when a patient's transplant is functioning well. Their caution is influenced by retrospective studies showing higher rates of allograph failure and death in patients on mTOR inhibitors than those on calcineurin inhibitors [79]. However, conversion is more likely to be successful when graft function is stable. Caroti et al., showed that kidney transplant patients with stable renal function (creatinine clearance >40 ml/min and proteinuria <0.8 g/24 h) can be safely transitioned from

Table 10.3 Common immunosuppressive medications utilized in organ transplant recipients

Immunosuppressive medication	Examples	Primary mechanism of action	Effect on squamous cell carcinoma
Mammalian target of rapamycin (mTor) inhibitor	Sirolimus	Decreases IL-2 mediated signal transduction and increases E-cadherin expression	Probable Decrease in Incidence
	Everolimus		
Glucocorticoids	Prednisone	Inhibition of macrophage production of numerous cytokinses IL-1, IL-2, IL-6	Possible Increased Incidence
	Prednisolone		
	Methylprednisolone		
Calcineurin inhibitor	Cyclosporine A	Decreases IL-2 Production and Increases TGF-Beta Production	Increased Incidence
	Tacrolimus		
Purine analog	Azathioprine	Inhibitor of Purine Synthesis	Increased Incidence
Purine Biosynthesis Inhibitor	Mycophenolate Mofitil	Reversible inhibitor of inosine monophosphate dehydrogenase in purine (guanine) biosynthesis	Probable Increase in Incidence
Anti-thymocyte Globulin	Equine antithymocyte globulin	Immune complex mediated depletion of B and T Lymphocytes	No effect
	Rabbit antithymocyte globulin		
Anti-CD3 Antibodies	Muromonab-CD3	Depletion of T cells via anti-CD3 monoclonal antibiody	No effect
Anti-CD 25 Antibodies	Basiliximab (mouse derived)	Monoclonal antibody to the α chain (CD25) of IL-2 receptor of T cells	Single study suggests possible biologic benefit. Clinical data lacking
	Daclizumab (human derived)		

Table 10.4 Patients to consider for oral retinoids, capecitabine, or alterations in immunosuppression

Numerous NMSCs per year (5–10/year)
Innumerable actinic keratoses and multiple NMSCs
Accelerating frequency of NMSCs
Multiple NMSCs in high-risk locations (head and neck)
Eruptive keratoacanthomas
High-risk NMSC (>20 % risk of metastasis)
Metastatic NMSC

a standard calcineurin based regimen (cyclosporine, mycophenolate mofetil, and corticosteroids) to everolimus and low dose cyclosporine [80]. In contrast, three of six patients with creatinine clearance <40 ml/min and proteinuria >0.4 g/24 h had deterioration of their renal function after medication conversion. This serves as a reminder to clinicians with a primary focus on CSCC treatment to have discussions with the transplant team regarding mTOR conversion at times of graft stability.

Patients who might be candidates for oral retinoids, capecitabine, or alterations of immunosuppression are listed in Table 10.4.

While the vast majority of CLL patients do not receive therapy due to the chronic indolent nature of most CLL variants, patients who develop high-risk CSCCs warrant at least a discussion with their hematologist/oncologist. In some cases, treatment of CLL may induce a more competent immune system and a less oncogenic environment. As previously noted, retinoids may prove to serve both roles in the future [53, 54]. When a patient with CLL develops a significant NMSC, consultation with hematology/oncology is warranted as the development of SCC may be a symptom of their underlying CLL potentially needing treatment. Velez et al. found that patients with high-Rai stage CLL and high-risk skin cancer had high mortality from skin cancer indicating that more advanced CLL may drive skin cancer progression; however, treatment of CLL did not appear to impact outcomes. It may be that early intervention in the course of CLL prior to marked immune system alteration is needed to impact skin cancer outcomes. This warrants further study [25].

The concept of secondary prevention extends to HIV patients and HAART therapy. Prior to HAART therapy, during the height of the HIV/AIDS epidemic, it appeared there might be a marked increase in the incidence of skin cancer, similar to organ transplant recipients. HAART therapy appears to be preventing this earlier presentation and progression of SCC; however, as HIV patients are living longer and more normal lives with higher CD4 counts and lower viral loads, these patients are developing the "classic" UV induced SCCs, at a slightly higher rate than the general population. Even though the primary and secondary prevention of HAART may be working for HIV patients and their high-risk tumors, the incidence of HIV patients with SCCs will likely increase as this patient population ages.

Summary

The management of SCC requires an intentional interplay of therapy targeting both local and systemic factors. Minimizing the local factors that might predispose the patient to SCC (e.g. HPV, UV) for example, with sun protection, is critical. Managing systemic immunosuppression or immune dysfunction requires a delicate balance to create an environment where SCC risk is minimized while maintaining the immunosuppression needed for patients with organ transplants or rheumatologic disease. At times reconstituting the immune system, such as starting anti-retroviral drug therapy in HIV patients, will improve the patient's over condition and decrease SCC risk. Other times, such as in organ transplant recipients, it requires a balancing of transplant organ function against the risk of SCC development. As we learn more about specific functions of the myriad aspects of the immune system, we will hopefully be better situated to manage the balance between immunity, tolerance, and carcinogenesis for overall health. Meanwhile, immunosuppressed patients require regular surveillance and counseling regarding how best to minimize their skin cancer risk.

References

1. Schwarz T. The dark and the sunny sides of UVR-induced immunosuppression: photoimmunology revisited. J Invest Dermatol. 2010;130(1):49–54.
2. Czesnikiewicz-Guzik M, Lee WW, Cui D, et al. T cell subset-specific susceptibility to aging. Clin Immunol. 2008;127(1):107–18.
3. Boehnke K, Falkowska-Hansen B, Stark HJ, Boukamp P. Stem cells of the human epidermis and their niche: composition and function in epidermal regeneration and carcinogenesis. Carcinogenesis. 2012;33(7):1247–58.
4. White AC, Tran K, Khuu J, et al. Defining the origins of Ras/p53-mediated squamous cell carcinoma. Proc Natl Acad Sci U S A. 2011;108(18):7425–30.
5. Meyer KC, Klatte JE, Dinh HV, et al. Evidence that the bulge region is a site of relative immune privilege in human hair follicles. Br J Dermatol. 2008;159(5):1077–85.
6. Chen CJ, Sung WW, Su TC, et al. High expression of interleukin 10 might predict poor prognosis in early stage oral squamous cell carcinoma patients. Clin Chim Acta. 2013;415:25–30.
7. Pandey S, Mercer SE, Dallas K, Emanuel PO, Goldenberg G. Evaluation of the prognostic significance of follicular extension in actinic keratoses. J Clin Aesthet Dermatol. 2012;5(4):25–8.
8. Plikus MV, Gay DL, Treffeisen E, Wang A, Supapannachart RJ, Cotsarelis G. Epithelial stem cells and implications for wound repair. Semin Cell Dev Biol. 2012;23(9):946–53.
9. Nguyen TH, Yoon J. Squamous cell carcinoma. In: Rigel D, Firedman RJ, Dzubow LM, Reintgen DS, Bystryn JC, Marks R, editors. Cancer of the skin. New York: Elsevier; 2005. p. 133–50.
10. Weber F, Bauer JW, Sepp N, et al. Squamous cell carcinoma in junctional and dystrophic epidermolysis bullosa. Acta Derm Venereol. 2001;81:189–92.
11. Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. Lancet. 1998;351(9119):1833–9.
12. Franceschi S, Dal Maso L, Arniani S, et al. Risk of cancer other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. Cancer and AIDS registry linkage study. Br J Cancer. 1998;78(7):966–70.

13. Garlassi E, Harding V, Weir J, et al. Nonmelanoma skin cancers among HIV-infected persons in the HAART era. J Acquir Immune Defic Syndr. 2012;60(2):e63–5.
14. Silverberg MJ, Leyden W, Warton EM, Quesenberry Jr CP, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. J Natl Cancer Inst. 2013;105(5):350–60.
15. Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. Arch Dermatol. 2002;138(6):758–63.
16. Hausauer AK, Maurer T, Leslie KS, Parvataneni R, Stuart SE, Chren MM. Recurrence after treatment of cutaneous basal cell and squamous cell carcinomas in patients infected with human immunodeficiency virus. JAMA Dermatol. 2013;149(2):239–41.
17. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst. 2000;92(18):1500–10.
18. Durante AJ, Williams AB, Da Costa M, Darragh TM, Khoshnood K, Palefsky JM. Incidence of anal cytological abnormalities in a cohort of human immunodeficiency virus-infected women. Cancer Epidemiol Biomarkers Prev. 2003;12(7):638–42.
19. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. AIDS. 1998;12(5):495–503.
20. Wilkins K, Dolev JC, Turner R, LeBoit PE, Berger TG, Maurer TA. Approach to the treatment of cutaneous malignancy in HIV-infected patients. Dermatol Ther. 2005;18(1):77–86.
21. Mehrany K, Weenig RH, Pittelkow MR, Roenigk RK, Otley CC. High recurrence rates of squamous cell carcinoma after Mohs' surgery in patients with chronic lymphocytic leukemia. Dermatol Surg. 2005;31(1):38–42.
22. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005;53(6):1067–71.
23. Mehrany K, Byrd DR, Roenigk RK, et al. Lymphocytic infiltrates and subclinical epithelial tumor extension in patients with chronic leukemia and solid-organ transplantation. Dermatol Surg. 2003;29(2):129–34.
24. Toro JR, Blake PW, Bjorkholm M, Kristinsson SY, Wang Z, Landgren O. Prior history of nonmelanoma skin cancer is associated with increased mortality in patients with chronic lymphocytic leukemia. Haematologica. 2009;94(10):1460–4.
25. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Neel VA, Davids MS, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150(3):280–7.
26. Urbanska M, Nowak G, Florek E. Cigarette smoking and its influence on skin aging. Przegl Lek. 2012;69(10):1111–4.
27. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med. 1993;329(16):1147–51.
28. Ulrich C, Jurgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case–control study. Br J Dermatol. 2009;161 Suppl 3:78–84.
29. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009;58(RR-11):1–166.
30. Christenson LJ, Cherikh WS, Otley CC, Salasche SJ, Kauffman HM. Allograft and overall survival of patients with posttransplant skin cancer. Dermatol Surg. 2011;37(2):183–91.
31. Ritchie SA, Patel MJ, Miller SJ. Therapeutic options to decrease actinic keratosis and squamous cell carcinoma incidence and progression in solid organ transplant recipients: a practical approach. Dermatol Surg. 2012;38(10):1604–21.

32. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003;348(17):1681–91.
33. Stasko T, Brown MD, Carucci JA, et al. Guidelines for the management of squamous cell carcinoma in organ transplant recipients. Dermatol Surg. 2004;30(4 Pt 2):642–50.
34. Jensen P, Moller B, Hansen S. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol. 2000;42 (2 Pt 1):307.
35. Wisgerhof HC, Wolterbeek R, de Fijter JW, Willemze R, Bouwes Bavinck JN. Kidney transplant recipients with cutaneous squamous cell carcinoma have an increased risk of internal malignancy. J Invest Dermatol. 2012;132(9):2176–83.
36. Thomas BR, Barnabas A, Agarwal K, et al. Patient perception of skin-cancer prevention and risk after liver transplantation. Clin Exp Dermatol. 2013;38(8):851–6.
37. Alessi SS, Sanches JA, Oliveira WR, Messina MC, Pimentel ER, Festa Neto C. Treatment of cutaneous tumors with topical 5% imiquimod cream. Clinics (Sao Paulo). 2009; 64(10):961–6.
38. Cusini M, Salmaso F, Zerboni R, et al. 5% imiquimod cream for external anogenital warts in HIV-infected patients under HAART therapy. Int J STD AIDS. 2004;15(1):17–20.
39. Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. Lancet Oncol. 2013;14(4):346–53.
40. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):263–79.
41. Ulrich C, Bichel J, Euvrard S, et al. Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. Br J Dermatol. 2007;157 Suppl 2:25–31.
42. Saiag P, Bauhofer A, Bouscarat F, et al. Imiquimod 5% cream for external genital or perianal warts in human immunodeficiency virus-positive patients treated with highly active antiretroviral therapy: an open-label, noncomparative study. Br J Dermatol. 2009;161(4):904–9.
43. De Socio GV, Simonetti S, Rosignoli D, Minga P, Tomassini GM, Baldelli F. Topical cidofovir for severe warts in a patient affected by AIDS and Hodgkin's lymphoma. Int J STD AIDS. 2008;19(10):715–6.
44. Kralund HH, Broesby-Olsen S, Bistrup C, Lorentzen HF. Substantial effect of topical cidofovir 1% on recalcitrant warts in a renal-transplanted adolescent: a case report. Transplantation. 2011;91(7):e52–4.
45. Juschka U, Hartmann M. Topical treatment of common warts in an HIV-positive patient with imiquimod 5% cream. Clin Exp Dermatol. 2003;28 Suppl 1:48–50.
46. Summers P, Richards-Altmon P, Halder R. Treatment of recalcitrant verruca vulgaris with Candida antigen in patient with human immunodeficiency virus. J Drugs Dermatol. 2009;8(3):268–9.
47. Shah M, Murphy M, Price JD, Lacey CJ. Intralesional bleomycin for the treatment of non-genital warts in HIV-infected patients. Acta Derm Venereol. 1996;76(1):81–2.
48. Kovach BT, Sams HH, Stasko T. Systemic strategies for chemoprevention of skin cancers in transplant recipients. Clin Transplant. 2005;19(6):726–34.
49. Kovach BT, Stasko T. Skin cancer after transplantation. Transplant Rev (Orlando). 2009;23(3):178–89.
50. Rook AH, Jaworsky C, Nguyen T, et al. Beneficial effect of low-dose systemic retinoid in combination with topical tretinoin for the treatment and prophylaxis of premalignant and malignant skin lesions in renal transplant recipients. Transplantation. 1995;59(5):714–9.
51. George R, Weightman W, Russ GR, Bannister KM, Mathew TH. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. Australas J Dermatol. 2002;43(4):269–73.

52. Otley CC, Stasko T, Tope WD, Lebwohl M. Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. Dermatol Surg. 2006;32(4):562–8.
53. Bruno S, Ghiotto F, Tenca C, et al. N-(4-hydroxyphenyl)retinamide promotes apoptosis of resting and proliferating B-cell chronic lymphocytic leukemia cells and potentiates fludarabine and ABT-737 cytotoxicity. Leukemia. 2012;26(10):2260–8.
54. Saeed AT, Murphy P, Napoletano S. Role of synthetic retinoic acid derivatives in chronic lymphocytic leukemia and multiple myeloma. BMC Proc. 2013;7 Suppl 1:O3.
55. Hasson A, Navarrete-Dechent C, Nicklas C, de la Cruz C. Topical photodynamic therapy with methylaminolevulinate for the treatment of actinic keratosis and reduction of photodamage in organ transplant recipients: a case-series of 16 patients. Indian J Dermatol Venereol Leprol. 2012;78(4):448–53.
56. Willey A, Mehta S, Lee P. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy. Dermatol Surg. 2010;36(5):652–8.
57. 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(2):320–8.
58. Helsing P, Togsverd-Bo K, Veierod MB, Mork G, Haedersdal M. Intensified fractional CO laser-assisted photodynamic therapy versus laser alone for organ transplant recipients with multiple actinic keratoses and wart-like lesions: a randomized half-side comparative trial on dorsal hands. Br J Dermatol. 2013.
59. Otley CC. Organization of a specialty clinic to optimize the care of organ transplant recipients at risk for skin cancer. Dermatol Surg. 2000;26(7):709–12.
60. 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;38:1582–603.
61. National Comprehensive Cancer Network. Basal cell and squamous cell skin cancers. NCCN clinical practice guidelines in oncology, version 1. 2013. http://www.nccn.org/professionals/physician_gls/PDF/nmsc.pdf. Accessed 01 May 2013.
62. Ad Hoc Task Force, Connolly SM, Baker DR, Coldiron BM, Fazio MJ, Storrs PA, Vidimos AT, 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. J Am Acad Dermatol. 2012;67:531–50.
63. de Graaf YG, Basdew VR, van Zwan-Kralt N, Willemze R, Bavinck JN. The occurrence of residual or recurrent squamous cell carcinomas in organ transplant recipients after curettage and electrodesiccation. Br J Dermatol. 2006;154(3):493–7.
64. Smoller BR, Warnke RA. Cutaneous infiltrate of chronic lymphocytic leukemia and relationship to primary cutaneous epithelial neoplasms. J Cutan Pathol. 1998;25(3):160–4.
65. Kaplan AL, Cook JL. Cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. Skinmed. 2005;4(5):300–4.
66. Bellman BA, Eaglstein WH, Miller J. Low dose isotretinoin in the prophylaxis of skin cancer in renal transplant patients. Transplantation. 1996;61(1):173.
67. Shuttleworth D, Marks R, Griffin PJ, Salaman JR. Treatment of cutaneous neoplasia with etretinate in renal transplant recipients. Q J Med. 1988;68(257):717–25.
68. Endrizzi B, Ahmed RL, Ray T, Dudek A, Lee P. Capecitabine to reduce nonmelanoma skin carcinoma burden in solid organ transplant recipients. Dermatol Surg. 2013;39(4):634–45.
69. O'Bryan K, Sherman W, Niedt GW, et al. An evolving paradigm for the workup and management of high-risk cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2013;69(4):595–602.e1.
70. Leard LE, Cho BK, Jones KD, et al. Fatal diffuse alveolar damage in two lung transplant patients treated with cetuximab. J Heart Lung Transplant. 2007;26(12):1340–4.

71. Pennington BE, Stasko T. NMSC in organ transplant recipients and other high-risk groups. J Natl Compr Canc Netw. 2004;2(1):31–41.
72. Leblanc Jr KG, Hughes MP, Sheehan DJ. The role of sirolimus in the prevention of cutaneous squamous cell carcinoma in organ transplant recipients. Dermatol Surg. 2011;37(6):744–9.
73. Kuhn DJ, Dou QP. Direct inhibition of interleukin-2 receptor alpha-mediated signaling pathway induces G1 arrest and apoptosis in human head-and-neck cancer cells. J Cell Biochem. 2005;95(2):379–90.
74. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet. 1998;351(9103):623–8.
75. Otley CC, Coldiron BM, Stasko T, Goldman GD. Decreased skin cancer after cessation of therapy with transplant-associated immunosuppressants. Arch Dermatol. 2001;137(4): 459–63.
76. Moloney FJ, Kelly PO, Kay EW, Conlon P, Murphy GM. Maintenance versus reduction of immunosuppression in renal transplant recipients with aggressive squamous cell carcinoma. Dermatol Surg. 2004;30(4 Pt 2):674–8.
77. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. J Clin Oncol. 2013;31(10):1317–23.
78. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367(4):329–39.
79. Isakova T, Xie H, Messinger S, et al. Inhibitors of mTOR and risks of allograft failure and mortality in kidney transplantation. Am J Transplant. 2013;13(1):100–10.
80. Caroti L, Zanazzi M, Paudice N, et al. Conversion from calcineurin inhibitors to everolimus with low-dose cyclosporine in renal transplant recipients with squamous cell carcinoma of the skin. Transplant Proc. 2012;44(7):1926–7.

Index

C.D. Schmults (ed.), *High-Risk Cutaneous Squamous Cell Carcinoma*,
DOI 10.1007/978-3-662-47081-7