# Basal Cell Carcinoma

## Advances in Treatment and Research

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*Editors*
Michael R. Migden
The University of Texas MD Anderson Cancer Center, Departments of Dermatology and Head and Neck Surgery, Mohs Surgery Center
Houston, TX
USA

Sirunya Silapunt
University of Texas McGovern Medical School at Houston, Department of Dermatology
Houston, TX
USA

Leon Chen
The University of Texas MD Anderson Cancer Center, Department of Dermatology
Houston, TX
USA

University of Texas McGovern Medical School at Houston, Department of Dermatology
Houston, TX
USA

ISBN 978-3-030-26886-2 ISBN 978-3-030-26887-9 (eBook)
https://doi.org/10.1007/978-3-030-26887-9



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

*To my father who inspired me by his dedication to medicine and always putting his patients' interests first. To my wife for her love and support along the winding road.*

*Michael R. Migden, MD*

*To my parents, Ming-Meei (Rose) and Te-Hsiung (Ted), for their unconditional love and unwavering support. Thank you for always believing in me and inspiring me to dream big.*

*To my dearest wife, Patty, for her patience, understanding, and love. Thank you for being the rock of our family.*

*Lastly, to my sons, Levi and Luke, who were born during the writing of this book. You two have brought the greatest joy to our lives.*

*Leon Chen, MD*

*To my parents, Sopon and Jaree Silapunt, for their love, understanding, and never-ending support. To my husband for his love and daily inspiration.*

*Sirunya Silapunt, MD*

# Preface

We embarked on this journey to write about basal cell carcinoma not only because millions of individuals are affected by it every year but also there are many unanswered clinical questions faced by dermatologists and Mohs surgeons as well as other specialists. The treatment of this disease has largely been procedural: either with Mohs micrographic surgery, surgical excision, or destruction. Mohs micrographic surgery allows 100% of the tumor margin examined while sparing unnecessary tissue removal, and a step-by-step illustration of this surgical technique is detailed in this book. More recently, good options for patients with advanced basal cell carcinoma who are deemed poor surgical candidates have been developed. With the approval of vismodegib in 2012 and sonidegib in 2015 by the US Food and Drug Administration, patients with advanced basal cell carcinoma now have a viable alternative to disfiguring or morbid extensive surgery. Given the success of immunotherapy with program cell death 1 inhibitors in a wide variety of cancer types, multiple ongoing trials are investigating the efficacy and safety of immunotherapy for the treatment of advanced basal cell carcinoma.

We have assembled a multidisciplinary panel of specialists from diverse fields such as dermatology, dermatopathology, head and neck surgery, Mohs micrographic surgery, radiation oncology, and oculoplastic surgery to participate in the writing of *Basal Cell Carcinoma: Advances in Treatment and Research*. This book provides an in-depth coverage of treatment for localized basal cell carcinomas including topical therapy, destruction, photodynamic therapy, local immunotherapy with interferon, and laser treatment. This book also includes an extensive review on combination therapies and comparative studies of various treatment modalities for basal cell carcinoma.

In cases of extensive, locally advanced basal cell carcinoma invading deeper structures, head and neck surgery offers highly effective deeper en bloc surgical extirpation for oncologic control. The role of radiation therapy as definitive or adjuvant therapy can be found in chapter "Radiotherapy for Basal Cell Carcinoma." The chapter authors discuss different radiotherapy modalities such as orthovoltage irradiation, electron beam therapy and brachytherapy, as well as practical case studies of difficult-to-treat basal cell carcinomas.

Tumors located adjacent or within the orbit can present various challenges. These include higher risk for recurrence, higher complexity of reconstruction to preserve vision, and restoration of aesthetics. In chapter "Special Consideration for Periocular Basal Cell Carcinoma," the authors share their clinical pearls in treatment of tumor and effective reconstruction of the orbital region.

*Basal Cell Carcinoma: Advances in Treatment and Research* provides the most comprehensive overview of evidence-based treatment approaches for basal cell carcinoma, the most common cancer worldwide. The first part of this book details epidemiology, risk factors, pathophysiology, and different histologic subtypes of basal cell carcinoma highlighted with high-resolution histopathology images. The second part of the book provides an in-depth review and practical pearls of different treatment modalities including topical therapy, local immunotherapy with interferon, cryotherapy, electrodesiccation and curettage, radiotherapy, and surgical approaches with Mohs micrographic surgery, head and neck surgery, and oculoplastic surgery. The final part of the book highlights the utilization of innovative technology such as photodynamic therapy and laser for the treatment of basal cell carcinoma as well as emerging systemic therapeutic options utilizing hedgehog pathway inhibitors and immunotherapy for the difficult-to-treat advanced disease states. It is our intention that this book will serve as an informative and evidence-based guide for physicians, mid-level providers, trainees, and healthcare personnel for years to come.

Houston, TX, USA Michael R. Migden
Houston, TX, USA Leon Chen
Houston, TX, USA Sirunya Silapunt

# Contents

# Contributors

**Anne Lynn S. Chang, MD** Stanford University School of Medicine, Department of Dermatology, Redwood City, CA, USA

**Leon Chen, MD** The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

**Jonathan L. Curry, MD** The University of Texas MD Anderson Cancer Center, Department of Pathology, Anatomical, Houston, TX, USA

**Hung Q. Doan, MD, PhD** The University of Texas MD Anderson Cancer Center, Department of Dermatology, Division of Internal Medicine, Houston, TX, USA

**Reinhard Dummer, MD** Faculty of Medicine, University of Zürich, Zürich, Switzerland

**Bita Esmaeli, MD, MA, FACS** The University of Texas MD Anderson Cancer Center, Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, Houston, TX, USA

**Danna K. Fullen, BSRT** The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology-Therapy, Houston, TX, USA

**Neil D. Gross, MD** The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX, USA

**G. Brandon Gunn, MD** The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX, USA

**Sagar Kansara, MD** Baylor College of Medicine, Department of Otolaryngology, Houston, TX, USA

**Natalie Kash, MD** University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

**Michael R. Migden, MD** The University of Texas MD Anderson Cancer Center, Departments of Dermatology and Head and Neck Surgery, Mohs Surgery Center, Houston, TX, USA

**William H. Morrison, MD** The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX, USA

**Priyadharsini Nagarajan, MD, PhD** The University of Texas MD Anderson Cancer Center, Department of Pathology, Anatomical, Houston, TX, USA

**Zeena Y. Nawas, MD** The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

**Sweet Ping Ng, MBBS, FRANZCR** Peter MacCallum Cancer Centre, Department of Radiation Oncology, Melbourne, VIC, Australia

**Tri H. Nguyen, MD** Texas Surgical Dermatology PA, Spring, TX, USA

**Jae Phan, BA** The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology-Research, Houston, TX, USA

**Egle Ramelyte, MD** University Hospital Zürich, Dermatology Department, Zürich, Switzerland

**Gaetana Restivo, PhD** University Hospital Zürich, Dermatology Department, Zürich, Switzerland

**Ho-Seok Sa, MD, PhD** The University of Texas MD Anderson Cancer Center, Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, Houston, TX, USA

Asan Medical Center, University of Ulsan, Department of Ophthalmology, Seoul, South Korea

**Oded Sagiv, MD** The University of Texas MD Anderson Cancer Center, Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, Houston, TX, USA

The Sheba Medical Center, The Goldschleger Eye Institute, Ramat Gan, Israel

**Waqas R. Shaikh, MD, MPH** Georgia Dermatology Partners, Atlanta, GA, USA

The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

**Sirunya Silapunt, MD** University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

**Michael T. Tetzlaff, MD, PhD** The University of Texas MD Anderson Cancer Center, Department of Pathology, Anatomical, Houston, TX, USA

**Stephen B. Tucker, MD** University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

**Christopher M. K. L. Yao, MD** The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX, USA

# Editor Biographies

**Michael R. Migden** professor, Departments of Dermatology and Head and Neck Surgery, MD Anderson Cancer Center, specializes in Mohs micrographic surgery, complex reconstruction, and clinical research in cutaneous oncology. He is the principal investigator of various clinical trials that evaluate the use of hedgehog pathway inhibitors and immunotherapy for advanced nonmelanoma skin cancer, devices for detection of cutaneous malignancy, and methods for documenting skin biopsy site location for treatment. His research has been published in *The New England Journal of Medicine*, *The Lancet Oncology*, and other high-impact peer-reviewed journals. Dr. Migden is the author of multiple book chapters and speaks nationally and internationally on cutaneous reconstruction, hedgehog pathway inhibitors, immunotherapy therapy, and the use of digital media in surgical education.

**Leon Chen** received his medical degree from the University of Texas McGovern Medical School at Houston and continued his fellowship training for Micrographic Surgery and Dermatologic Oncology (Mohs) at MD Anderson Cancer Center after completing dermatology residency at the MD Anderson Cancer Center/University of Texas McGovern Medical School combined program. His deep passion for cutaneous oncology has led him to author numerous research manuscripts, and his research has been presented at national and international dermatology meetings. His clinical interests include treating skin cancers with both surgical and nonsurgical modalities.

**Sirunya Silapunt** is a board-certified dermatologist and currently serves as an associate professor of the Department of Dermatology at the University of Texas McGovern Medical School at Houston. Dr. Silapunt is a faculty in Micrographic Surgery and Dermatologic Oncology (Mohs) Fellowship Program, clinical associate professor at MD Anderson Cancer Center, and an associate program director for the American Society for Dermatologic Surgery (ASDS) Cosmetic Dermatologic Surgery Fellowship Accreditation Program. Dr. Silapunt treats a wide variety of skin conditions, and a large part of her practice consists of skin cancer and varicose

vein treatments. She also has a special focus in laser and cosmetic dermatology. Dr. Silapunt has authored more than 50 peer-reviewed research manuscripts and numerous book chapters. She is an editor of the textbook *Procedures in Cosmetic Dermatology Series: Treatment of Leg Veins*, Second Edition. Her academic achievement and expertise in the field of dermatology have made her an invited speaker at various national and international conferences.

# Chapter 1
# Epidemiology and Risk Factors of Basal Cell Carcinoma


**Waqas R. Shaikh and Zeena Y. Nawas**

## Epidemiology

### *Introduction*

Basal cell carcinoma (BCC) is the most common cancer worldwide among the Caucasian population [1]. The majority of BCCs are diagnosed in Europe, the United States, and Australia. In the United States, accurate estimates of the burden of BCC are difficult to measure due to the exclusion of BCC from national cancer registries. In the 2012 US commercial insurance population, 822,593 persons were found to have a new BCC [2]. Among the 2012 Medicare population, 726,840 persons were found to have BCC [3]. Asgari et al. estimated the annual incidence of BCC in the United States to be approximately 2 million with an increasing rate of 0.87% per year [4]. However, other studies have shown increasing rates of 2% per year [1]. This increasing incidence is thought to be due to a combination of factors including increased awareness among the general population, increased diagnosis among physicians and healthcare providers, more surgical treatment of disease, improved surveillance methods, aging general population, ozone layer depletion, and increased ultraviolet radiation exposure [5].

W. R. Shaikh
Georgia Dermatology Partners, Atlanta, GA, USA

The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

Z. Y. Nawas (✉)
The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA
e-mail: zynawas@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_1

## *Geography*

Due to the strong association with ultraviolet radiation (UVR) among Caucasians [6], there is a strong inverse relationship between BCC incidence and geographic latitude (Table 1.1) [5]. This heavily influences incidence rates across regions and countries. For example, in higher latitude Alberta, Canada (53° N), incidence rates range from 77 to 94 per 100,000 person-years, whereas in lower latitude Arizona (34° N) incidence rates range from 497 to 936 per 100,000 person-years [5]. The highest incidence rate in the world occurs in Australia (26° S) with an incidence of 1269–1813 per 100,000 person-years given its majority Caucasian population living in a low-latitude region [5].

**Table 1.1** Overview of incidence rates and trends of basal cell carcinoma worldwide. (Reproduced with permission [5])

| Continent | Country | Latitude[a] | Incidence rate[b] | Standardization | Period[c] | Trends (EAPC) | Reference |
|---|---|---|---|---|---|---|---|
| Europe | Finland | 61° N | F: 90·2; M: 104·8 | ESR | 2009 | – | De Vries et al. [7] |
| | Scotland | 56° N | F: 81; M: 123 | ESR | 2006 | – | De Vries et al. [7] |
| | Denmark | 56° N | F: 96·6; M: 91·2 | WSR | 1978–**2007** | F: 4·6%; M: 3·7% | Birch-Johansen et al. [8] |
| | Lithuania | 55° N | F: 47·4; M: 46·4 | ESR | 1996–**2010** | F: 2·6%; M: 3·3% | Jurciukonyte et al. [9] |
| | UK | 55° N | F: 135·4; M: 172·1 | ESR | 2000–2011 | – | Reinau et al. [10] |
| | Northern Ireland | 54° N | 86·8 | ESR | 2000–2006 | – | Lomas et al. [1] |
| | Ireland | 53° N | F: 85·7; M: 98·0 | WSR | 1994–2003 | – | Carsin et al. [11] |
| | England | 52° N | 76·2 | ESR | 2000–2006 | – | Lomas et al. [1] |
| | Netherlands | 51° N | F: 157·3; M: 164·7 | ESR | 2002–**2009** | F: 7·9%; M: 6·8% | Flohil et al. [12] |
| | Germany | 51° N | 82·2 | ESR | 2006–**2010** | 6·8% | Rudolph et al. [13] |
| | Croatia | 45° N | F: 24·5; M: 33·6 | WSR | 2003–2005 | – | Lipozenčić et al. [14] |
| | Serbia | 44° N | F: 27·8; M: 31·0 | WSR | 1999–**2011** | 6·1% | Videnović et al. [15] |
| | Spain | 41° N | 128·0 | WSR | 2006–2007 | – | Bielsa et al. [16] |
| | Malta | 35° N | F: 70; M: 84 | ESR | 2009 | – | De Vries et al. [7] |

**Table 1.1** (continued)

| Continent | Country | Latitude[a] | Incidence rate[b] | Standardization | Period[c] | Trends (EAPC) | Reference |
|---|---|---|---|---|---|---|---|
| North America | Canada (AB) | 53° N | F: 119·6; M: 147·0 | CANSR | 2000–**2006** | −0·8% | Jung et al. [17] |
| | Canada (MB) | 53° N | F: 77·4; M: 93·9 | WSR | 1971–**2000** | 2·4% | Demers et al. [18] |
| | USA (NH) | 43° N | F: 165·5; M: 309·9 | USASR | 1979–1980, **1993–1994** | F: 4·4%; M: 4·4% | Karagas et al. [19] |
| | USA | 37° N | F: 1019; M: 1488 | ASR | 2004–**2006** | – | Wu et al. [20] |
| | USA (CA) | 36° N | F: 774; M: 1069 | USASR | 1998–**2012** | 0·9%; F: 1·1% | Asgari et al. [21] |
| | USA (NM) | 34° N | F: 485·5; M: 930·3 | USASR | 1998–1999 | – | Athas et al. [22] |
| | USA (AZ) | 34° N | F: 497·1; M: 935·9 | USASR | 1996 | – | Harris et al. [23] |
| Asia | Jordan | 33° N | F: 8·8; M: 6·2 | WSR | 1991–2000 | – | Rawashdeh et al. [24] |
| | Israel | 31° N | F: 158; M: 225 | ESR | 2006–2011 | −0·7% | Sella et al. [25] |
| | Singapore | 1° N | 4·5 | – | 2003–2006 | – | Sng et al. [26] |
| Africa | Kenya | 0° | 0·0065[d] | CIR | 1968–1997 | – | Munyao et al. [27] |
| | South Africa | 30° S | F: 1·7[d]; M: 3·0[d] | ASR | 2000–2004 | – | Norval et al. [28] |
| South America | Brazil | 27° S | 295·2 | CIR | 2008 | – | Custódio et al. [29] |
| | Chile | 53° S | 3·9 | CHLSR | 1994–2000 | – | Abarca et al. [30] |
| Oceania | PNG | 6° S | 0·3 | CIR | 1960–1980 | – | Foster et al. [31] |
| | Australia | 25° S | F: 745; M: 1041 | WSR | 2002 | – | Staples et al. [32] |
| | Australia (QLD) | 26° S | F: 1269; M: 1813 | WSR | 1997–2006 | – | Richmond-Sinclair et al. [33] |
| | New Zealand | 40° S | F: 215; M: 383 | WSR | 1997–2006 | F: 4·4%; M: 3·1% | Brougham et al. [34] |

*AB* Alberta, *ASR* age standardized rate, *AZ* Arizona, *CA* California, *CANSR* Canadian standardized rate, *CHLSR* Chile standardized rate, *CIR* crude incidence rate, *EAPC* estimated annual percentage change, *ESR* European standardized rate, *MB* Manitoba, *NH* New Hampshire, *NM* New Mexico, *PNG* Papua New Guinea, *QLD* Queensland, *USASR* USA standardized rate, *WSR* world standardized rate

[a]Estimate (rounded) of the latitude (N, northern hemisphere; S, southern hemisphere), based on latitudes from www.worldatlas.com (accessed 18 April 2016)

[b]Per 100,000 person years, both sexes combined or separated

[c]The years represent the period to which the incidence rates belong; if in **bold**, the incidence rate belongs to that specific year

[d]Incidence rate for native Africans

## *Demographics*

Gender and age have strong influences on BCC incidence rates. Male gender and older age strongly increase the risk of BCC [10, 35]. Among the very elderly (age ≥ 80 years), incidence rates range from 13 to 12,112 per 100,000 person-years with the highest rates among males [36]. However, among young adults especially women, BCC incidence rates are steadily increasing [8, 37, 38]. In the general population, BCC incidence has increased 145% from 1976 to 2010 with the greatest relative increase among women ages 40–49 (246%) and women ages 30–39 (191%) [39]. This is thought to be due to increased frequency of indoor tanning among this subset of the population [40].

## *Location and Histologic Subtype*

The most common location for BCC is the head and neck region (65%) followed by the torso (24%) and extremities (11%) [39]. Within the head and neck region, the most common sites of involvement are the nose, cheeks, and forehead, respectively [41]. Nodular BCC is the most common histologic subtype accounting for 53% of cases with 90% occurring on the head and neck [39, 41]. The next most common is superficial BCC accounting for 20% of cases with the trunk being the most common site of involvement (46%) [41]. Aggressive histologic subtypes which include infiltrating micronodular, metatypical, and morpheaform account for 21% of cases [39]. Figure 1.1a–g shows examples of clinical and dermoscopic photos of various subtypes of BCC.

## *Morbidity and Mortality*

Morbidity and mortality from BCC are rare. Locally advanced BCC (LABCC) is defined as locally invasive BCC not amenable to standard surgical and radiation therapy or metastatic disease to lymph nodes and other organs [2]. LABCC constitutes 0.8% of BCCs with 4399 incident cases per year in the United States [2]. Metastatic BCC (MBCC) accounts for 0.04% of all BCCs with 108 incident cases annually in the United States [2]. The most frequent sites of metastasis are lymph nodes (54%), lungs (28%), and bone marrow (24%) [42]. The median survival for MBCC is 54 months, and the 1-year survival rate is 73.2% [42].

Among persons with the history of BCC, there is an increased risk of both cutaneous and non-cutaneous malignancies [43]. After an initial BCC, there are 29% lifetime risk and 36% 5-year risk of developing a subsequent BCC [43]. The

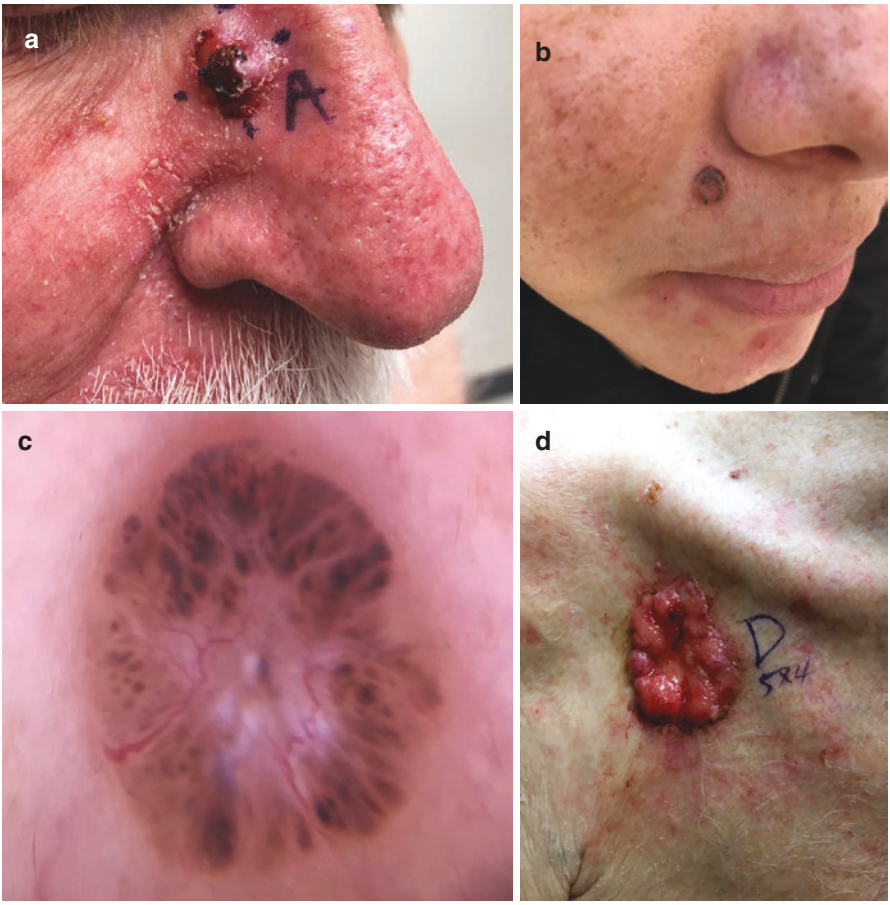


**Fig. 1.1** (**a**) A large ulcerated nodular basal cell carcinoma on the right nasal sidewall extending to the right medial cheek. (Photo courtesy of Leon Chen, MD). (**b**) A pigmented basal cell carcinoma on the right upper cutaneous lip of a young Hispanic female. (Photo courtesy of Leon Chen, MD). (**c**) Dermoscopic image of the same pigmented basal cell carcinoma in 1B that showed arborizing vessels, spoke-wheel structures, and white strands in the center. (Photo courtesy of Leon Chen, MD). (**d**) A large exophytic nodular basal cell carcinoma with spontaneous bleeding on the right upper chest of a farmer. (Photo courtesy of Leon Chen, MD). (**e**) A subtle nodular basal cell carcinoma on the right lower eyelid initially mistaken for an eye stye. (Photo courtesy of Sirunya Silapunt, MD). (**f**) A superficial basal cell carcinoma on the right forearm. (Photo courtesy of Sirunya Silapunt, MD). (**g**) A large locally advanced ulcerated sclerosing basal cell carcinoma on the left cheek. (Photo courtesy of Leon Chen, MD)

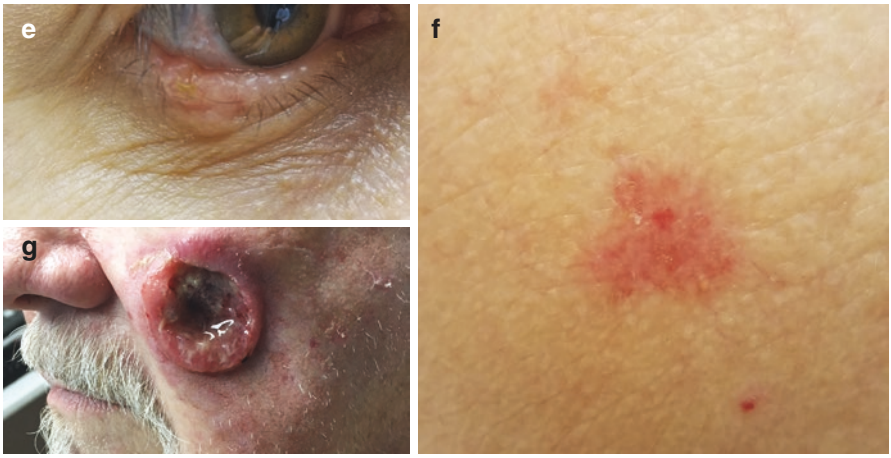


**Fig. 1.1** (continued)

5-year risk increases to 75% for patients with a history of two or more BCCs [44]. In addition, there is 4% and 0.5% lifetime risk of developing a subsequent squamous cell carcinoma (SCC) and malignant melanoma, respectively [43]. History of BCC increases the risk of developing a secondary primary malignancy by 12–49% with the highest risk of development of salivary gland malignancy, melanoma, oropharyngeal carcinoma and non-Hodgkin's lymphoma, leukemia, myeloma, and lung carcinoma [45]. However, these associations do not seem to increase the risk of all-cause mortality [46, 47].

## *Economic Burden*

The cost burden for skin cancer of all types is high in several countries [48]. Cost for BCC is difficult to determine due to several registries and studies combining BCC with SCC under the umbrella terms keratinocyte carcinomas (KCs) or non-melanoma skin cancers (NMSC). The highest healthcare costs for KC are in the United States, Australia, Germany, and the United Kingdom, respectively [48]. However, the highest cost per capita is in Australia, New Zealand, Denmark, and Sweden, respectively [48]. Among the US Medicare population, KCs are among the five most expensive cancers to treat [49]. In the United States, the average annual cost of treating KC increased from $2.7 billion during 2002–2006 to $4.8 billion during 2007–2011 [50]. This was a 74% increase in cost for KC compared to a 25% increase in cost for other cancers during the same time periods [50]. There is also a significant difference in healthcare cost between advanced BCC and non-advanced BCC cohorts. Annual healthcare costs in 2014 for advanced BCC cost were $32,403

compared to $16,044 for non-advanced BCC [51]. The major driver in cost difference between the two cohorts is outpatient treatment with radiation therapy [51]. In addition to direct healthcare costs, there are indirect costs. The average indirect cost, such as absence from work, lost productivity, activity restriction, and caregiver cost, per treated BCC is $1235 in the United States [52]. The annual indirect cost in the United States is $3–5 billion [53].

### *Prevention*

Prevention strategies are thought to be critical in reducing the burden of BCC, but strong evidence is poor or lacking. Primary prevention efforts aim to reduce the incidence of BCC. Reduction in UVR exposure with sun avoidance and sun protection behaviors is theorized to reduce risk of BCC [54]. The United States Preventive Services Task Force (USPSTF) recommends counseling fair-skinned children, adolescents, and young adults aged 10–24 years about minimizing UVR exposure in order to reduce risk of skin cancer in general [55]. However, a recent Cochrane review study found only one randomized controlled trial examining sun protection for preventing BCC [56]. The study demonstrated no difference in development of BCC between the daily sunscreen group and the beta-carotene supplement group and the placebo group [57]. Chemoprevention strategies such as topical tretinoin, beta-carotene, oral retinoids, and selenium have been inconsistent or failed to demonstrate a reduction in BCC development [5, 58–65]. However, a recent systematic review and meta-analysis showed a 10% risk reduction of BCC with any oral nonsteroidal anti-inflammatory drug use [66]. However, this finding needs further study with a randomized control trial. Sustained nicotinamide supplementation has been shown to reduce the incidence of BCC by 20% in a high-risk population, defined with a recent history of two or more NMSC [67, 68]. Secondary prevention efforts include early detection of and screening for BCC. Although the USPSTF found insufficient evidence regarding the effectiveness of visual skin examination for the early detection of skin cancer including BCC in asymptomatic adults [69], a recent systemic review based on World Health Organization screening criteria found that current data supports early detection and management of BCC on the face given its impact on treatment costs and surgical and reconstructive complexity [70].

## Risk Factors

### *Introduction*

There are several risk factors associated with the development of BCC. The most recognized of which is exposure to UVR in sunlight [71, 72].

## *UV Radiation*

Sun exposure is generally accepted as the major cause of BCC [71–74]. Fair skin, red or blond hair, and light eye color are associated with BCC as independent risk factors due to greater susceptibility to UVR damage (see "Genes" section below) [5, 71, 75, 76]. The relationship between sun exposure and development of BCC is complex and dependent on the timing, pattern, and amount of exposure [71, 73, 74, 76]. The risk of developing BCC is significantly increased by exposure to the sun during childhood and adolescence than exposure to the sun later in life [35, 73, 77, 78].

In a 2002 study, the use of indoor tanning devices was shown to be associated with BCC (odds ratio [OR] 1.5; 95% confidence interval [CI]: 1.1, 2.1), even after adjustment for history of sunburns, sunbathing, and sun exposure [79]. Several studies have since confirmed this association [78, 80–82]. Other studies have shown that indoor tanning was associated with an increased risk of early-onset BCC (OR 1.69; 95% CI: 1.15, 2.48) [40] (OR 1.6; 95% CI: 1.3, 2.1) [82] and that the strongest association was observed for first exposure as an adolescent or young adult [82, 83]. Particularly due to risk of melanoma, tanning devices have been identified as a carcinogen by the US Department of Health and Human Services since 2000 and by the World Health Organization since 2009 [84–86]. More recently, the US Food and Drug Administration issued new regulations strengthening warnings for indoor tanning devices, and several states have placed restrictions on the use of tanning devices by minors [87]. Tanning salons are banned in Brazil and Australia [88].

Psoralen plus ultraviolet A light (PUVA) therapy is used for treating psoriasis and other cutaneous disorders. A 30-year observational prospective study of a 1380 patient cohort with severe psoriasis has shown that BCC risk increases with increasing PUVA exposure. In addition, the study showed that the risk of SCC increases significantly more with increasing PUVA exposure [89]. The psoriasis/PUVA study also showed that high levels of ultraviolet B exposure increase the risk of BCC in PUVA-treated patients [89, 90]. However, a study of 3867 patients treated with narrowband ultraviolet B (nb-UVB) phototherapy found no association between nb-UVB exposure alone (without PUVA) and any skin cancer [91]. Furthermore, for nb-UVB- and PUV-treated patients, the study confirmed an association with BCC. It should be noted that an earlier study by the same authors had shown a slight association between nb-UVB and BCC [92], and other smaller studies have also confirmed the lack of association [93, 94].

## *Photosensitizing Medications*

An observational case-control study of 5072 individuals found a slight increase in risk of BCC (OR 1.2; 95% CI: 0.9, 1.5), in particular early-onset BCC (age $\leq$ 50) (OR 1.5; 95% CI: 1.1, 2.1) associated with photosensitizing medication use [95]. In the same study, tetracycline class of antibiotics, primarily used for treatment of acne and skin rashes, was associated with BCC (OR 1.8; 95% CI: 1.2, 2.8) and specifi-

cally early-onset BCC (OR 2.0; 95% CI: 1.2, 3.4), with evidence of a higher risk with longer duration of treatment. Although some studies found an association between some diuretics and BCC [95–97], other studies found no association [98, 99].

## *Ionizing Radiation*

Exposure to therapeutic ionizing radiation as used in treatment of acne vulgaris [100], tinea capitis [101, 102], eczema, and cancers [100, 103–105] increases the risk of BCC. The association is especially strong for BCC arising within the radiation treatment field (OR 2.6; 95% CI: 1.5, 4.3), among patients treated with radiation therapy before age 20 (OR 3.4; 95% CI: 1.8, 6.4), patients whose BCCs occurred 40 or more years after radiation treatment (OR 3.2; 95% CI: 1.8, 5.8), and patients treated with radiation for acne (OR 11; 95% CI 2.7, 49) [100]. Although, the use of ionizing radiation for treating skin conditions like acne has declined, there has been a rapid increase in the use of computerized tomography and fluoroscopically guided diagnostic and interventional procedures that deliver substantially greater radiation does to the skin than standard X-rays [100].

A study of radiation exposure among US radiologic technologists found evidence that chronic occupational exposure to ionizing radiation at low to moderate levels can increase the risk of BCC and that this risk may be modified by pigmentation characteristics [106].

Studies of the survivors of the atomic bomb explosions in Japan show an association between ionizing radiation and BCC [107–109]. One study found that the risk decreased markedly as the age at exposure increased. The study concluded that the basal layer of the epidermis appears to be quite sensitive to radiation carcinogenesis, particularly at a young age, whereas the suprabasal layer seems to be more resistant, as evidenced by the lack of an association with SCC [107]. The same study found no evidence for an interaction between ionizing and ultraviolet radiation.

## *Chemical Exposures*

Arsenic is one of the main causes of BCC in sun-protected areas and frequently results with multiple tumors, especially on the trunk [110–114].

## *Immunosuppression*

SCC and BCC account for more than 90% of all skin cancers in transplant recipients, with an increasing incidence as the duration of immunosuppressive therapy increases. It affects 50% or more of the white transplant recipients [115]. In renal transplant patients, studies have shown an increase by a factor ranging from 7 up to

16 [116–118]. Whereas BCC is more prevalent than SCC in the general population, the prevalence is reversed in transplant recipients [76, 115, 117].

The risk of BCC in transplant patients appears to be associated with the immunosuppressive therapy [119, 120]. Tapering immunosuppressive treatment usually decreases the rate of cutaneous carcinogenesis and is therefore recommended for patients with multiple or aggressive lesions [115]. A recent study of hematopoietic stem cell transplant (HSCT) recipients in Denmark had an increased risk of BCC with a hazard ratio (HR) of 3.1 (95% CI: 1.9, 5.2) compared with the background population [118]. This is consistent with prior studies and a recent systemic review of cutaneous malignant neoplasms in HSCT recipients [121, 122]. All these studies found that the use of total body irradiation (TBI) as part of the conditioning regimen significantly increased the risk of BCC. Furthermore, the risk of BCC due to TBI is larger for patients who are younger at the time of exposure to radiation, especially at ages less than 10 years [104], consistent with other studies of ionizing radiation [101, 102, 107]. However, the Danish study showed that patients who underwent HSCT but were not exposed to TBI did not have a higher risk for BCC compared to the background population [118]. Furthermore, graft-versus-host disease in these patients may increase the risk of BCC [121, 122].

The use of glucocorticoids in non-transplant patients was found to increase the risk for BCC [98, 111, 123, 124]. A recent study of oral prednisone use did not find a statistically significant association with BCC, but the study's population was already subject to much higher risk of skin carcinoma than the general population [125]. Studies of the association between immunosuppressants other than glucocorticoids and BCC in rheumatoid arthritis patients have conflicting results [124, 125]. Several studies have demonstrated an increased risk of BCC in HIV-positive patients [126–128]. However, no association between HIV-related immunodeficiency and BCC was found [126, 129].

## *Genes*

People with fair complexion, light/red hair color, light eye color, and poor ability to tan are at the highest risk of BCC [5, 71, 75, 76]. Pigmentation is a polygenic trait, but the melanocortin 1 receptor gene (MC1R) plays a major role in determining skin and hair color [130]. Several studies have shown that MC1R gene variants are risk factors for BCC, independent of the pigmentation phenotype [131–133]. Furthermore, other genes that have similar effect on pigmentation phenotype (ASIP and TYR) also have variants that are associated with increased risk of BCC independent of the phenotype [134].

A personal and/or family history of skin cancer is also a risk factor for BCC [5, 135]. Furthermore, a study showed that family history of skin cancer is associated with early-onset basal cell carcinoma independent of MC1R genotype [136].

Based on genome-wide association studies (GWAS), several genetic variants that have no obvious effect on pigmentation or UV susceptibility were associated with increased risk for BCC. However, some of these variants may influence the

growth and differentiation of cells in the basal layers of the skin and may have an association with other cancers [137–141] or may be involved in DNA repair pathways [102]. A complete list of associations can be found in the GWAS Catalog [141].

Multiple genetic disorders are associated with increased risk for BCC. The presence of multiple and/or early-onset BCC should raise suspicion of an underlying genetic condition. Specific disorders, namely, Gorlin, xeroderma pigmentosum, Bazex-Dupré-Christol, and Rombo syndromes, are characterized by the incidence of BCC. In addition, other disorders have BCC as a common but an ancillary feature as shown in Table 1.2 [142].

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is an autosomal dominant disorder characterized by macrocephaly, congenital malformations and bone anomalies, medulloblastoma, multiple early-onset BCCs, pits of the palms and soles, jaw keratocysts, a variety of other tumors, and developmental abnormalities [143, 144]. It is caused by mutations inactivating PTCH1 gene that results in inappropriate activation of the hedgehog pathway [76, 145]. The prevalence of this disease is estimated at 1:30,827. Histologically, the appearance of NBCCS-associated BCC is similar to typical BCC. However, BCCs occur in early childhood but usually present in late teens or early adulthood [144].

Xeroderma pigmentosum (XP) consists of a group of autosomal recessive disorders characterized by defects in unscheduled DNA repair. Compared to the general population, XP patients under the age of 20 years have a 10,000-fold increase in the frequency of NMSC. The median age at diagnosis of first NMSC is 9 years [146]. Strict UV avoidance can significantly decrease skin cancer formation [147].

Bazex-Dupré-Christol syndrome is a rare disorder, characterized by follicular atrophoderma (usually occurring on dorsal hands and feet), hypotrichosis, localized hypohidrosis, milia, epidermoid cysts, and multiple, primarily facial, BCCs. The BCCs develop during the second decade of life. In most families, the inheritance pattern is X-linked dominant [148].

**Table 1.2** Genetic syndromes with basal cell carcinoma as an ancillary feature

| *Disorders of DNA replication/repair function* |
|---|
| Bloom syndrome |
| Werner syndrome |
| Rothmund-Thomson syndrome |
| Muir-Torre syndrome |
| *Disorders of the folliculo-sebaceous unit* |
| CYLD-associated syndromes including Brooke-Spiegler syndrome |
| Schöpf-Schulz-Passarge syndrome |
| Cowden syndrome |
| *Syndromes with immunodeficiency* |
| Cartilage-hair hypoplasia |
| Epidermodysplasia verruciformis |
| *Disorders of melanin biogenesis* |
| Oculocutaneous albinism |
| Hermansky-Pudlak syndrome |

Rombo syndrome is a rare disorder that has many of the features of Bazex-Dupré-Christol syndrome. It is characterized by atrophoderma vermiculatum, hypotrichosis, blepharitis, milia, trichoepitheliomas, acral and facial peripheral vasodilation with cyanosis, and BCCs. The skin lesions are most pronounced on the face and become visible between 7 and 10 years of age. BCCs are frequent and develop at around 35 years of age [149].

## Conclusion

BCC is the most common cancer in Caucasians, and its incidence is increasing worldwide. It results in significant economic burden and healthcare costs in countries where the disease is prevalent. BCC is a complex disease, with both environmental and genetic factors contributing to its development. UVR exposure in sunlight is the most important risk factor. Other recognized risk factors include radiation therapy, chronic arsenic exposure, long-term immunosuppressive state, and the basal cell nevus syndrome. Prevention is likely to reduce the burden of BCC.

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# Chapter 2
# Pathophysiology of Basal Cell Carcinoma and Its Associated Genetic Syndromes


**Anne Lynn S. Chang**

## Introduction

Basal cell carcinomas (BCCs) are the most common human malignancy and arise from the basal cell layer of the epidermis. Since the epidermis is the first line of defense from environmental insults such as ultraviolet radiation, BCCs are among the most highly mutated of human tumors. While the vast majority of patients with BCC develop the tumors in sporadic fashion, germline mutations in humans exist that can significantly increase the risk of BCC. Since basal cells are exposed to ultraviolet (UV) radiation, recessive germline mutations can lead to cancers when the normal copy is mutated by environmental insults such UV radiation. A summary table off genetic syndromes associated with BCC is shown in Table 2.1.

## Basal Cell Nevus Syndrome (BCNS)

The familial syndrome of BCNS was first described in 1960 [1] with many subsequent pedigrees described characterized by multiple and early-onset basal cell carcinomas, frontal bossing, skeletal abnormalities, jaw cysts, hypertelorism, and palmoplantar pitting. Less commonly, medulloblastoma, calcification of the falx cerebri, or agenesis of the corpus callosum may occur. Diagnosis of BCNS can be made on clinical grounds alone, though genetic testing confirms the diagnosis.

The genetic basis of BCNS was first explored in the 1990s, leading to the association of the PATCHED1 gene with this syndrome in 1996 [2]. Subsequently, additional mutations such as PATCHED2 and SUFU were found to also confer

A. L. S. Chang (✉)
Stanford University School of Medicine, Department of Dermatology, Redwood City, CA, USA
e-mail: alschang@stanford.edu



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_2

**Table 2.1** Genetic syndromes associated with basal cell carcinoma

| Pathophysiology | Syndrome | Key clinical features | Inheritance pattern | Known mutations |
|---|---|---|---|---|
| Hedgehog signaling pathway overexpression | Basal cell nevus syndrome (Gorlin-Goltz) | Early-onset multiple BCC | Autosomal dominant | Most common mutations in PTCH1 |
| | | Frontal bossing | | |
| | | Skeletal deformities | | |
| | | Jaw cysts | | |
| | | Hypertelorism | | |
| | | Medulloblastoma | | |
| | | Palmoplantar pitting | | |
| DNA repair deficiency | Xeroderma pigmentosum | Early-onset multiple skin cancers including BCCs | Autosomal recessive | Multiple, including XPA, B, C, D, E, F, G, V |
| Pigmentation deficiency | Oculocutaneous albinism | Both types I and II have BCC, other skin cancers, nystagmus, photophobia, impaired visual acuity, strabismus | Autosomal recessive | Type I: Tyrosinase gene<br>Type II: P gene |
| | | Type I has pink-red nevi, white hair, blue-gray irides, whereas type II has pigmented nevi, cream to yellow-brown hair and blue to yellow-brown irides | | |
| Other | Bazex-Dupre-Christol syndrome | BCC<br>Follicular atrophoderma<br>Hypotrichosis | X-linked dominant | Xq24-q27 region |
| | Rombo syndrome | BCCs in the 30s<br>Vermiculate Atrophoderma<br>Milia<br>Hypotrichosis<br>Trichoepitheliomas<br>Peripheral vasodilation with cyanosis | Autosomal dominant | Unknown |

predisposition to multiple BCCs. Since these genes are all within the Hedgehog signaling pathway, important for midline development in the embryo, abnormalities in these genes can explain why many of the clinical features involve midline structures (e.g., hypertelorism, frontal bossing, agenesis of the corpus callosum). Abnormal signaling of the Hedgehog signaling after embryonic development is complete, due to loss of the one normal copy of PATCHED1 in BCNS patients, for instance, can drive basal cells to become cancerous, at a much higher frequency than normal individuals. In addition, BCNS patients can be exquisitely sensitive to radiation [3]. Hence, radiotherapy for skin cancers should be used with caution by radiation oncologists.

Recent clinical advances utilizing drugs that target the Hedgehog signaling pathway have greatly reduced the BCC burden of BCNS patients. Currently, two drugs

that bind and inhibit the Hedgehog signaling pathway, vismodegib and sonidegib, are US Food and Drug Administration approved for advanced BCCs, though their utility in BCNS patients is quite clear [4]. Long-term outcomes of BCNS patients on these drugs remain to be explored.

## Bazex-Dupre-Christol Syndrome

Bazex-Dupre-Christol syndrome is characterized by multiple BCCs starting in the second decade of life. The other two key features include congenital hypotrichosis and follicular atrophoderma of the extensor surfaces. Multiple families have been described with this triad of conditions, and less consistent features have included milia and trichoepitheliomas [5]. The inheritance pattern of Bazex-Dupre-Christol syndrome is X-linked dominant, whereas Rombo syndrome (described below) is autosomal dominant.

## Rombo Syndrome

Rombo syndrome was first described in 1981 [6], in which autosomal dominant transmission across at least four generations leads to early-onset and frequent basal cell carcinomas in the mid-1930s. Features of this syndrome were visible in the first decade of life, including peripheral vasodilation with cyanosis and follicular atrophy of the skin. In adults, milia-like papules and telangiectasias on the face became prominent. Skin atrophy (termed "vermiculate" due to the wormlike appearance), lost or abnormal eyelashes and eyebrows, and less commonly trichoepitheliomas were also observed. Histologic analysis revealed areas of elastin clumping as well as areas of elastin loss.

Outside of this original family, one other family with Rombo syndrome has been described with similar features plus short stature and prominent midface [7]. In addition, biopsies of chest papules revealed mid-dermal cystic structures with squamous epithelium and vellus hairs. As seen in the Rombo family described by Michaëlsson et al., histological analysis displayed irregular elastin deposits. Since solar elastosis is visible from chronic ultraviolet exposure, abnormal DNA repair or cell cycle regulation has been hypothesized as the etiology of the skin findings.

## Additional Genetic Syndromes with Increased Risk of Basal Cell Carcinoma

Additional genetic syndromes are associated with increased risk of BCC and are due to a variety of mechanisms which ultimately lead to mutations that drive abnormal basal cell growth. These include oculocutaneous albinism (types I and II),

whereby deficiencies in the melanin production pathway lead to reduced shielding of DNA from ultraviolet radiation and subsequent increased BCC risk.

The tumor suppressor gene BAP1 (BRCA1-associated protein 1) confers predisposition to multiple types of cancer when mutated, including BCCs. While originally recognized to associate with melanomas, mesotheliomas, and clear cell renal cancer, more recently multiple BCCs have been added to this syndrome [8–10]. Knowledge of these associations by dermatologists would prompt more careful skin surveillance and education about aggressive photo-protective measures for patients with a constellation of the cancers described above and/or known BAP1 carriers.

Another tumor suppressor gene, BRCA2, has been shown to increase the risk of BCCs [11]. Other cancers associated with this gene include breast and ovarian cancers and melanoma. With the onset of genetic testing for families with increased cancer risk, patients who test positive as BRCA2 carriers should consider routine skin cancer surveillance with a dermatologist as part of their healthcare maintenance and adopt photo-protective measures to prevent skin cancers.

Xeroderma pigmentosum (XP) is associated with increased BCC risk, as well as other skin cancer, central nervous system, and lung cancer risk [12]. The pathogenesis of this condition is based on defects in DNA repair enzymes (helicase and endonucleases) upon ultraviolet radiation exposure or in post-replication repair (Table 2.1) presumably leading to mutations in pathways driving BCC development. The most common types are patients with mutations in XPA, C, and V, comprising 75% of all patients. Signs of XP are visible within the first few years of life with severe photosensitivity starting in infancy. Subsequently, in childhood and adolescence, accelerated photodamage leads to lentigos, actinic keratoses, keratoacanthomas, BCC, squamous cell cancer, and melanoma [12]. In addition, there can be narrowing of the mouth and nares and ectropion. In XPA and XPD, progressive neurologic symptoms may occur, including mental degeneration, deafness, and hyper- or hyporeflexia. Aggressive photo-protection is necessary to reduce skin cancer development and shortened life span.

Finally, the genetic underpinnings of BCCs can range from targeted mutations in the Hedgehog signaling pathway, all the way to defects in tumor suppressors and deficiencies in melanin synthesis leading to DNA damage that promotes BCC growth. Future research leveraging our understanding of the genetic basis of BCCs may eventually significantly reduce the burden of BCCs worldwide.

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# Chapter 3
# Histopathology of Basal Cell Carcinoma and Its Variants


**Priyadharsini Nagarajan, Michael T. Tetzlaff, and Jonathan L. Curry**

## Introduction

Basal cell carcinomas (BCCs) are epithelial tumors that arise from basal layer of the epidermis or follicular infundibulum. BCCs typically occur on sun-exposed skin in adult patients beginning in their fourth decade onwards; however, may also be seen in the pediatric population in association with xeroderma pigmentosum or basal cell nevus syndrome (Gorlin-Goltz syndrome). BCCs can be classified into five principal clinical types: nodular/ulcerative, infiltrative, multifocal/superficial, pigmented and fibroepithelioma of Pinkus, in descending order of incidence. These clinical types generally reflect their respective histopathologic growth patterns, although considerable overlap may occur.

## Common Histologic Features

Most BCCs are derived from follicular bulge cells or outer root sheath keratinocytes and are characterized by certain common histologic features of both the tumor cells and the peritumoral stroma, which is also an essential part of the tumor.

The tumor nests consist of monomorphous small- to medium-sized epithelioid cells lacking intercellular bridges, with minimal cytoplasm and high nuclear to cytoplasmic ratio. The nuclei are typically ovoid and hyperchromatic without prominent nucleoli (Fig. 3.1). Although most of the tumor cells tend to exhibit a cuboidal shape, the cells situated along the peripheral edge of the nests tend to be

P. Nagarajan (✉) · M. T. Tetzlaff · J. L. Curry (✉)
The University of Texas MD Anderson Cancer Center, Department of Pathology, Anatomical, Houston, TX, USA
e-mail: pnagarajan@mdanderson.org; jlcurry@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_3

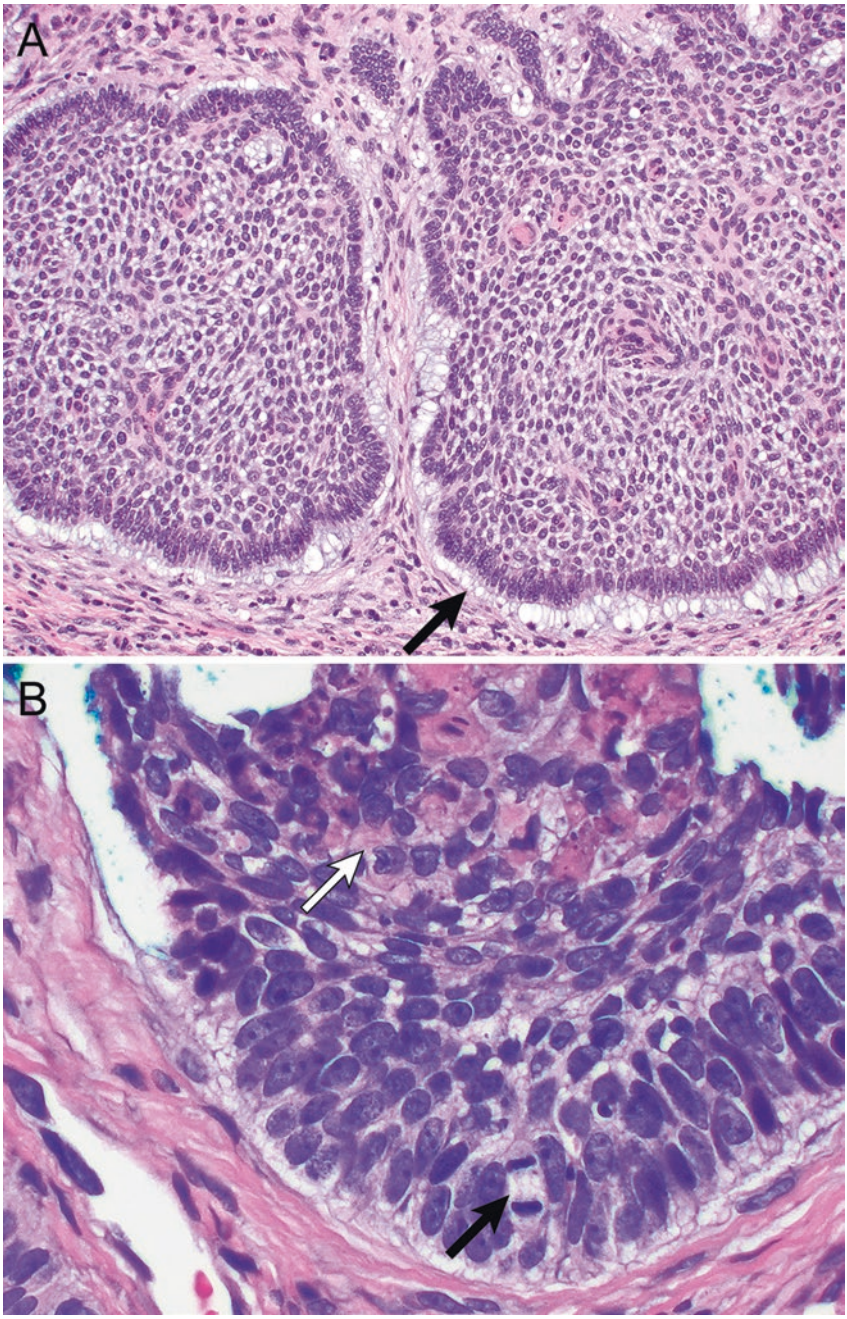



**Fig. 3.1** Histologic features characteristic of basal cell carcinomas. (**a**) The tumor cells are typically cuboidal in the center of the nests with columnar cells arranged along the periphery of the nests in a palisading pattern and peritumoral mucin deposition (black arrow) (Hematoxylin and eosin, original magnification: 200×). (**b**) Apoptotic bodies (white arrow) and mitotic figures (black arrow) are typically evident throughout the tumor nests (Hematoxylin and eosin, original magnification: 600×)

more columnar and are arranged so that their long axes are parallel to each other, while being perpendicular to the basement membrane, i.e., in a peripheral palisading pattern. Apoptotic bodies and mitotic figures are common. Majority of the BCCs appear to originate from the overlying epidermis, while exclusive follicular connection may also be rarely seen.

The peritumoral stroma is hypocellular and rich in hyaluronic acid and other neutral mucins. In some variants, mucin production can be noted within tumoral islands as well (Fig. 3.2). Mucin contracts upon fixation and processing, resulting in artifactual separation of the tumor nests from the surrounding stroma, which is further accentuated by a reduction in hemidesmosome constituents such as bullous pemphigoid antigen and basilar adhesion molecules in BCC [1–4]. Peripheral palisading and stromal clefting may be minimal in the infiltrative variants of BCC.

Amorphous dull pink to amphophilic material, consistent with amyloid, may be present in the stroma (Fig. 3.3). It is keratin-derived, likely from the ongoing tumoral apoptosis; it is typically weakly positive with Congo red stain, although apple green refringence under polarized light may not be apparent. It is most commonly noted in nodular type and almost seldom in the infiltrative variants.

Immunohistochemical studies are usually not required for diagnosis in most cases. However, in superficial biopsies and in cases with poor histologic preservation, extensive squamous differentiation or atypical stromal features, positivity for EpCAM (Ber-EP4), androgen receptor, BCL2, and CD10 may be helpful in the diagnosis of BCC [5–7]. BCL2 expression is relatively low in infiltrative variants of BCC. Differentiation of BCC from trichoepithelioma and trichoblastoma (TE/TB) can be challenging, particularly in superficial or partial biopsies. In such situations, a panel of immuno histochemical markers (CK20, CD34, CD10, and D2–40) can aid in arriving at the correct diagnosis [8]. CK20 will highlight Merkel cells in TE/TB, whereas BCC are typically negative, particularly in the deep portion; peritumoral stromal positivity for CD34 and CD10 is common in TE/TB, whereas the BCC stroma is typically negative; tumor cells in BCC are often CD10-positive; D2–40 is diffusely positive in TE/TB, whereas it is weak or negative in BCC [8]. Neuroendocrine differentiation is rare, noted in less than 5% of tumors [9, 10]; however, the clinical significance of this finding is unclear.

## Histologic Variants

The common histologic types comprise nodular/nodulocystic/ulcerative, superficial, infundibulocystic/hamartomatous, infiltrative, and morpheaform/sclerosing types, while fibroepithelioma of Pinkus is relatively rare. Other infrequent variants are characterized by typical growth patterns which may be part of one of the more common types; tumors exclusively composed of one of the following patterns are relatively rare: clear cell, adenoid, micronodular, metatypical/basosquamous, pleomorphic, metaplastic (carcinosarcoma), keratotic, and keloidal. BCCs with

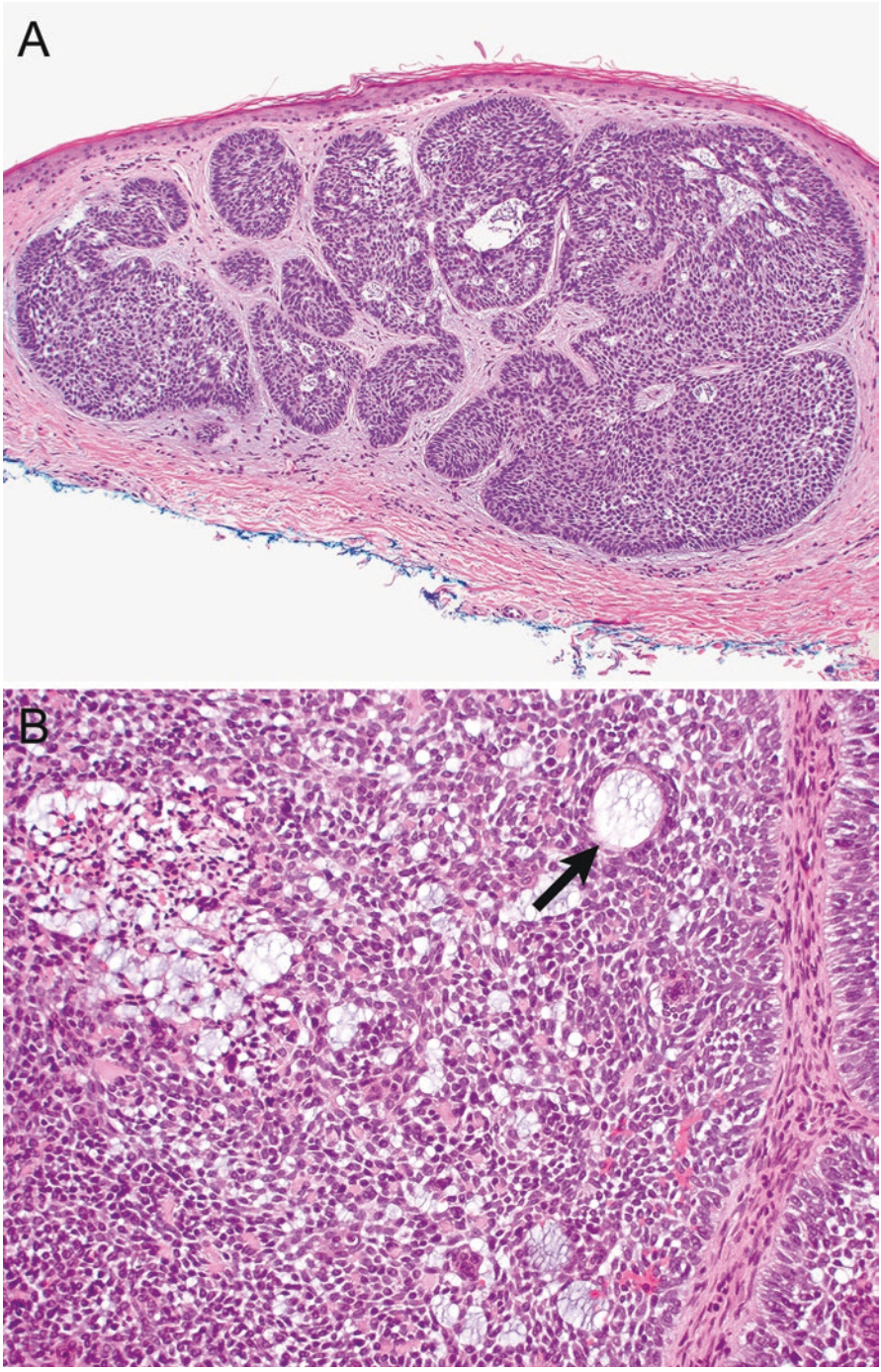



**Fig. 3.2** Characteristic stromal features in basal cell carcinoma. (**a**) Tumor nest surrounded by loose hypocellular amphophilic stroma rich in mucin (Hematoxylin and eosin, original magnification: 100×). (**b**) Mucin deposition within the tumor nest (black arrow; Hematoxylin and eosin, original magnification: 200×)

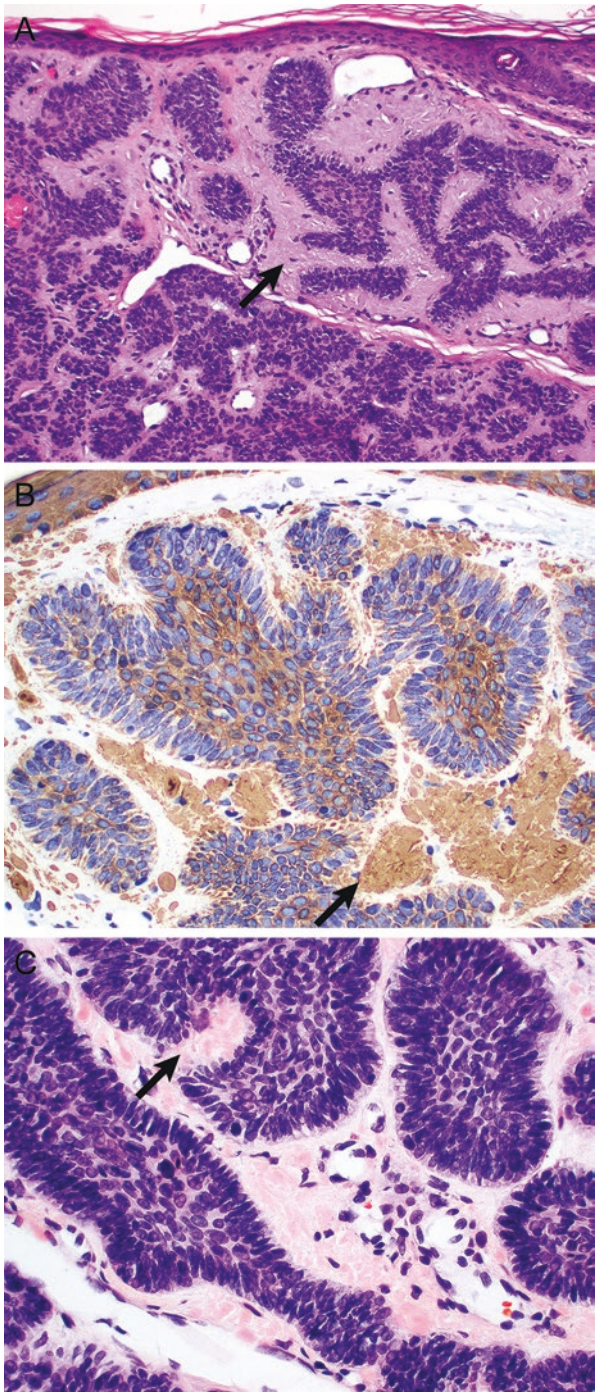



**Fig. 3.3** Amyloid deposition in basal cell carcinoma. (**a**) Tumor nest surrounded by dull eosinophilic acellular material (arrow, Hematoxylin and eosin, original magnification: 200×). (**b**) Immunohistochemical study for keratin cocktail highlights this material, supporting derivation from keratin (anti-cytokeratin cocktail [AE1/AE3, MNF116, Zym5.2, Cam5.2], original magnification: 400×). (**c**) Keratin-derived amyloid is weakly positive for Congo red (Histochemical stain, original magnification: 400×)

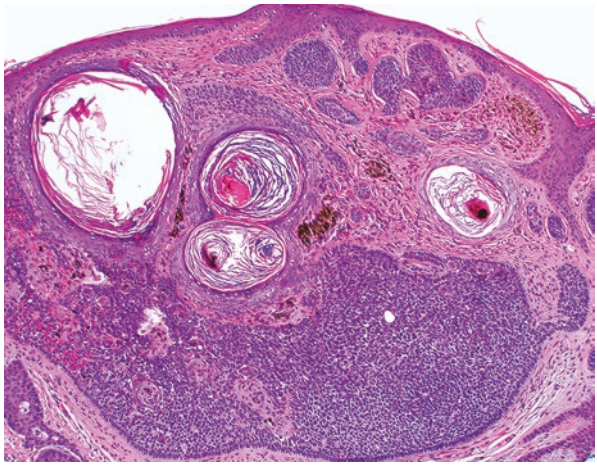


**Fig. 3.4** Pigmented basal cell carcinoma. The tumor has nodular growth pattern with prominent melanin accumulation within the peritumoral stroma and the horn pseudocysts (Hematoxylin and eosin, original magnification: 200×)

granular and signet ring cell features, sebaceous, eccrine, apocrine, and matrical differentiation, are even more uncommon.

Pigmentation is most frequently seen in nodular and infundibulocystic variants and rarely in superficial types. Melanin deposition may occur within the tumor cells and/or in the peritumoral stroma (Fig. 3.4). Increased endothelin-1 signaling and ultraviolet B light-induced enhanced expression of endothelin B receptor have been associated with melanin accumulation in BCC [11–13]. Pigmented variant is common in sun-exposed parts of the body such as head and neck.

## *Nodular Basal Cell Carcinoma*

Nodular/ulcerative/nodulocystic BCC is the most frequent variant and presents as a smooth pearly papule with branching vascular proliferation. Head and neck is the most common site for this variant. The lesion develops a rolled border as it enlarges. Ulceration is also common in nodular type BCC, and may become the dominant characteristic, particularly in the face, resulting in unrelenting ulceration into the surrounding tissues, also known as "rodent ulcers." The characteristic histologic features of the nodular type of BCC include small- to large-sized irregularly shaped nests of basaloid cells with prominent peripheral palisading, peritumoral clefting, and loose myxoid stroma (Fig. 3.5). Breakdown of tumor cells in the center of the nests with cystic degeneration may occur, with collection of pools of mucin and scant cellular debris within the degenerative cystic areas. Observation of empty halos on hematoxylin and eosin stained sections may be a clue for tumor nests drop out from tissue samples.

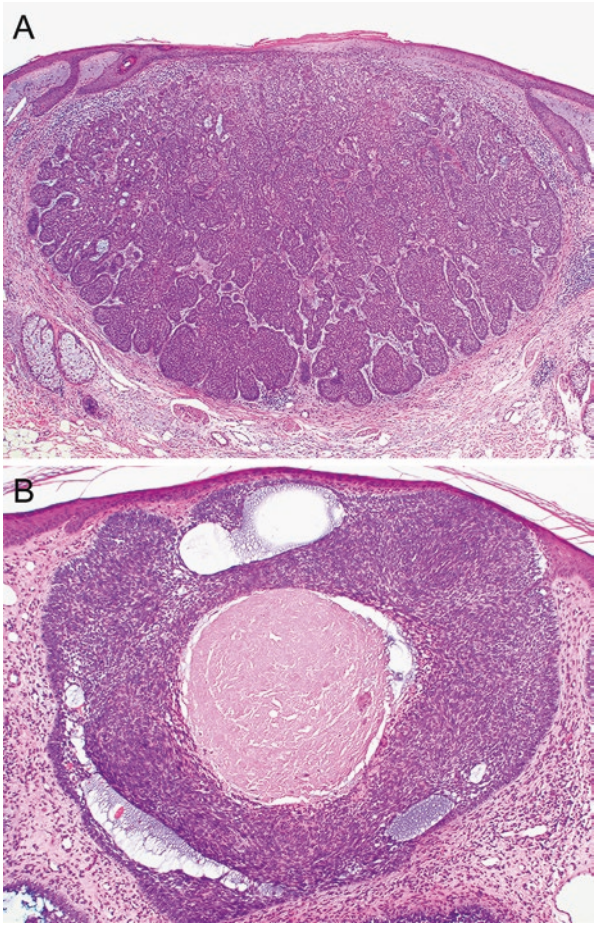



**Fig. 3.5** Nodular basal cell carcinoma. (**a**) Large well-defined lesion with proliferation of basaloid cells, surrounded by myxoid stroma (Hematoxylin and eosin, original magnification: 40×). (**b**) Cystic degeneration with tumor breakdown in the center, mucin accumulation, and keratin debris deposition (Hematoxylin and eosin, original magnification: 100×)

Squamous differentiation is not uncommon in these tumors and may range from focal (Fig. 3.6a) to extensive, sometimes with cellular atypia, raising the possibility of a squamous cell carcinoma (Fig. 3.6b), consistent with, metatypical type of BCC [14, 15]. Although other features, such as myxoid stroma and peritumoral clefting, can aid in the diagnosis, arriving at the definite diagnosis can be challenging especially in superficial biopsies. In these cases, "invasive carcinoma with basaloid and squamous differentiation" may be the most appropriate diagnosis. Evaluation of the entire lesion will be necessary to arrive at the correct diagnosis. Patients with metatypical type of BCC are at a higher risk for developing metastasis [16].

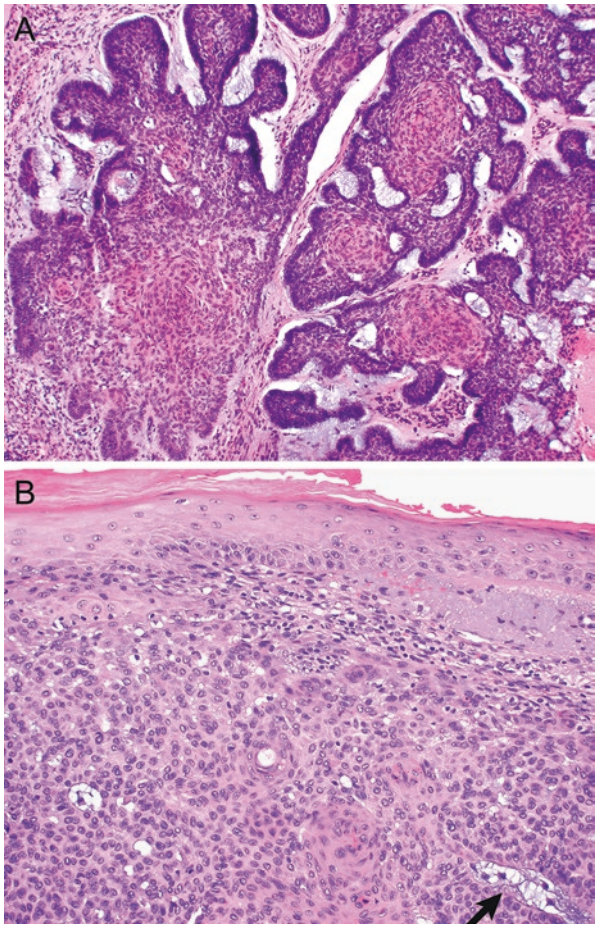



**Fig. 3.6** Squamous differentiation in basal cell carcinoma. (**a**) Multifocal squamous differentiation without atypia in nodular basal cell carcinoma (Hematoxylin and eosin, original magnification: 100×). (**b**) Basal cell carcinoma displaying prominent squamous differentiation (metatypical basal cell carcinoma) with cellular atypia and focal mucinous peritumoral stroma; basaloid cells are not conspicuous (Hematoxylin and eosin, original magnification: 200×)

## *Superficial Basal Cell Carcinoma*

Small, superficial nests of BCC suspended from the epidermis into the papillary dermis are typical of superficial basal cell carcinoma (Fig. 3.7). This variant commonly affects the trunk and extremities of young women and presents as an erythematous occasionally scaly patch or plaque [17]. Due to multifocal nature of the tumor and its discontinuous pattern of growth, the horizontal extent of superficial variants of BCC can be difficult to assess. Therefore, topical therapies may be as efficacious as surgical resection in the management of this tumor. However, tumor thickness greater than 0.4 mm may be a predictor of recurrence after topical imiquimod therapy [18, 19].

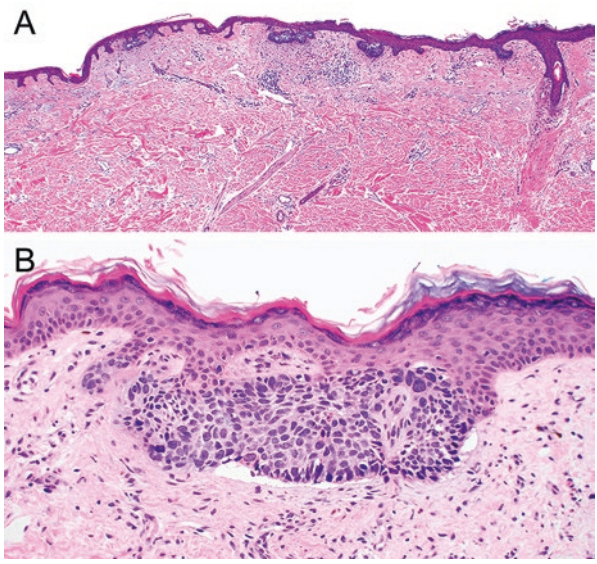



**Fig. 3.7** Superficial basal cell carcinoma. (**a**) Proliferation of small basaloid nests that appear to emanate from the basilar epidermis (Hematoxylin and eosin, original magnification: 40×). (**b**) Focal peripheral palisading, myxoid stroma, and stromal clefting are common (Hematoxylin and eosin, original magnification: 200×)

## *Infundibulocystic/Hamartomatous Basal Cell Carcinoma*

Infundibulocystic or hamartomatous variant of BCC is most common in the face of older adults and displays more prominent follicular differentiation [20, 21]. The lesions are small papules, characterized by symmetric, well-circumscribed proliferation of anastomosing cords of basaloid cells with focal peripheral palisading, minimal peritumoral clefting, and scant stroma (Fig. 3.8). Small cysts with follicular infundibular differentiation are typical of this variant; squamous differentiation is common as well. Histologic features of this lesion overlap with basaloid follicular hamartoma and trichoepithelioma [22].

## *Fibroepithelioma of Pinkus*

Fibroepithelioma of Pinkus is a rare variant of BCC that displays some features of a trichoblastoma [23]. It presents as a fleshy or firm, pink to tan thick nodular plaques in lower back and upper thighs [24, 25], with a stuck-on appearance. Exposure to radiation therapy has been postulated to be a risk factor.

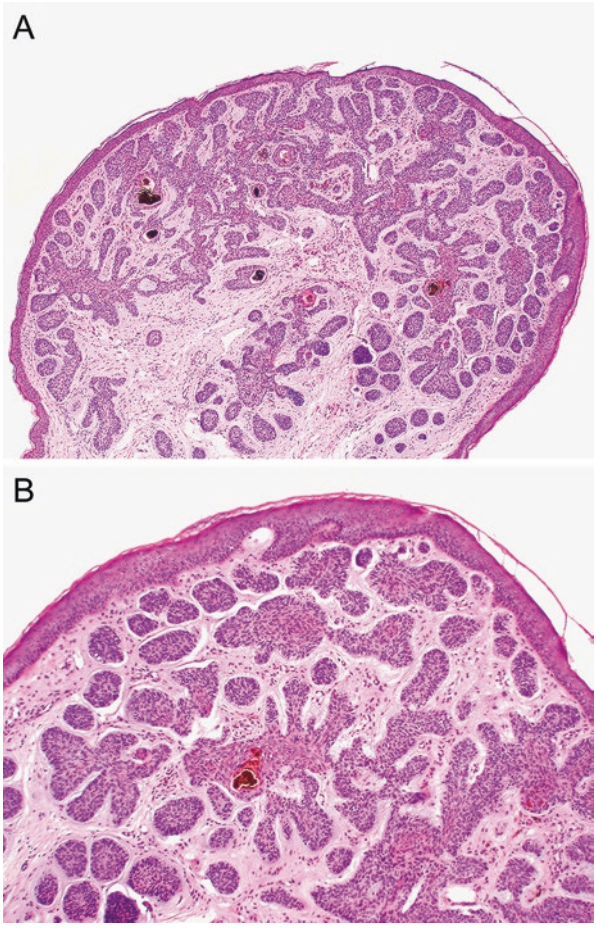



**Fig. 3.8** Infundibulocystic basal cell carcinoma. (**a**) Papule with symmetric proliferation of anastomosing cords of basaloid cells. The lesion is also pigmented (Hematoxylin and eosin, original magnification: 20×). (**b**) Peripheral palisading is present focally along with small cysts with follicular infundibular type epithelium (Hematoxylin and eosin, original magnification: 200×)

Histologically, the lesions are characterized by endophytic growth of thin delicate strands of 2–3 basaloid epithelial cells in thickness (Fig. 3.9). The strands anastomose and interconnect with each other repeatedly, compartmentalizing islands of stroma. This growth pattern has been attributed to extension of BCC along pre-existing eccrine ductal network [26, 27]. Peripheral palisading and stromal clefting can be seen in most cases, at least focally. Focal follicular differentiation such as formation of primitive hair germ and cysts is also a common feature of fibroepitheliomas [28].

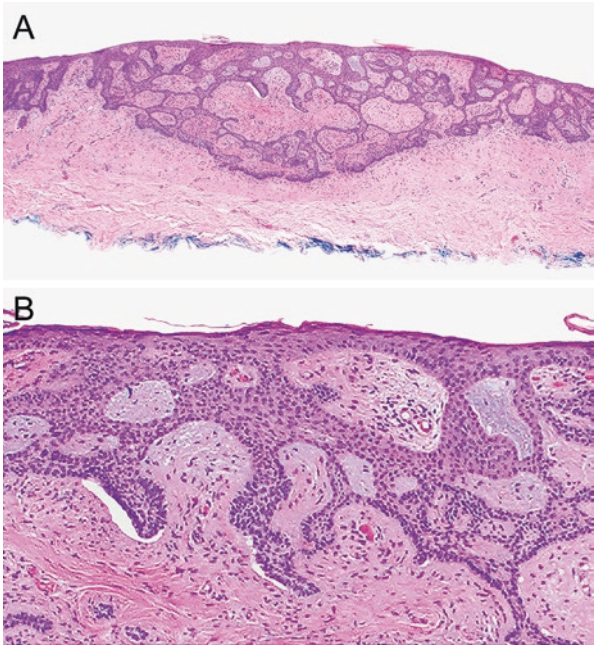



**Fig. 3.9** Fibroepithelioma of Pinkus-type basal cell carcinoma. (**a**) Endophytic growth of interconnecting stands of basaloid cells (Hematoxylin and eosin, original magnification: 40×). (**b**) Peripheral palisading, stromal clefting, and variably myxoid peritumoral stroma are characteristic (Hematoxylin and eosin, original magnification: 200×)

## *Infiltrative Basal Cell Carcinoma*

Infiltrative basal cell carcinoma is characterized by a pink plaque-like lesion with scaly or smooth surface [29]. Histologic features include proliferation of irregular, angulated nests and thin strands of basaloid cells (Fig. 3.10), with very focal peripheral palisading and peritumoral clefting. However, the stroma is variably myxoid and cellular, without prominent fibrosis. Perineural invasion occurs more frequently than in other BCC subtypes. The tumor widely infiltrates the dermis with poor circumscription, sometimes even extending into the underlying subcutis and skeletal muscle. Invasion of calvarium and other osseous structures is rare, but is most commonly seen in those arising in head and neck (Fig. 3.10).

## *Morpheaform Basal Cell Carcinoma*

Morpheaform basal cell carcinoma is an infiltrative variant with fibrotic stroma (Fig. 3.11) and high propensity for perineural invasion [30]. Clinically, the lesion resembles morphea due to the fibrosis and presents as a depressed, indurated

scar-like plaque. Single-cell infiltration may be present, particularly at the peripheral edges; therefore, determining the extent of the tumor can be challenging. Immunohistochemical studies for keratin and/or p63 may be helpful for evaluation of margin status and ensuring completeness of excision [31].

An extremely infrequent variant is the "keloidal" BCC in which the peritumoral stroma is composed almost exclusively of thick bundles of type I collagen (Fig. 3.12) [32, 33]. This variant is common in the ear [34]. It is unclear if the abundance of collagen I is inherent to the tumor or is related to the anatomic location.

## *Micronodular Basal Cell Carcinoma*

Micronodular BCC is another infiltrative variant characterized by diffuse proliferation of small nests of basaloid cells; the average nest is 3–5 cells thick in diameter (Fig. 3.13). Rarely, the nests may be elongated, with trabecular pattern

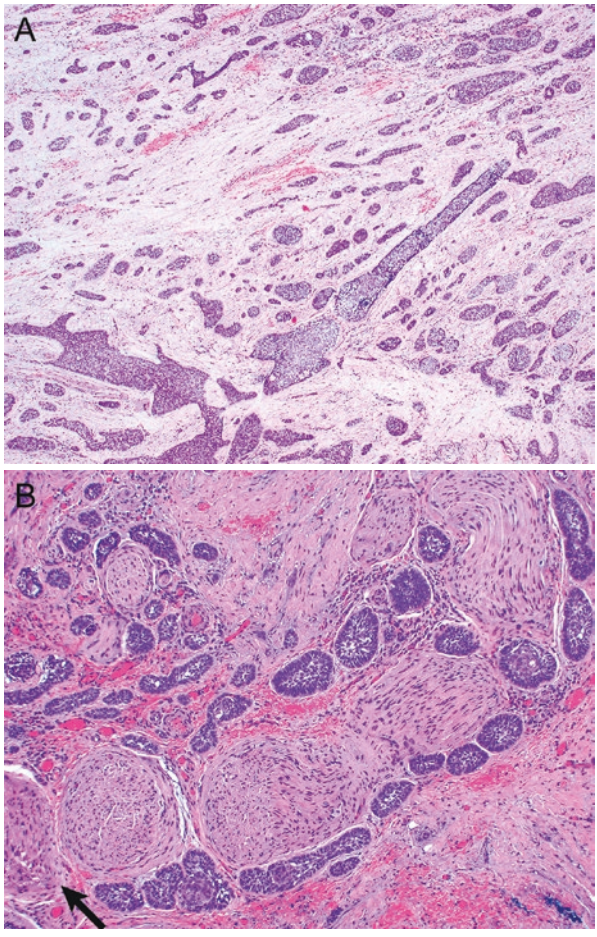



**Fig. 3.10** Infiltrative basal cell carcinoma. (**a**) Diffuse proliferation of variably sized angulated nests and cords of basaloid cells surrounded by pale variably myxoid peritumoral stroma (Hematoxylin and eosin, original magnification: 40×). (**b**) Perineural invasion of a large caliber nerve fiber (Hematoxylin and eosin, original magnification: 100×). (**c**) Invasion of skeletal muscle (Hematoxylin and eosin, original magnification: 40×) and (**d**) bone (Hematoxylin and eosin, original magnification: 40×)

**Fig. 3.10** (continued)

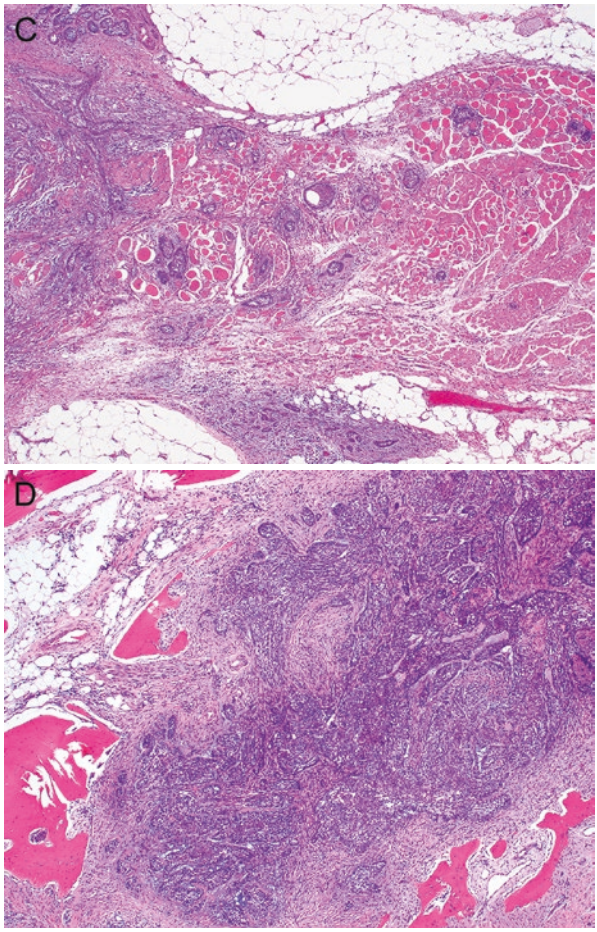
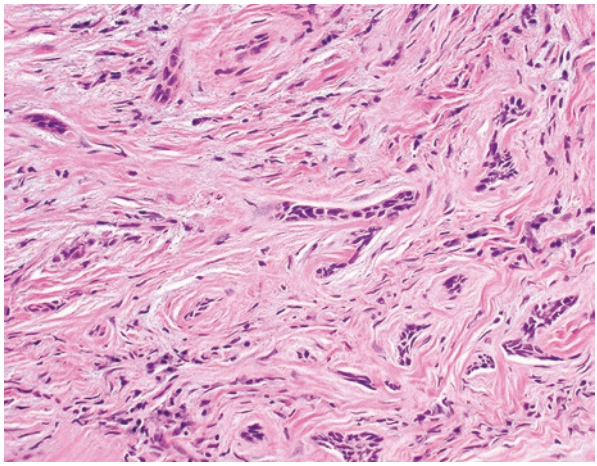



**Fig. 3.11** Morpheaform basal cell carcinoma with thin cords of basaloid cells infiltrating a fibrotic stroma (Hematoxylin and eosin, original magnification: 200×)



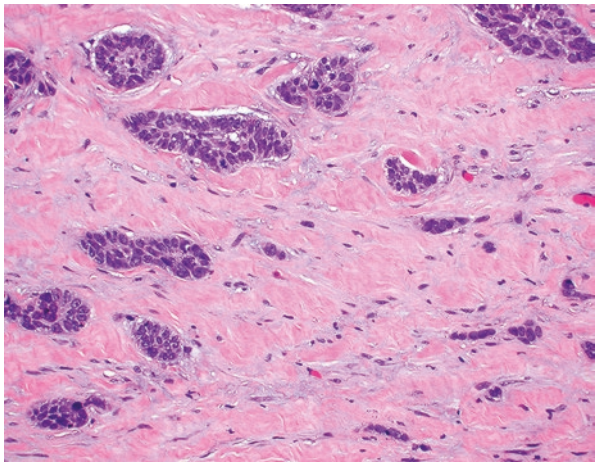


**Fig. 3.12** Keloidal variant of morpheaform basal cell carcinoma is characterized by deposition of dense collagen bundles surrounding small nests and thin cords of basaloid cells (Hematoxylin and eosin, original magnification: 400×)

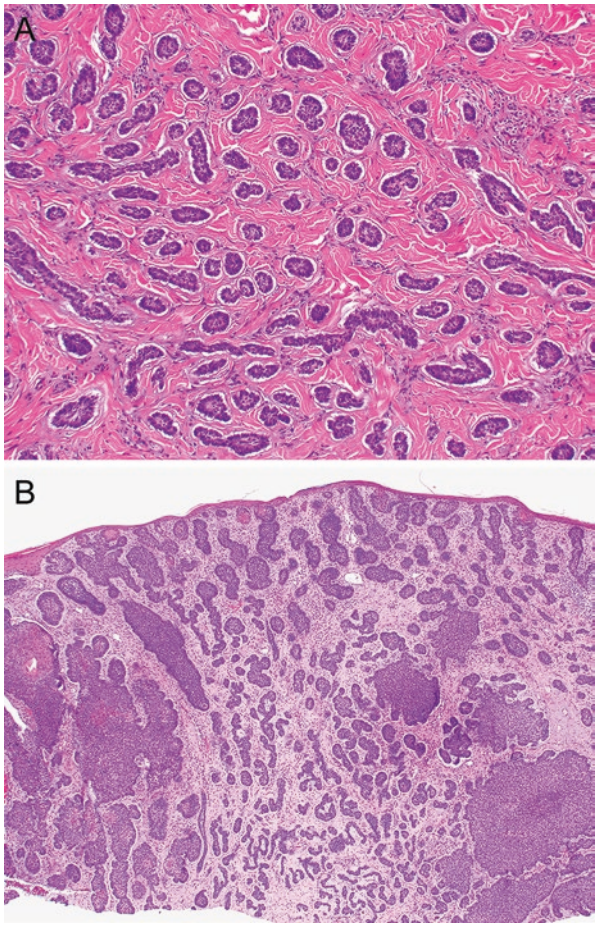
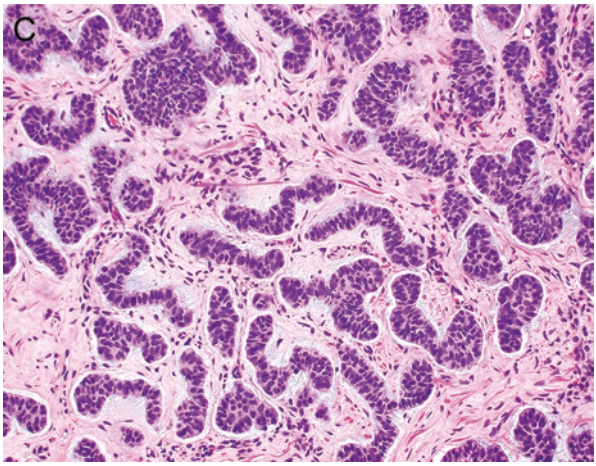



**Fig. 3.13** Micronodular basal cell carcinoma. (**a**) Infiltrative pattern of growth composed of small nests of basaloid cells with minimal surrounding mucinous stroma (Hematoxylin and eosin, original magnification: 100×). (**b**) Large tumor with nodular and focal micronodular pattern in the center (Hematoxylin and eosin, original magnification: 40×). (**c**) Myxoid stroma surrounding tumor nests (Hematoxylin and eosin, original magnification: 200×)

**Fig. 3.13** (continued)




of growth. This pattern can be present rarely exclusively within a tumor or more commonly admixed with other patterns such as infiltrative and nodular. Due to the small size of tumor nests and lack of other typical features such as peripheral palisading, stromal clefting, and stromal mucin, assessment of margins may be difficult.

## *Clear Cell Basal Cell Carcinoma*

Clear cell changes in BCC is an uncommon phenomenon and has been attributed to accumulation of excess glycogen or secondary to cytoplasmic aggregation of degenerative lysosomal vacuoles [35–37]. Clear cell changes may be focal or rarely diffuse, with the entire tumor composed of only clear cells (Fig. 3.14). In most cases, at least a portion of the tumor consists of more typical BCC. Peripheral palisading and mucinous peritumoral stroma are typically preserved, facilitating the diagnosis. Such changes are most common in nodular and rarely superficial variants.

## *Adenoid Basal Cell Carcinoma*

Adenoid, also known as the reticulated or pseudoglandular pattern may be seen in an otherwise typical nodular BCC. The characteristic histologic feature is growth of basaloid cells encircling mucinous stroma, resulting in multiple mucin-filled gland-like spaces (Fig. 3.15).

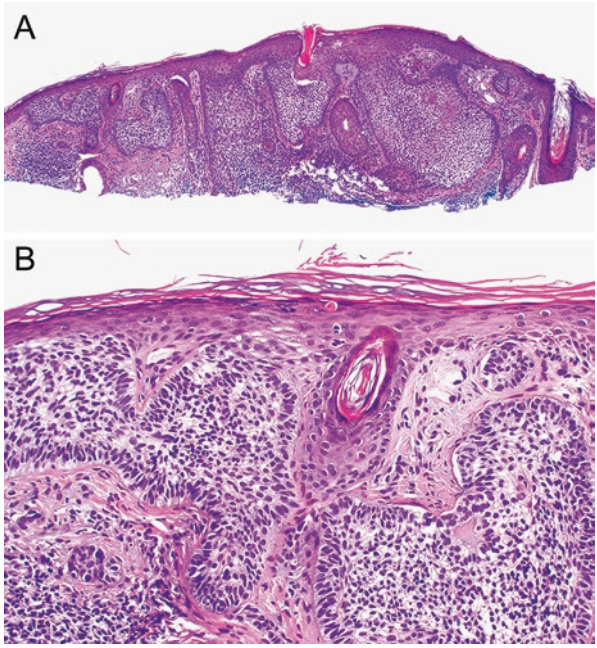



**Fig. 3.14** Clear cell basal cell carcinoma. (**a**) Basal cell carcinoma with superficial and nodular patterns of growth with diffuse clear cell changes (Hematoxylin and eosin, original magnification: 40×). (**b**) Peripheral palisading and peritumoral clefting are typically preserved in addition to rare apoptotic bodies and mitotic figures (Hematoxylin and eosin, original magnification: 200×)

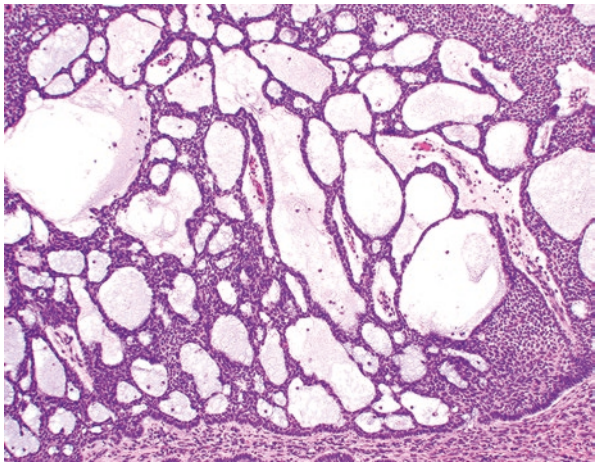


**Fig. 3.15** Adenoid basal cell carcinoma composed of reticulated proliferation of thin basaloid cords encircling mucinous material resulting in pseudoglandular appearance (Hematoxylin and eosin, original magnification: 100×)

## *Pleomorphic Basal Cell Carcinoma*

Occasionally, some of the tumor cells may be large with prominent nuclear pleomorphism, hyperchromasia, hyperlobation, and even multinucleation, also known as the so-called "monster" cells (Fig. 3.16) [38]. They are typically surrounded by otherwise typical cuboidal tumor cells with basaloid features. In rare instances, these

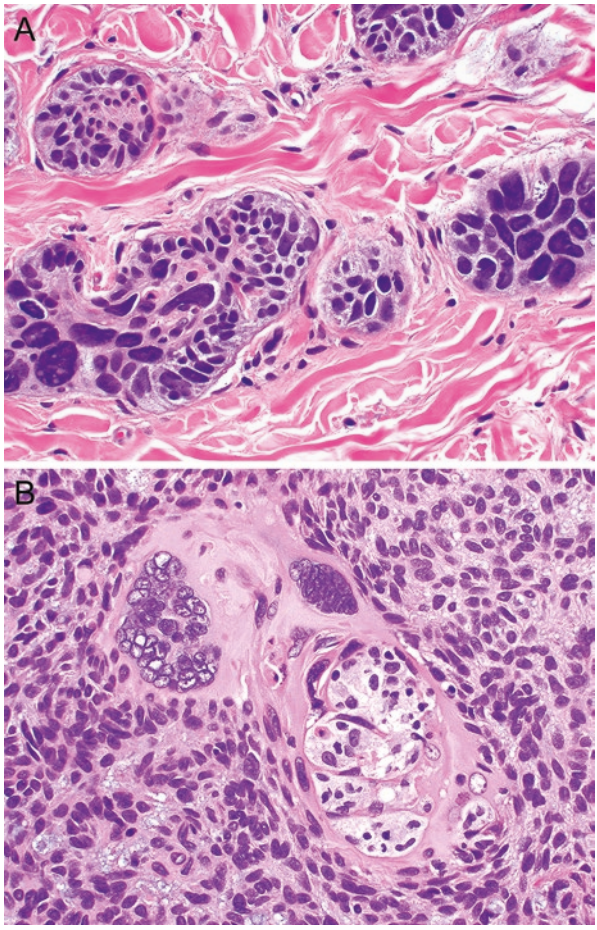



**Fig. 3.16** Pleomorphic basal cell carcinoma (**a**) characterized by large cells with atypical variably shaped hyperchromatic nuclei (Hematoxylin and eosin, original magnification: 400×). (**b**) Pleomorphic cells may be restricted to areas of squamous differentiation (Hematoxylin and eosin, original magnification: 400×)

changes may be restricted to areas of squamous differentiation. These histomorphologic features have been shown to be unrelated to ancient or senescent changes [39]. The pleomorphic cells are characterized by aneuploidy [40]. However, there is no correlation with prognosis.

## *Keratotic Basal Cell Carcinoma*

This uncommon variant is characterized by the presence of squamous differentiation and variably sized horn pseudocysts in association with nests of basaloid cells, typical of BCC (Figs. 3.4 and 3.17) [41]. This variant has significant morphologic overlap with TE/TB.

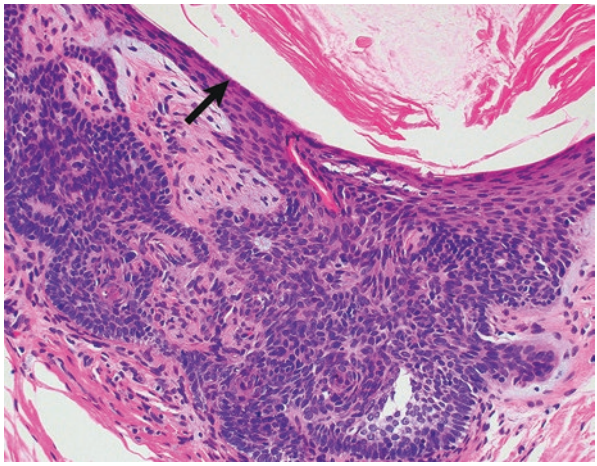


**Fig. 3.17** Keratotic basal cell carcinoma, with a large horn pseudocyst (arrow). (Distinction from trichoepithelioma can be challenging. Hematoxylin and eosin, original, magnification: 200×)

## *Basal Cell Carcinoma with Matrical Differentiation*

While follicular differentiation may be seen in certain variants of BCC, recapitulation of pilomatrical differentiation is extremely unusual [42]. The lesions are typically located in sun-exposed skin of the head and neck, followed by trunk and limbs [43]. The lesion displays foci of matrical differentiation admixed with otherwise typical BCC, which is often the predominant component. Matrical differentiation may manifest most commonly as shadow/ghost cells (Fig. 3.18) or matrical/supramatrical cells; infrequently as trichohyaline granules or blue-gray corneocytes or a variable combination of these features [43]. In majority of the cases, the matrical component is cytologically benign; however, in rare cases, significant pleomorphism may be seen in the matrical component of the tumor. Immunohistochemical studies may be needed to confirm, particularly in cases with preponderance of matrical component; nuclear localization of β-catenin is typically absent or minimal in BCC with matrical differentiation, while nuclear β-catenin is diffuse in true pilomatrical neoplasms [43, 44]. Focal rupture and granulomatous lymphohistiocytic infiltrate may be present.

## *Basal Cell Carcinoma with Ductal Differentiation*

While follicular differentiation in BCC is fairly frequent, true recapitulation of glandular characteristics is unusual. Rarely, entrapment of pre-existing eccrine ducts may be noted. Whereas, proliferation of ductal structures as part of the neoplasm is

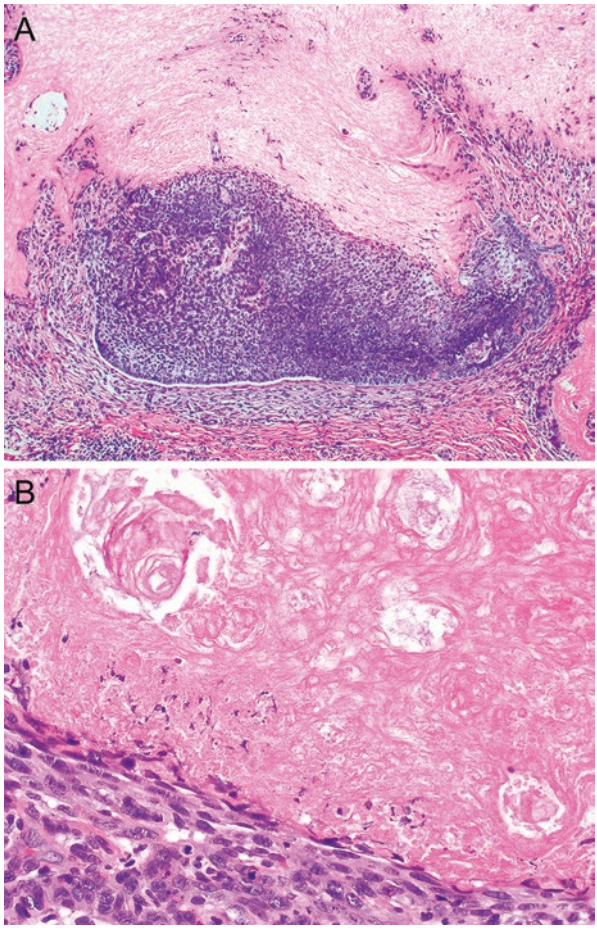



**Fig. 3.18** Basal cell carcinoma with matrical differentiation. (**a**) Typical basal cell carcinoma with clefting, peritumoral myxoid stroma, and abundant ghost cell differentiation (Hematoxylin and eosin, original magnification: 100×). (**b**) Pilomatrical differentiation with abrupt transition of basaloid tumor to ghost cells (Hematoxylin and eosin, original magnification: 400×)

an uncommon phenomenon (Fig. 3.19) [45]. The head and neck skin, particularly that of eyelid, appears to have a predilection for developing these tumors. Glandular differentiation is relatively more frequent in women. Eccrine and apocrine differentiation has been reported in association with BCC.

## *Metaplastic Basal Cell Carcinoma*

Metaplastic BCCs are characterized by combined proliferation of epithelial and stromal elements, both of which are malignant, i.e., primary cutaneous carcinosarcomas with BCC as their epithelial component [46]. These are rare rapidly growing tumors

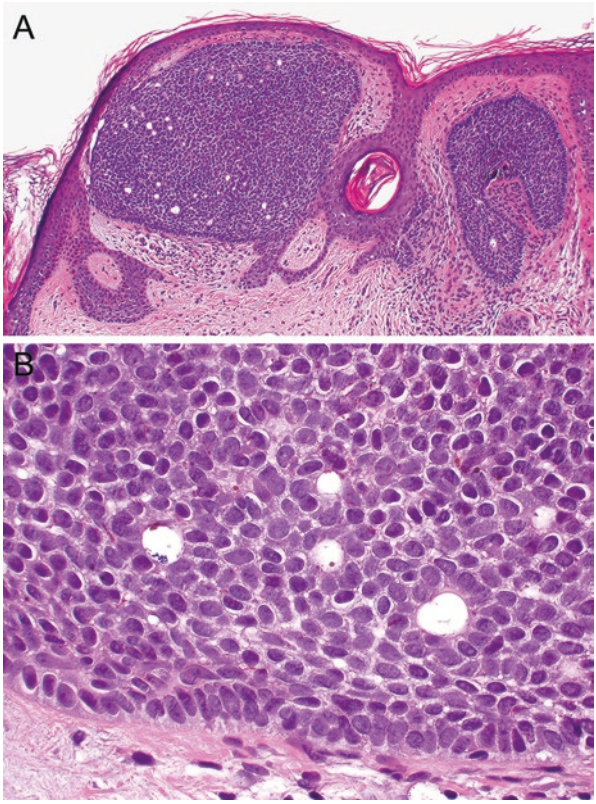



**Fig. 3.19** Basal cell carcinoma with ductal differentiation. (**a**) Typical nodular basal cell carcinoma with peritumoral myxoid stroma displaying several ductal structures (Hematoxylin and eosin, original magnification: 100×). (**b**) Peripheral palisading and ductal structures (Hematoxylin and eosin, original magnification: 600×)

with aggressive behavior with high propensity for recurrence and metastasis [47]. The epithelial component can display nodular, infiltrative, or even fibroepithelioma of Pinkus-like morphology. Pleomorphic undifferentiated sarcoma is the most frequent malignant mesenchymal component and is characterized by hypercellularity of the stroma and atypical cells with pleomorphism, mitotic figures, and scattered multinucleated cells within the stroma (Fig. 3.20). Heterologous differentiation is uncommon, of which osteosarcoma is the most frequent type [48]. The epithelial and stromal components overexpress p53 and p16 [47] and may have identical copy number variations and loss of heterozygosity patterns [49].

## High-Risk Features

Of the various types of BCC, those with infiltrative, morpheaform, micronodular, and keloidal growth patterns are associated with aggressive behavior [50, 51]. Metatypical BCC with atypical squamous component and metaplastic BCC with sarcomatous components are also prone to recurrence and metastasis and thus, a worse prognosis. Certain anatomic locations, in particular mid-face and ears, are

common sites of recurrence [52, 53]. Long-standing or advanced lesions and those arising in radiation fields tend to behave aggressively [54]. Recurrence after prior surgical resection is also a poor prognostic factor. Tumor size greater than 2 cm is associated with poor outcome; in particular, tumor size greater than 5 cm is associated with 25% increase in the risk for metastasis [55, 56]. Acquired immunosuppression and presence perineural or lymphovascular invasion also enhances the risk for metastasis [57–59].

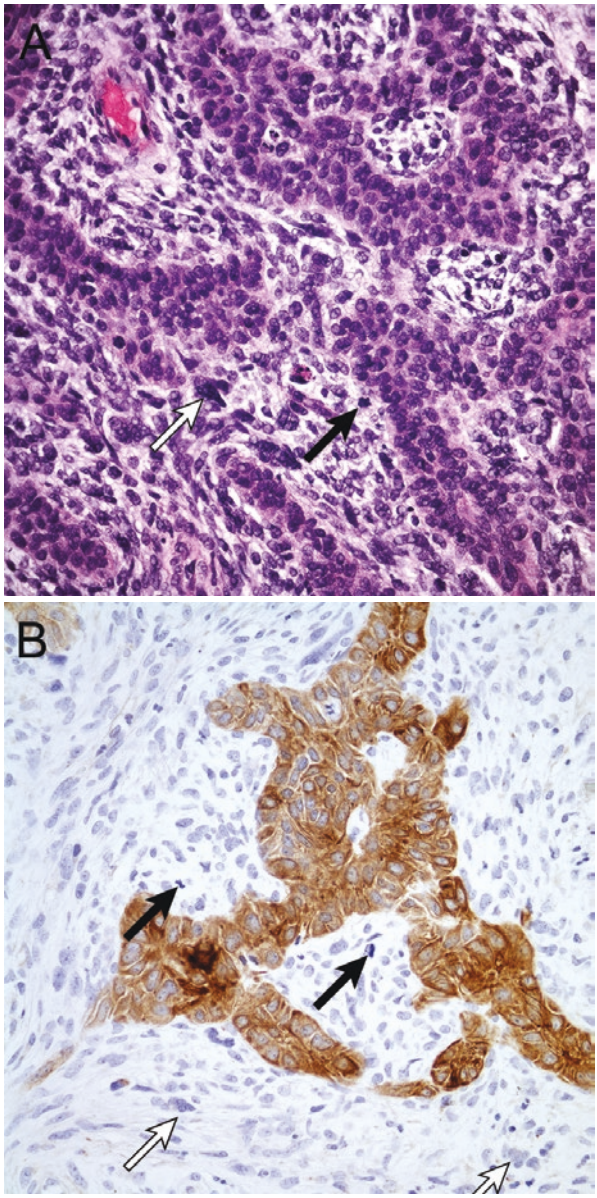
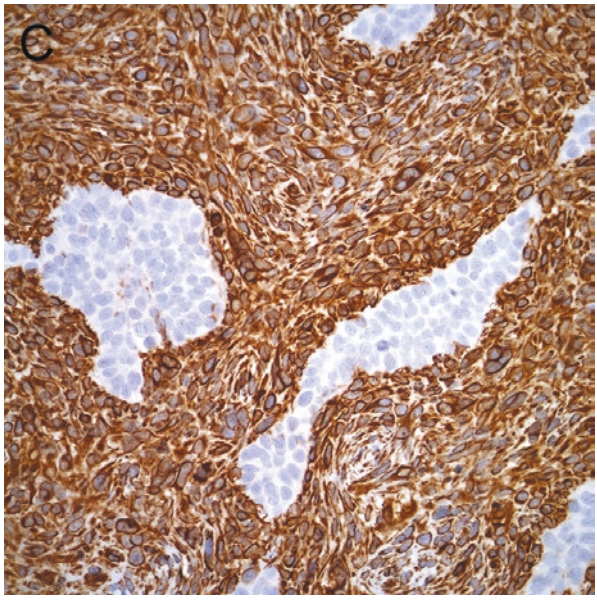



**Fig. 3.20** Basal cell carcinosarcoma. (**a**) Infiltrative proliferation of elongated and irregularly shaped nests of basaloid cells surrounded by hypercellular stroma with atypical cells, consistent with undifferentiated pleomorphic sarcoma (Hematoxylin and eosin, original magnification: 400×). (**b**) Cytokeratin AE1/AE3 immunohistochemical study highlights the malignant epithelial component. Mitotic figures (black arrows) and multinucleated cells (white arrows) (Anti-cytokeratin AE1/AE3, original magnification: 400×). (**c**) Vimentin immunohistochemical study highlights the malignant mesenchymal component (Anti-vimentin, original magnification: 400×)

**Fig. 3.20** (continued)

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# Chapter 4
# Topical Therapy for the Treatment of Basal Cell Carcinoma


**Natalie Kash and Sirunya Silapunt**

## Introduction

The National Comprehensive Cancer Network (NCCN) identifies risk factors for recurrence in basal cell carcinoma (BCC). Locations are stratified by risk. High-risk locations include the "mask areas" of the face (central face, eyelids, eyebrows, periorbital area, nose, lips, chin, mandible, preauricular and postauricular areas, and ears), genitalia, hands, and feet. Medium-risk locations are the cheeks, forehead, scalp, neck, and pretibia [1]. Low-risk sites are the trunk and extremities excluding the ankles and sites included in high- and medium-risk locations as above [1]. High-risk features include location in a high-risk area; size ≥10 mm in a medium-risk location; size ≥20 mm in a low-risk location; poorly defined borders; recurrent BCC; history of immunosuppression; history of prior radiotherapy (RT) at the site; presence of an aggressive growth pattern on histology including morpheaform, basosquamous, sclerosing, mixed, infiltrative, or micronodular features in any part of the tumor; and perineural involvement [1]. The absence of the aforementioned high-risk features and histology showing superficial or nodular features characterize low-risk BCCs.

Surgical therapy (ST), including surgical excision (SE) and Mohs micrographic surgery (MMS), has become the mainstay of BCC treatment in those who can tolerate surgery given increased efficacy, lower recurrence rate (RR), and the ability to postoperatively evaluate margins. In fact, the NCCN 2018 Clinical Practice Guidelines in Oncology for BCC recommend electrodesiccation and curettage (ED&C) in non-hair-bearing areas, standard excision with 4 mm clinical margins with postoperative margin assessment, or RT for nonsurgical candidates as primary treatment options for low-risk BCCs. For the primary treatment of high-risk BCCs,

N. Kash · S. Silapunt (✉)
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA
e-mail: Sirunya.Silapunt@uth.tmc.edu



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_4

the NCCN guidelines include MMS, surgical resection with complete circumferential margin assessment, standard excision with wider surgical margins and postoperative margin assessment, and RT for nonsurgical candidates as treatment options [1]. However, it is important to consider individual patient factors such as comorbidities, patient preferences, tumor features, risks of treatment, cosmesis, and function in deciding a treatment modality for BCC that is appropriate for the individual tumor and patient at hand. In those who are not ideal surgical candidates, there are a number of nonsurgical therapies. Nonsurgical treatment options for BCC include topical therapy (which will be included in this chapter), cryotherapy (CT), ED&C, photodynamic therapy (PDT), and laser therapy (LT) (see Chaps. 6, 11, and 12). The NCCN recommends that topical therapies, CT, and PDT be considered in cases of low-risk, superficial BCCs in patients where ST and RT are contraindicated or impractical [1]. Additional nonsurgical treatment options including RT, intralesional therapy, and systemic therapy such as targeted therapy and immunotherapy will be discussed in other chapters (see Chaps. 10, 5, 13, and 14).

## Background

Topical treatments including 5% imiquimod cream, 5% 5-fluorouracil (5-FU) cream, and ingenol mebutate (PEP005) gel are treatment options in the treatment of superficial BCCs. Topical 5-FU 5% cream or solution and 5% imiquimod cream are FDA-approved for the treatment of superficial BCCs in addition to actinic keratoses (AKs) [2, 3]. Topical 5-FU is also available as a 2% cream or a 0.5% controlled-release microsphere formulation for the treatment of AKs; however, these formulations have not been well-studied and are not FDA-approved for the treatment of BCCs [4]. Ingenol mebutate gel is currently only FDA-approved for the treatment of AKs but has also been studied in the treatment of superficial BCCs [3]. The most recent NCCN guidelines list topical therapy, including topical imiquimod cream and topical 5-FU cream, as appropriate treatment options along with other superficial therapies such as CT and PDT in cases of low-risk, superficial BCCs where ST and RT are not appropriate [1].

## Mechanism of Action

### *Imiquimod*

Imiquimod, a member of the imidazoquinoline family, is a nucleoside analogue which mainly acts as an immunomodulator [5]. The mechanism of action of imiquimod which has been the most well-described is its activity as an agonist of both Toll-like receptor (TLR)-7 and TLR-8 [5]. The TLR activity leads to the phosphorylation of inhibitory κB leading to the induction of transcription of a number of genes for

both pro-inflammatory cytokines including tumor necrosis factor α (TNF-α), interferon α, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, interleukins (ILs) 2, 6, 8, and 12, and chemokines [5–10]. This leads to the activation of cells of both the innate immune system and the adaptive immune system, mainly through the activation of Th1 T-helper cells with inhibition of the Th2 immune response [11, 12]. In addition, imiquimod has been shown to lead to the activation of cytotoxic, CD8+ T-cells [13–16].

Other downstream effects of imiquimod that contribute to its antitumor effects include activation of natural killer (NK) cells, induction of perforin in cytotoxic CD8+ T-cells, decreased adenosine receptor signaling pathway activity, and activation of apoptosis [5, 17–21]. Finally, imiquimod has been shown to potentially have a pro-apoptotic effect through caspase activation and the production of B-cell lymphoma/leukemia protein-2 proteins [5, 21–23]. Thus, taken together, imiquimod has antitumor activity through immunomodulation, largely through TLR-7 and TLR-8 signaling, as well as through multiple other potential mechanisms such as induction of apoptosis [5].

## *5-Fluorouracil*

The fluorinated pyrimidine, 5-FU, is a uracil analogue with fluorine. The fluoropyrimidine destabilizes deoxyribonucleic acid (DNA) mainly by blocking the production of thymidine monophosphate through the inhibition of thymidylate synthase and through metabolite misincorporation into DNA and ribonucleic acid (RNA) [24]. Thymidine is required for DNA replication and repair, and rapidly dividing cells, such as tumor cells, require more thymidine and are more sensitive to the effects of 5-FU [24, 25]. The 5-FU metabolite, fluorodeoxyuridine monophosphate, combines with 5,10-methylene tetrahydrofolate and thymidylate synthase forming a stable complex, which results in inhibition of thymidylate synthase [24, 26, 27].

Additionally, there are pathways independent of the thymidylate synthase pathway involved in the cellular damage caused by 5-FU [24]. For example, decreased deoxythymidine monophosphate leads to decreased deoxythymidine triphosphate, which changes levels of the other three deoxynucleotides through feedback loops [28]. Alterations in deoxynucleotide ratios interfere with DNA synthesis and repair leading to DNA damage and cell death [29, 30]. Additionally, metabolites of 5-FU misincorporate into DNA and RNA leading to disruption in DNA and RNA formation [24, 31–36].

Aside from effects on DNA and RNA, there may also be immunologic effects of topical 5-FU. A study by Mansell et al. found that 11/15 patients with skin cancers including BCCs not previously treated with 5-FU developed a delayed hypersensitivity reaction to 5-FU with conversion from negative skin testing to positive skin testing after treatment and that this positively correlated with cure [37]. The authors hypothesized that topical 5-FU may trigger an immune response against these cells and that this immunologic effect may also play a role in the anti-cancer activity of 5-FU [37].

A number of studies have investigated changes in BCCs with topical 5-FU therapy on light and electron microscopy [38–41]. Hodge et al. performed sequential biopsies in a single case of superficial BCC before, during, and after treatment with topical 2% 5-FU under occlusion and reported a number of histologic and ultrastructural changes only in the tumor cells and neighboring keratinocytes, not in unaffected cells [41]. These changes included disruption of the basal lamina, loss of keratinocyte adhesion, vesicle formulation, reduction in the number of tonofilaments, degeneration of mitochondria, nuclear hyperchromatism and pleomorphism, increased mitoses, a lymphohistiocytic infiltrate, and eventual tumor cell death [41].

More recently, 5-FU has been shown by in vitro studies to increase the expression of the tumor suppressor gene, p53, which is thought to thereby lead to cell cycle arrest and apoptosis [25, 42–46]. The metabolism of 5-FU mostly occurs in the liver, and 5-FU is catabolized to dihydrofluorouracil by the enzyme, dihydropyrimidine dehydrogenase (DPD) [24, 47].

Selectivity of 5-FU for rapidly proliferating premalignant and malignant cells over normal cells has been observed in a number of studies and is thought to be secondary to the higher demand for DNA, RNA, and thus pyrimidine in these cells [24, 25, 48–50].

## *Ingenol Mebutate*

Ingenol mebutate, also known as ingenol-3-angelate and PEP005, is a diterpene ester derived from the sap of *Euphorbia peplus* known to induce cell death and cause tissue damage [51, 52]. Ingenol mebutate is thought to lead to tumor destruction initially through primary necrosis and later through protein kinase C (PKC) activation and stimulation of an immune response [53, 54]. The immediate effects of ingenol mebutate include plasma membrane damage resulting in mitochondrial swelling and dysfunction and cell death [53].

In tumor cells treated with ingenol mebutate, the initial cytotoxicity is followed by immune stimulation [53, 54]. Ingenol mebutate has been shown to activate the classic and novel PKCs leading to decreased cell proliferation and increased secretion of the pro-inflammatory cytokine IL-6 [53, 55–58].

Further, it is hypothesized that PKC activation leads to neutrophil influx in ingenol mebutate-treated skin [54, 59–61]. Neutrophil activity was demonstrated by Challacombe et al. to be a key in preventing tumor relapse in treatment with ingenol mebutate [54]. Ingenol mebutate was shown to increase levels of IL-8 and TNF-α and activate vascular endothelial cells resulting in neutrophil binding and activation [54]. The authors additionally found that T-cells, NK cells, and macrophages do not appear to be necessary in the immune response triggered by ingenol mebutate required for sustained tumor clearance [54].

More recently, Li et al. demonstrated that ingenol mebutate is able to penetrate through the epidermis and dermis and cause subepidermal and subcutaneous hemorrhage in mice [62].

## Efficacy

### *Imiquimod*

There have been prospective studies of imiquimod 5% cream for the treatment of BCCs. These include a prospective, multicenter study by Quirk et al. out of Australia and New Zealand that evaluated 5% imiquimod cream (once daily for 6 weeks) for the treatment of primary, biopsy-proven superficial BCCs (≥0.5 $cm^2$ in area, ≤2.0 cm in diameter) [63]. They reported a 12-week cure rate (CR) of 94.1% (159/169) [63]. The 5-year sustained CR (of those who were initially noted to respond at 12-week follow-up) was 85.4% [95% CI 79.3–91.6%]. They noted no serious adverse events that were thought to be related to treatment [63]. The authors noted that these CRs were lower than studies of SE for BCC [63].

A European multicenter prospective study followed patients with biopsy-proven superficial BCCs (area >0.5 $cm^2$, diameter ≤2.0 cm) treated with 5% imiquimod cream (once daily, 5 times per week, 6 weeks) for 5 years [64]. They reported a 12-week CR of 90% (163/182) and found the 5-year CRs among initial responders to be 84.5% and 86.9% when calculated by the Kaplan-Meier method and the life-table method, respectively [64]. They found the 5-year overall treatment success rate to be 77.9% [64].

A small, prospective study from the ophthalmology literature by Prokosch et al. evaluated the long-term (7-year) clinical clearance of five biopsy-proven nodular BCCs located on the eyelid treated with 5% imiquimod cream (5 times weekly, 6 weeks) [65]. They noted a 0% RR in 4/5 patients [65]. One patient did not tolerate imiquimod and declined to continue [65]. The authors concluded that imiquimod may be an effective treatment option for nodular BCCs located on the eyelid, but larger and randomized studies were required to better evaluate efficacy (see section "Comparative Studies") [65].

The efficacy rates of imiquimod in the treatment of BCC reported by these prospective non-randomized studies vary and may reflect differences in the treatment regimen of application in addition to other factors such as tumor characteristics, patient characteristics, and the statistical methods used in calculating the clearance and RRs. It is difficult to accurately compare these published efficacy rates to efficacy rates from non-comparative studies of other treatment modalities for BCC given variation in the factors listed above.

A systematic review by Love et al. included prospective studies, retrospective studies, and case studies on topical imiquimod cream and topical 5-FU cream for the treatment of BCC and squamous cell carcinoma (SCC) with a minimum of four subjects and minimum of 6-month follow-up [66]. The systematic review included 15 studies with 1482 tumors on imiquimod for superficial BCCs, 11 studies with 438 tumors on imiquimod for nodular BCCs, 1 study with 43 tumors on imiquimod for infiltrative BCCs, 1 study with 31 tumors on 5-FU for superficial BCCs, and no studies on 5-FU for nodular or infiltrative BCCs [66]. They reported CRs for imiquimod of 43–100%, 42–100%, and 56–62% for superficial, nodular, and infiltrative

BCCs, respectively [66]. This was compared to the CR of 90% for 5-FU for superficial BCCs [66]. The authors noted that there was variation in the treatment regimen of application and lack of long-term follow-up in the studies included [66]. However, since that time randomized controlled trials comparing topical 5-FU and imiquimod in the treatment of superficial BCC have been published (see section "Comparative Studies") [67–69].

A systematic review and meta-analysis by Roozeboom et al. included both randomized and non-randomized trials from 1946 to 2010 with a minimum follow-up of 12 weeks of different treatment modalities for primary, superficial BCCs and found no statistically significant difference in either the 12-week CR or 1-year tumor-free survival between imiquimod and PDT (see section "Efficacy" in Chap. 11) [70]. Of note, a randomized controlled trial directly comparing imiquimod, 5-FU, and PDT had not been published at this time and, thus, was not included in the meta-analysis; however, since that time there have been a number of randomized controlled trials comparing imiquimod cream to vehicle cream as well as to other treatment modalities including SE, PDT, and topical 5-FU (see section "Comparative Studies") [67–69, 71, 72]. Figure 4.1 demonstrates an example of imiquimod treatment of a BCC.

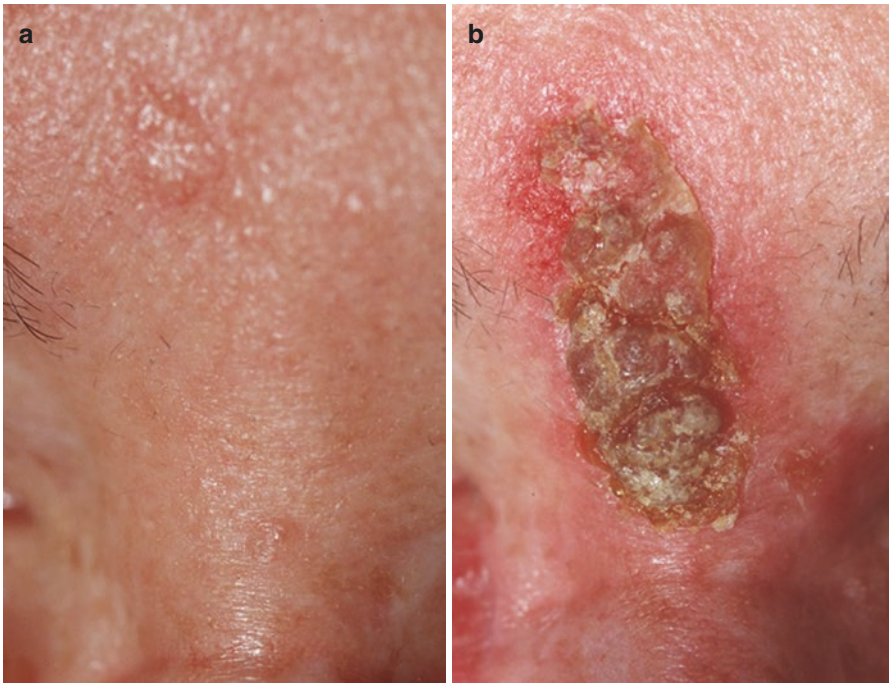
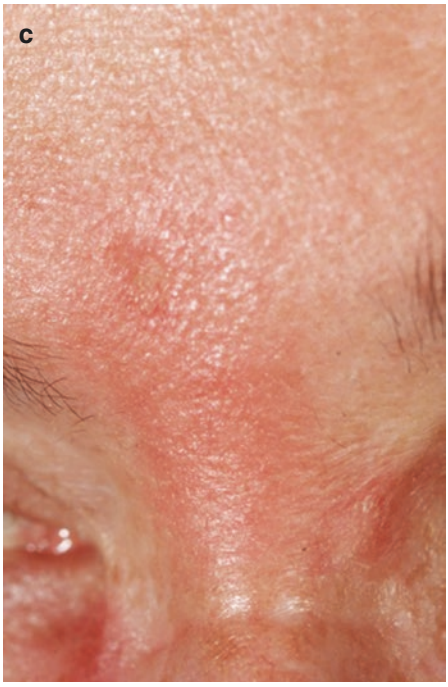



**Fig. 4.1** A nodular BCC located on the glabella before treatment with imiquimod cream (**a**), during treatment with an inflammatory reaction (**b**), and resolution of the lesion after treatment (**c**). (Photos courtesy of Reinhard Dummer, MD)

**Fig. 4.1** (continued)




## *5-Fluorouracil*

Topical 5-FU was described as effective for the treatment of clinical and subclinical multiple superficial BCCs with minimal to no scarring even when applied to a large body surface area (<50%) as early as the 1960s and 1970s [73]. Stoll et al. in their 1967 study investigated the efficacy of topical 0.005–20% 5-FU for multiple superficial BCCs and found that topical 0.005–0.5% 5-FU had low rates of tumor clearance [74]. The same group in a series of 20 patients by Klein et al. noted CRs of >80% for 5% 5-FU and 20% 5-FU, and they found no significant difference in CRs for 20% 5-FU versus 5% 5-FU with more localized skin reactions and scarring with the 20% preparation [74]. Thus, the group largely investigated topical 5% 5-FU in future studies [73]. The authors did note lesions resistant to 5% or 20% 5-FU which resolved with 30% 5-FU applied daily under occlusion for up to 3 months [73]. The authors reported that based on their data from 31 patients with multiple superficial BCCs treated with 1–30% 5-FU, the rate of tumor resolution was >80% [73]. They noted that most adverse events were localized skin reactions, and they found no evidence of systemic toxicity clinically or based on laboratory evaluation [73]. They did not note the development of resistance to topical 5-FU after multiple courses of treatment, but they did report earlier and more intense localized skin reactions at the treatment site with second or multiple treatments in some patients [73].

The FDA approved 5% 5-FU cream or solution for the treatment of superficial BCCs following a study of superficial BCCs showing a 93% treatment success rate after treatment with topical 5% 5-FU cream or solution for an average treatment period of 6 weeks [2]. The study included 113 tumors in 52 patients treated with either 5% 5-FU cream or solution and reported an overall treatment success rate of 92.9% (105/113) with a 96.0% (24/25) success rate in patients treated with the solution and a 92.0% (81/88) success rate in patients treated with the cream [2].

Later, a prospective, non-randomized, study by Gross et al. evaluated the CR of topical 5-FU cream for the treatment of biopsy-proven superficial BCCs on the trunk and extremities [75]. These tumors were treated with 5% 5-FU cream twice daily for up to 12 weeks or stopped sooner if clinical resolution was achieved [75]. This was followed by SE at 3 weeks after the completion of treatment for histopathologic evaluation which showed a histologic CR of 90% [75]. The mean time to clinical cure was 10.5 weeks, highlighting that longer treatment courses of 5% 5-FU cream may be needed than those often used in other studies (often 4–6 weeks) (see section "Comparative Studies") [75].

The systematic review by Love et al. (see subsection "Imiquimod" in section "Efficacy" for details) found a CR of 90% with topical 5-FU versus 43–100% with imiquimod for superficial BCCs [66]. There were no studies included on topical 5-FU for nodular or infiltrative BCCs [66].

Special considerations in the treatment of superficial BCCs with topical 5-FU are multifocal and extensive superficial BCCs. There are limited reports specifically on the treatment of multifocal and extensive superficial BCCs with topical 5-FU. For example, van Ruth and Jansman reported two patients with extensive BCCs treated with total body application of topical 5% 5-FU with clearance of the majority of these lesions [76]. One patient had a history of extensive light therapy for mycosis fungoides and was treated with topical 5% 5-FU 2 times per week with 20 grams applied with each application for a total of 4 weeks [76]. The other patient had a history of nevoid BCC syndrome and was treated with topical 5% 5-FU twice daily for 6 weeks with 6.5 grams with each application. They measured systemic absorption and found that 5-FU levels were undetectable (<10 μg/L) in all samples [76]. They concluded that totally body application of topical 5% 5-FU may be a safe and appropriate treatment option for the majority of lesions in patients with extensive multifocal superficial BCCs [76]. Naik et al. described a patient with multifocal BCCs with six areas of biopsy-proven superficial BCCs located on the face treated with topical 5% 5-FU ointment twice daily (except the lesion on the lid margin) for an unspecified duration with no recurrence at 6-month post-treatment [77]. The authors concluded that topical 5-FU may be a treatment option in multifocal superficial BCCs located on the face (not on the lid margin) where ST may be disfiguring [77]. Of note, the NCCN recommends limiting the use of topical 5-FU to superficial BCCs with low-risk features including low-risk locations [1]. However, larger prospective studies and comparative studies are needed to investigate the efficacy and safety of topical 5-FU cream for the treatment of multifocal superficial BCCs, including those located on the face, and of total body topical 5-FU cream for the treatment of extensive superficial BCCs.

Epstein reported RRs for topical 25% 5-FU cream alone and topical 25% 5-FU cream preceded by light curettage for the treatment of clinically "thin" BCCs, with seven known biopsy-proven nodular BCCs [78]. Topical 5-FU was applied weekly under occlusion for a total of 3 weeks in both groups [78]. He reported a 5-year cumulative RR of 21% in the topical 5-FU alone group and 6% in the topical 5-FU preceded by curettage group [78]. He reported good to excellent cosmetic results in >80% of patients in both groups [78]. He concluded that topical 5-FU with curettage has an acceptable RR, and the higher RR of this study compared to other studies for superficial BCCs may reflect inclusion of non-superficial BCCs (such as the seven known nodular BCCs) and 5-FU cream being applied only once weekly [78].

The efficacy of topical 5-FU for superficial BCC has generally been described as acceptable as above; however, topical 5-FU is not recommended for the treatment of deep BCCs, such as nodular or infiltrative tumors, given lower efficacy and the potential to treat only superficial portions of the tumor thereby concealing and preventing detection of deep tumor persistence and growth.

A preliminary placebo-controlled study by Klein et al. comparing a number of topical agents in the treatment of nodular BCC did not allow determination of long-term RRs given that all tumors were excised at 1-month post-treatment (see subsection "5-Fluorouracil" in section "Comparative Studies") [79]. The same group performed a non-randomized prospective study of 36 biopsy-proven nodular BCCs treated with 20% 5-FU under occlusion applied daily for 1 month [80]. Patients had a biopsy at 1-month post-treatment to evaluate for tumor with a repeat course of topical 5-FU in patients found to have persistent tumor [80]. They were then followed monthly for 20 months with any persistent tumor treated with the most appropriate treatment such as ST, ED&C, or RT [80]. The CR following one course of 5-FU at 1-month post-treatment was 66.7% (24/36) [80]. They found that 6 of the 24 BCCs initially found to have no evidence of persistent BCC clinically or histologically at 1-month post-treatment then showed evidence of tumor in the next 3–10 months with a 20-month CR of 50% (18/36) [80]. The authors found no statistically significant correlation between tumor resolution and patient age, tumor size, or tumor location [80]. The authors concluded that topical 5-FU has lower CRs and higher RRs than standard BCC therapies and was not an appropriate treatment for nodular BCCs [80].

Similarly, Reymann reported data from a prospective non-comparative trial investigating the RR of 95 nodular BCCs treated with 5% 5-FU ointment from 1966 to 1968 with 10-year follow-up [81]. The authors reported a 10-year RR of 21.4% (12/56) and concluded that topical 5-FU alone is in not an appropriate treatment for nodular BCC given its high RR [81].

The concerns regarding undetected deep growth with deep BCCs treated with topical 5-FU are based largely on a report by Mohs et al. of 103 patients with recurrent, invasive BCCs following treatment with topical 1–5% 5-FU cream for 1–5 weeks subsequently treated with MMS [82]. Of note many of these patients' tumors were recurrent after treatment with another treatment modality such as ST, RT, ED&C, or CT [82]. They noted that in almost one fourth of the cases, there was no evidence of recurrence based on clinical exam of overlying skin with nodularity

noted only with deep palpation in many cases [82]. This apparent clearance superficially with deep persistence and growth of tumor following treatment with topical 5-FU was further supported by histologic examination in many of these cases with scar and no tumor noted in superficial levels, tumor noted in the deep dermis or subcutis, and extension of many tumors past the clinical tumor borders in deep planes of the deep dermis or along fascia, nerves, periosteum, or perichondrium [82].

Thus, topical 5-FU is only recommended as a potential treatment in low-risk, primary, superficial BCCs in which ST is contraindicated or not appropriate. Of note the efficacy of topical 0.5% 5-FU cream has not been well-studied for the treatment of BCCs.

A number of formulations and techniques have been described in efforts to increase the permeability and tissue penetration of topical 5-FU cream. These have included the addition of nanoparticles to cream formulation, microneedling prior to application, and occlusion with application [83–85].

Hadjikirova et al. followed 32 patients with biopsy-proven superficial BCC treated with 5-FU with a polybutylcyanoacrylate nanocarrier (applied once daily for 35–40 days) [85]. The authors found a histologically confirmed complete response rate (CRR) of 96.9% (31/32) [85]. The authors evaluated for evidence of systemic absorption and effects on the immune system and found no significant difference in treated patients versus healthy controls [85]. They concluded that treatment with topical 5-FU with polybutylcyanoacrylate as a nanoparticle drug carrier system was a potentially effective and well-tolerated treatment option for superficial BCCs [85]. However, long-term follow-up studies allowing determination of long-term RRs and comparative studies are still needed to further investigate 5-FU cream with nanoparticle drug carriers.

Microneedling has been shown to increase skin permeability to molecules of varying sizes including nanoparticles by creating holes in the stratum corneum [84, 86–90]. Naguib et al. performed an in vitro study in a mouse model to investigate the effects of microneedling on 5-FU tissue penetration [90]. They treated one group with microneedling (500 μm length and 50 μm base diameter) and the other with no microneedling [90]. Topical 5-FU was then applied in both groups, and tissue permeability was measured [90]. The authors reported 4.5 times higher 5-FU permeability in the microneedling group compared to the no microneedling group and concluded that microneedling may be useful in treating skin tumors [90]. Of note, prospective and comparative studies are still needed in human BCCs to evaluate the efficacy of 5-FU with microneedling.

Topical 5-FU cream under occlusion has also been studied. Stoll and Klein in 1969 performed a small prospective study of seven patients with multiple superficial BCCs [91]. They selected four similar biopsy-proven superficial BCCs from each patient to produce two sets of pairs in each patient (with and without occlusion with 5% 5-FU cream and with and without occlusion with 20% 5-FU cream) to allow for determination of the effect of occlusion on the efficacy of topical 5-FU cream [91]. In all groups 5-FU was applied daily for 2 weeks, and histologic evaluation was performed at 4 weeks after treatment [91]. The histologic CRs were 71.4% (5/7), 42.9% (3/7), 85.7% (6/7), and 57.1% (4/7) in the 5% under occlusion,

5% without occlusion, 20% under occlusion, and 20% without occlusion groups, respectively [91]. The localized adverse events including local ulceration were highest in the occlusion groups (similar between the 5% and 20% 5-FU cream under occlusion groups) [91]. The authors found that histologic CRs were statistically significantly higher in the occlusion versus non-occlusion groups for both 5% and 20% 5-FU creams [91]. They concluded that although occlusion is associated with higher rates of localized adverse events, it increases the efficacy of topical 5-FU cream in the treatment of superficial BCCs [91].

Additionally, a study by Fang et al. reported increased permeability of skin to topical 5-FU with iontophoresis, electroporation, and 2940 nm erbium-doped yttrium aluminum garnet (Er:YAG) laser [92]. They found that electroporation disrupted the stratum corneum and permeability was higher with iontophoresis and electroporation combined than either disruptive technique alone [92]. Ablation with Er:YAG laser had higher permeability to 5-FU than iontophoresis or electroporation, and the permeation was further increased when combined with iontophoresis [92]. See section "Combination Therapies" for a prospective non-randomized study by Nguyen et al. further investigating the utility of ablative laser treatment (carbon dioxide in that study) combined with topical 5-FU for the treatment of BCCs [93].

## *Ingenol Mebutate*

There are a number of case reports and case series reporting successful treatment of BCCs with ingenol mebutate, while larger prospective and comparative studies with long-term follow-up are limited for this relatively new topical agent in the treatment of BCC.

For example, *E. peplus* sap was reported as a home remedy for the treatment of skin cancer including BCC [94, 95]. Ramsay et al. performed a prospective phase I/II study of *E. peplus* sap (100–300 μL applied once daily for 3 consecutive days) for the treatment of BCC, SCC, and SCC in situ [52]. The authors reported the long-term clinical response rate for superficial BCCs <16 mm in diameter to be 78% (7/9) [52].

The active ingredient from *E. peplus* sap was formulated as either a 0.05% or 0.015% gel, and further studies have investigated the safety and efficacy of ingenol mebutate gel. For example, Cantisani et al. reported successful treatment, based on 3-month post-treatment clinical evaluation, of a large, 4-cm, clinically superficial BCC located on the back of a patient treated with ingenol mebutate 0.05% gel applied twice on 2 consecutive days [96].

Later, Jung et al. reported a case of a 5.2 × 4.5 cm biopsy-proven superficial BCC on the forehead of an 84-year-old female treated with 2 cycles of topical ingenol mebutate 0.015% gel [97]. The first cycle of ingenol mebutate was applied once daily for 4 consecutive days [97]. A 10-week post-treatment biopsy showed residual tumor. The patient was then treated with a second course of ingenol mebutate 0.015% gel, and 10-week post-treatment clinical evaluation and biopsy showed no clinical or

histologic evidence of residual tumor [97]. The authors concluded that ingenol mebutate 0.015% gel may be an effective treatment option for superficial BCCs [97].

Bettencourt performed a retrospective chart review and reported a case series of seven patients with nine biopsy-proven superficial BCCs located on the trunk who refused ST and were treated with topical ingenol mebutate 0.05% gel [98]. In all lesions, ingenol mebutate was applied to the lesion and surrounding 0.5 mm margin once daily [98]. There was variability in the treatment regimen if ingenol mebutate was applied under occlusion (6 lesions) or not (3 lesions) and in the treatment duration (2 days for 1 lesion, 4 days for 2 lesions, 7 days for 6 lesions) [98]. The author reported that all of the nine sites had no clinical evidence of persistent tumor at 2–4-week post-treatment or at subsequent follow-ups with the longest follow-up period of 14 months [98]. Histologic clearance was confirmed by biopsy in six lesions [98]. The author in the discussion did note that there was one patient in the retrospective chart review who had no clinical evidence of tumor initially at short-term follow-up but later had clinical evidence of recurrence at a follow-up visit months later and was subsequently treated with surgery [98]. The author concluded that 0.05% imiquimod mebutate gel may be a safe and effective treatment option for superficial BCCs when ST is contraindicated or not desired by the patient but noted that the study was limited by small sample size, retrospective nature, and short follow-up period [98].

More recently dermoscopy and confocal microscopy have been reported in a case series and case report, respectively, as methods of determining outcome and monitoring for evidence of persistent or residual tumor [99, 100].

For example, a case series of four patients by Diluvio et al. reported on seven superficial BCCs treated with topical ingenol mebutate gel [99]. There were four biopsy-proven superficial BCCs (two on the head and neck, two on the trunk) and three clinically diagnosed superficial BCCs on the trunk. In all lesions dermoscopic features of superficial BCC were noted [99]. The lesions located on the head and neck were treated with 0.015% ingenol mebutate gel daily for 3 consecutive days, and those located on the trunk were treated with 0.05% ingenol mebutate gel daily for 2 consecutive days [99]. At 1-month and 6-month post-treatment, lesions were examined dermoscopically and histologically [99]. In 5/7 lesions there was no dermoscopic or histologic evidence of tumor at 1-month or 6-month post-treatment [99]. In 2/7 lesions, at 1-month follow-up there was dermoscopic evidence of residual tumor, and those two lesions underwent an additional treatment cycle [99]. There was no dermoscopic or histologic evidence of tumor at 1-month or 6-month follow-up following the second cycle of treatment in either of the two lesions [99]. The authors concluded that ingenol mebutate may be an effective and well-tolerated treatment option for superficial BCCs and that dermoscopy may be a useful tool in diagnosing superficial BCCs and monitoring for residual or recurrent tumor following treatment [99].

However, a case report by Manubens et al. reported the utility of hand-held reflectance confocal microscopy over dermoscopy in making the initial diagnosis of and assessing outcome for BCCs treated with ingenol mebutate [100]. They reported on a patient with a history of approximately 30 prior BCCs who presented with 31 suspected BCCs based on clinical and dermoscopic evaluation with reflectance confocal microscopy diagnostic of BCC in 26 of these lesions [100]. These 26 BCCs were

treated with ingenol mebutate 0.05% gel applied once [100]. At 6-week post-treatment, response was assessed based on a combination of clinical and dermoscopic exam showing a response to treatment in 50% (13/26) of lesions [100]. However, reflectance confocal microscopy at the same time point revealed evidence of persistent tumor in nine lesions in which clinical and dermoscopic exam failed to detect evidence of residual tumor. The authors reported a response rate of 15% (4/26) based on reflectance confocal microscopy and concluded that ingenol mebutate had limited utility in the treatment of BCC and that reflectance confocal microscopy may be a useful tool to allow diagnosis and monitoring for persistent tumor [100]. Of note, the BCCs in this patient were not specified in the report to be limited to superficial BCCs [100].

A prospective open-label study compared 0.05% ingenol mebutate gel with aluminum disk occlusion (27 patients), OpSite occlusion (24 patients), and no occlusion (24 patients) in the treatment of superficial BCCs located on the trunk and extremities [101–103]. The clinical and histologic CRs were determined 6 months after treatment completion [101–103]. There was variation in the treatment regimen [101–103]. Twenty-two of 27 patients (81%) in the aluminum disk occlusion group received 1 dose of ingenol mebutate. Nineteen of 24 patients (86%) in the OpSite disk group and 23 of 24 patients (96%) in the no occlusion group received 3 doses of ingenol mebutate [101–103]. The authors found 6-month clinical CRs of 74.1%, 75.0%, and 75% and histologic CRs of 70.4%, 37.5%, and 54.2% in the aluminum disk occlusion, OpSite occlusion, and no occlusion groups, respectively [101–103]. They concluded that occlusion with an aluminum disk may improve efficacy of ingenol mebutate in the treatment of superficial BCCs especially given that the majority of patients in this group received only a single dose of ingenol mebutate [101–103]. They did note higher rates of localized skin reactions and scarring with ingenol mebutate under occlusion [101–103]. However, further studies including randomized studies with standardized treatment protocols are needed to further characterize differences in safety and efficacy between ingenol mebutate with and without occlusion.

Topical ingenol mebutate may be more effective when combined with other treatment modalities. For example, Erlendsson et al. demonstrated in porcine skin that pretreatment with 2940 nm Er:YAG laser increased the depth of penetration and the dermal deposition of ingenol mebutate noted using liquid chromatography-mass spectrometry [104]. Further studies are needed investigating the combination of topical ingenol mebutate with other treatment modalities such as LT to potentially increase efficacy [104].

Additionally, as ingenol mebutate is a relatively new topical agent, there are less prospective and retrospective studies on topical ingenol mebutate alone for the treatment of BCCs and only limited comparative trials (see section "Comparative Studies").

Variability in efficacy of ingenol mebutate in the treatment of BCC may reflect differences in tumor characteristics including location, size, and histologic subtype, treatment regimen including concentration used, number of applications, the use of occlusion, and cycles of treatment, outcome measures such as clinical versus histologic clearance, and follow-up time and highlights the need for larger prospective and comparative studies with longer follow-up.

## Safety

### *Imiquimod*

Localized site reactions are the most common adverse events reported with topical imiquimod cream (see Fig. 4.1b).

In 2 randomized, placebo-controlled trials of 364 patients comparing imiquimod cream (185 patients) to placebo cream (179 patients) for the treatment of superficial BCCs, adverse events were reported at a higher frequency with the imiquimod group compared to the placebo group [105]. Localized skin reactions that were >1% in the imiquimod group included erythema, flaking/scaling, induration, scabbing/crusting, edema, erosion, ulceration, and vesicle formation in 100%, 91%, 84%, 83%, 78%, 66%, 40%, and 31% of patients in the imiquimod group, respectively. A number of other adverse events were reported at higher rates in the imiquimod group compared to placebo including headache, lymphadenopathy, upper respiratory tract symptoms and infections, influenza-like symptoms, gastrointestinal effects, and fever [105]. Finally, in post-approval reports of topical imiquimod, other rare adverse events including cardiovascular, neurological, renal, and hematologic effects were identified [105].

Imiquimod is pregnancy category C and has not been studied in patients <18 years of age [105].

### *5-Fluorouracil*

Typically, adverse events with topical 5-FU cream are limited to localized skin reactions. Most commonly erythema, burning, pain, irritation, dryness, allergic contact dermatitis, photosensitivity, edema, erosion, and ulceration have been reported during treatment [2]. These localized skin reactions typically develop after 5–10 applications and may last up to 2 weeks [2, 73]. Given the photosensitivity, it is recommended that patients be diligent with photoprotection during their 5-FU treatment course [2]. Korgavkar et al. developed a severity scale to measure the degree of localized skin reactions to topical 5-FU based on erythema, crusting, erosions, and surface area of involvement on the face [106]. Of note, topical 5-FU cream should not be used near mucosal surfaces such as the eyes, eyelids, nostrils, or mouth to decrease the risk of systemic absorption and avoid localized adverse events including inflammation and ulceration [4].

Systemic 5-FU has a number of known adverse effects, and intravenous administration of 5-FU in patients with DPD enzyme deficiency can be life-threatening and lead to symptoms such as abdominal pain, bloody diarrhea, vomiting, fever, and chills [2, 25, 107–111].

The systemic absorption of topical 5-FU has been reported to be <10% and is not typically high enough to cause significant systemic toxicity. A study of topical 5-FU

ointment for the treatment of AKs in five patients by Dillaha et al. found systemic absorption of approximately 6% of topically applied radiolabeled 5-FU [112]. However, there have been rare reports of systemic toxicity from topical 5-FU. For example, one case of severe and life-threatening severe toxicity with topical 5% 5-FU cream in a DPD enzyme-deficient patient has been reported in the literature [2, 107]. The patient in this report developed severe colitis, neutropenia, and thrombocytopenia requiring hospitalization after applying 5% 5-FU cream for 1 week for a scalp BCC [107].

The systemic absorption of topical 5-FU has been found to be lower with the 0.5% controlled-release microsphere cream formulation compared to the 5% cream formulation [113]. In a prospective, parallel-group study of 0.5% versus 5% 5-FU cream for the treatment of AKs, the cumulative amount of fluorouracil excreted in the urine in patients treated with the 0.5% cream was 1/40 of that in patients treated with 5% cream, despite the 5-FU concentrations differing only by a factor of 10 [114]. Another study by the same group found that the percentage of fluorouracil retained in skin was higher in skin samples treated with the 0.5% formulations (86–92%) compared to the 5% formulation of 5-FU cream (54%) [115]. However, the efficacy of the 0.5% formulation of 5-FU cream for the treatment of BCCs has not been well-studied (see section "Efficacy") [2, 4].

Additionally, 5-FU is thought to possibly be mutagenic and affect fertility based on in vitro studies; however, no long-term in vivo animal studies have been performed [2]. In humans, one case of cleft lip and palate has been reported in a pregnant patient who used topical 5% 5-FU [2]. Miscarriage and ventricular septal defect have been reported with 5-FU cream applied to the mucous membranes in pregnant women further supporting that 5-FU should not be used in pregnant women or applied to mucous membranes [2]. Finally, 5-FU is considered pregnancy category X and is contraindicated in patients with DPD enzyme deficiency and those with known hypersensitivity to any cream component [2, 4].

### *Ingenol Mebutate*

The safety data on ingenol mebutate largely comes from studies in AKs given the greater number of studies on the agent for this indication. The most common adverse reactions to ingenol mebutate include nasopharyngitis, headache, and localized skin reactions such as local pain, pruritus, erythema, flaking, crusting, irritation, infection, and swelling including periorbital edema, pustules, erosions, and ulceration at the treated site [3]. These localized skin reactions have been reported to develop as early as during the first day of treatment, peak up to 1 week after treatment completion, and last for 2–4 weeks following treatment completion [3]. Hypersensitivity reactions including allergic reactions and anaphylaxis and allergic contact dermatitis have also been reported [3].

Contraindications for treatment with topical ingenol mebutate include a known hypersensitivity to ingenol mebutate or any of the ingredients in the formulation [3].

It should be applied topically to intact skin and should not be applied on or near mucosal sites [3]. Ingenol mebutate can cause a chemical conjunctivitis, corneal burn, eyelid edema, periorbital edema, eyelid ptosis, and eye pain when applied or transferred to the ocular or periocular area [3].

In vitro studies have shown that ingenol mebutate is metabolized by human hepatocytes but does not induce or inhibit enzymes in the cytochrome P450 system [3]. The carcinogenic potential and potential effects on fertility of ingenol mebutate have not been well-studied in animals [3].

Ingenol mebutate has not been well-studied in patients <18 years of age given the lack of AKs or BCCs in this population [3].

Ingenol mebutate is pregnancy category C as animal studies have shown associated fetal risks with systemic administration, but there have been no controlled studies of ingenol mebutate gel in pregnant women [3]. The effects of topical ingenol mebutate gel have not been studied in animal models. Studies have shown no significant systemic exposure to ingenol mebutate with topical application of ingenol mebutate gel to large treatment areas (100 $cm^2$ and 250 $cm^2$) in the treatment of AKs [3, 116, 117].

## Comparative Studies

### *Imiquimod*

#### Comparison of Different Treatment Regimens of Imiquimod to Vehicle Cream

A number of prospective, randomized controlled studies have compared different dosing regimens of imiquimod cream versus vehicle cream in the treatment of BCCs. One of the first was a single-center prospective, randomized controlled trial in the USA by Beutner et al. comparing 5% imiquimod cream with different treatment regimens in the treatment of 35 superficial or nodular BCCs [118]. They performed excisional biopsies to histologically evaluate the CR at 6 weeks [118]. They found the histologic CRs in the twice daily, once daily, 3 times weekly, 2 times weekly, once weekly, and vehicle groups to be 100%, 100%, 100%, 60% (3/5), 50% (2/4), and 9% (1/11), respectively [118]. They found a lower incidence and severity of the localized skin reactions in the treatment groups with lower frequency of application [118]. This small pilot study concluded that imiquimod 5% cream was an effective treatment compared to vehicle cream [118].

Schulze et al. conducted a double-blind, multicenter, randomized controlled trial in Europe comparing imiquimod 5% cream to vehicle cream applied daily for 6 weeks for the treatment of superficial BCCs [119]. They found a statistically significantly higher composite CR of 77% [95% CI 67–85%] and histologic CR of 80% [95% CI 70–87%] in the imiquimod group compared to the composite CR of 6% [95% CI 3–13%] and histologic CR of 6% [95% CI 3–13%] in the vehicle

cream group ($p < 0.001$) [119]. They also noted a higher rate of and higher severity of localized skin reactions in the imiquimod group [119].

Marks et al. performed a multicenter, randomized controlled trial in Australia and New Zealand comparing different doses of imiquimod 5% cream in the treatment of primary, superficial BCCs (0.5–2.0 $cm^2$ in area) in 95 patients [120]. The imiquimod cream was applied for 6 weeks, and histologic evaluation was performed at the completion of treatment [120]. They found histologic CRs, based on intention-to-treat analysis of 100% (3/3), 87.9% (29/33), 73.3% (22/30), and 69.7% (23/33) in the twice daily, once daily, twice daily 3 times per week, and twice daily 2 times per week groups, respectively [120].

A study by Geisse et al. compared different dosing regimens of 5% imiquimod cream to vehicle cream in the treatment of superficial BCC [121]. In all treatment groups, cream was applied for 12 weeks, and clinical and histologic evaluation were performed 6 weeks after completion of therapy [121]. They found a CRR of 100% (10/10), 87.1% (27/31), 80.8% (21/26), 51.7% (15/29), and 18.8% (6/32) in the twice daily imiquimod, once daily imiquimod, 5 times per week imiquimod, 3 times per week imiquimod, and vehicle groups, respectively [121]. All groups had acceptable safety profiles [121]. The authors concluded that once daily or 5 times per week dosing for a 12-week duration were effective and appropriate in the treatment of superficial BCCs [121].

Geisse et al. performed a double-blind, multicenter, randomized controlled trial comparing 5% imiquimod cream applied either once daily 5 times per week or once daily 7 times per week for 6 weeks to a vehicle cream applied using the same regimen in the treatment of superficial BCCs [122]. They excluded superficial BCCs that were <0.5 $cm^2$ in area, >2 cm in diameter, or located on the H-zone of the face or the anogenital area [122]. The 12-week composite CR, histologic CR, and rate of adverse events were all statistically significantly higher in the imiquimod groups compared to the vehicle control groups for both treatment schedules ($p < 0.001$) with composite and histologic CRs for vehicle creams ranging from 2% to 3% [122]. They noted no difference in 12-week CRs based on intention-to-treat analyses between the 7 times per week and 5 times per week imiquimod groups for either the composite CRs (73% versus 75%) or the histologic CRs (79% versus 82%) [122]. Additionally, they found higher rates of application site reactions in the 7 times per week imiquimod group compared to the 5 times per week imiquimod group ($p = 0.002$) [122]. They concluded that the efficacy of the 5 times per week imiquimod group was comparable to the 7 times per week group with lower rates of application site reactions and, thus, recommended a treatment regimen of imiquimod applied 5 times per week for 6 weeks for the treatment of superficial BCCs [122].

A randomized parallel study by Ezughah et al. concluded that for the treatment of superficial BCCs, treatment with imiquimod cream once daily for 5 weeks with a 1-week treatment-free interval (CR 88%) was more effective with comparable tolerability to treatment with imiquimod cream once daily for alternating weeks on and off treatment for an 8-week period (CR 43%) [123].

The efficacy of different dosing of imiquimod cream in the treatment of nodular BCCs has also been studied specifically with generally lower CRs compared to

those reported by studies in superficial BCCs (see above). Two studies by Shumack et al. found the histologic CRs with imiquimod cream dosing of once daily 7 days per week treatment group to be 71% (25/35) and 76% (16/21) in the 6-week study and 12-week study groups, respectively [124]. The authors concluded that treatment with 5% imiquimod cream once daily 7 days per week for a treatment duration of either 6 or 12 weeks was the most effective imiquimod treatment regimen (of those tested) in the treatment of nodular BCC [124].

Further, a single-center randomized controlled study out of Germany by Eigentler et al. compared 5% imiquimod cream applied 3 times a week for 8 weeks versus 12 weeks in the treatment of nodular BCCs (≤1.5 cm) [125]. At 8-week post-treatment, they evaluated clearance both clinically and histopathologically [125]. They noted complete clinical clearance in 78% (70/90) of patients and complete histopathologic clearance in only 64% (58/90) of patients [125]. They found no statistically significant difference in efficacy or safety between the 12-week and 8-week treatment groups [125]. Given the high rates of treatment failure and the presence of histopathologic evidence of tumor remnants in 17% (12/70) of patients with clinical clearance, the authors recommended excisional biopsy of the site after treatment completion [125].

There were two studies investigating the effect of occlusion on the effectiveness and tolerability of topical imiquimod in the treatment of superficial and nodular BCCs [126]. One study included superficial BCCs and the other nodular BCCs [126]. In both studies patients were randomized to imiquimod applied for 6 weeks either 3 days per week under occlusion, 3 days per week not under occlusion, 2 days per week under occlusion, or 2 days per week not under occlusion [126]. In the superficial BCC study, they found higher CRRs in the 3 days per week groups (87% with occlusion and 76% without occlusion) compared to the 2 days per week groups (43% with occlusion and 50% without occlusion) [126]. They found a statistically significant difference in the CRR in the 3 days per week with occlusion group compared to the 2 days per week with occlusion group ($p = 0.004$) [126]. They otherwise found no statistically significant difference in the CRRs between other groups compared including between occlusion and no occlusion groups for either 3 days per week or 2 days per week [126]. In the nodular BCC study, they reported no statistically significant differences in the CRRs found between the four groups (65%, 50%, 50%, and 57%) [126]. They found acceptable safety profiles with no serious adverse events in any of the treatment groups in the two studies [126]. The authors concluded that the use of occlusion in the treatment of superficial or nodular BCCs with imiquimod cream did not appear to have a significant impact on the efficacy or safety of treatment [126].

### Comparison of Imiquimod to Other Treatment Modalities

A multicenter, randomized controlled trial in the United Kingdom by Bath-Hextall et al. compared imiquimod 5% cream (once daily, 5–7 times per week, 6 weeks for superficial BCCs, 12 weeks for nodular BCCs) to SE (with 4 mm margins) for the treatment of nodular and superficial BCCs [71]. They found a 3-year treatment

success rate of 84% (178/213) in the imiquimod group compared to a success rate of 98% (185/188) in the SE group [71]. They found more itching and weeping in the imiquimod group compared to the SE group, no difference in the cosmetic outcomes (COs), and no serious adverse events thought to be related to treatment in either group [71]. They concluded that imiquimod cream was inferior to SE for the treatment of superficial and nodular BCCs but that it may be an appropriate treatment option in low-risk BCCs depending on patient- and tumor-specific factors [71]. A follow-up study reported similar findings at 5-year follow-up with a 5-year success rate of 82.5% (170/206) for the imiquimod group compared to 97.7% (173/177) in the SE group with a relative risk of success with imiquimod of 0.84 [95% CI 0.77–0.91] [72]. As part of this trial, the questionnaire filled out by patients indicated that overall patients preferred treatment with imiquimod cream over surgery regardless of prior BCC experience and treatment, which highlighted the importance of consideration of patient preference in addition to efficacy and tumor-specific factors during treatment discussion [127].

A randomized controlled trial in the ophthalmology literature by Garcia-Martin et al. compared imiquimod 5% cream (5 times weekly for 6 weeks, 15 patients) to RT (12 patients) for the treatment of biopsy-proven nodular BCC on the eyelid [128]. They reported 100% CRRs with histopathologic clearance within 3 months and continued clinical clearance at 24 months in both groups [128]. However, they noted poorer tolerability during treatment and better functionality and CO after treatment in the imiquimod group compared to the RT group [128].

A multicenter, prospective randomized trial compared 5% imiquimod cream (applied once daily for 5 consecutive days a week for 6 weeks), 5% 5-FU cream (applied twice daily for 4 weeks), and methyl aminolevulinate (MAL)-PDT (2 sessions with a 1-week interval between sessions, 630 nm, dose of 37 J/cm$^2$) for the treatment of superficial BCCs [67–69]. At 1-year follow-up, 5% imiquimod and 5% 5-FU cream were found to be cost-effective compared to MAL-PDT [67]. At 3 years, 5% imiquimod cream was found to be superior to MAL-PDT, and 5% 5-FU cream was shown to be not inferior to MAL-PDT [68]. The 3-year trial data demonstrated higher rates of localized pruritus, edema, erosion, and crust formation in the imiquimod and 5-FU groups compared to the MAL-PDT group [68]. The 5-year follow-up data which was recently reported by Jansen et al. found 5% imiquimod cream to be superior to both 5% 5-FU cream and MAL-PDT [69]. At 5 years, tumor-free survival was 80.5% in the imiquimod group [95% CI 74.0–85.6%], 70.0% in the 5-FU group [95% CI 62.9–76.0%], and 62.7% in the MAL-PDT group [95% CI 55.3–69.2%] [69]. Based on the calculated hazard ratios (HRs) for treatment failure, 5% imiquimod cream and 5% 5-FU were concluded to be superior to and non-inferior to MAL-PDT, respectively [69]. The study also concluded that imiquimod was superior to 5-FU in the treatment of superficial BCCs at 5 years. However, there have been non-randomized studies reporting higher CRs (90% in a study by Gross et al.) with treatment regimens with a longer treatment duration with 5-FU (6–12 weeks in the Gross et al. study) for the treatment of superficial BCCs, indicating the need for further comparative studies between 5% imiquimod cream and 5% 5-FU cream with longer courses of treatment [75].

A subgroup analysis was also performed by Roozeboom et al. with the 12-month data to determine if the superiority previously demonstrated by the authors of imiquimod over MAL-PDT in the treatment of superficial BCCs was consistent among different subgroups of superficial BCCs [129]. They found imiquimod to be a more effective treatment choice in the treatment of superficial BCCs in most treatment subgroups except in patients greater than 60 years old with superficial BCCs located on the lower extremities where MAL-PDT may be more effective [129].

### *5-Fluorouracil*

A small, preliminary placebo-controlled study of a number of topical agents by Klein et al. included topical 20% 5-FU, 20% methotrexate, 20% spiramycin, 0.02% actinomycin D, 0.005% nitrogen mustard, 20% 5-mercaptouracil, and 10% dimethylurethimine for the treatment of 31 primary, non-ulcerated nodular BCCs (not located on the nose, nasolabial fold, upper lip, oral commissure, eyelids, or canthus) [79]. All agents and placebo cream were applied every other day under occlusion for 1 month [79]. Treatment response was evaluated clinically and histologically at 1-month post-treatment [79]. The highest treatment response rate was in the 5-FU group with a histologic CR of 83.3% (5/6), and the 5-FU treatment group was the only treatment group to have a statistically significant difference in tumor regression rate compared to controls ($p < 0.001$) [79].

Romagosa et al. performed a single-center randomized controlled trial to determine if phosphatidylcholine increased the efficacy of 5-FU cream by allowing deeper penetration [130]. The authors found a 90% CR (9/10) in the 5% 5-FU in phosphatidylcholine group and a 57% CR (4/17) in the 5% 5-FU in petrolatum group; however the difference was not statistically significant [130].

Jansen et al. found 5% 5-FU cream (applied twice daily for 4 weeks) to be inferior to 5% imiquimod cream (applied once daily for 5 consecutive days a week for 6 weeks) and non-inferior to MAL-PDT in the treatment of superficial BCC at 5 years (see subsection "Imiquimod" in section "Comparative Studies") [69].

Treatment with intralesional, injectable 5-FU/epinephrine gel has also been studied with CRRs reportedly comparable to surgery [131].

Further randomized controlled trials comparing the efficacy of topical 5-FU cream to other treatment modalities such as ST were not found upon literature review and are needed to better characterize the efficacy of topical 5-FU cream for the treatment of BCC in the future. A number of techniques including adding agents such as lipid nanocarriers, performance of microneedling, and application under occlusion have been described to potentially increase the permeability and thus efficacy of 5-FU cream (see subsection "5-Fluorouracil" in section "Efficacy"). Comparative studies evaluating differences in the efficacy and tolerability of these different formulations and techniques of topical 5-FU cream in the treatment of BCCs are still needed. Additionally, non-comparative studies have reported increased efficacy with combination therapy with topical 5-FU cream and other treatment modalities such as

laser and CT (see subsection "5-Fluorouracil" in section "Efficacy" and section "Combination Therapies"); however, randomized controlled trials are still need to compare these combination therapies to topical 5-FU cream alone, LT alone, ST, CT alone, MAL-PDT, and other topical therapies for treatment of BCC.

### *Ingenol Mebutate*

There are very limited randomized controlled trials on topical ingenol mebutate in the treatment of BCCs [132]. These include a phase II randomized controlled trial by Siller et al. which investigated safety as the primary end point and efficacy as the secondary end point of topical ingenol mebutate gel for the treatment of primary biopsy-proven superficial BCCs (4–15 mm in diameter, thickness ≤4 mm) [132]. Sixty patients were randomized to Arm A (treatment on days 1 and 2) or Arm B (treatment on days 1 and 8) and then further randomized within each arm to receive either 0.0025% ingenol mebutate, 0.01% ingenol mebutate, 0.05% ingenol mebutate, or vehicle gel [132]. The gel was applied 7–28 days after the biopsy with a dose of 0.25–5.20 μg of ingenol mebutate per $cm^2$ [132]. Excision was performed to allow histologic determination of clearance on day 85 [132]. Localized skin reactions were the most commonly reported adverse events including erythema in >75% and flaking/scaling/dryness in >50% of patients in all groups [132]. The percentage of patients who developed localized skin reactions including edema, vesicle formation, erosion/ulceration, scabbing/crusting, and hypopigmentation was noted to be higher in the groups treated with higher concentrations of ingenol mebutate gel [132]. The majority of localized skin reactions and adverse events were graded as mild or moderate [132]. Severe localized skin reactions were found in ten patients, and six of them received the higher concentrations, 0.01% or 0.05%, of ingenol mebutate gel [132]. Adverse events including pain at the application site and headache were reported in more than one patient [132]. There were no serious adverse events reported [132].

Two patients in Arm A received only one application, and another two patients in Arm A had their second application on day 8 rather than on day 2 [132]. These patients were accounted for in the "as-treated" analysis versus in the "intent-to-treat" analysis [132]. The complete CRs and histologic CRs were found to be highest in the highest concentration ingenol mebutate group of 0.05%, and there was noted to be higher CRs in Arm A compared to Arm B although this difference was not found to be statistically significant [132]. In the 0.05% ingenol mebutate group, the complete clinical CRs and histologic CRs in Arm A were 63% and 71% based on the "intention-to-treat" analysis and "as-treated" analysis, respectively. The difference in histologic CRs between 0.05% ingenol mebutate gel and vehicle gel was statistically significant in Arm A ($p = 0.031$) but was not statistically significant in Arm B [132]. The authors concluded that topical 0.05% ingenol mebutate gel (applied on days 1 and 2) was superior to vehicle gel and may be a safe, relatively well-tolerated, and efficacious treatment option for superficial BCCs [132].

## Emerging Topical Treatments and Combination Therapies

A number of new topical agents have been described in the literature as potential treatment options for BCC. They have varying amounts of evidence supporting their efficacy.

Solasodine glycosides have been described as a potentially effective treatment for both benign and malignant skin tumors, and a commonly used formulation, BEC, is a cream containing 10% of a mixture of different solasodine glycosides [133]. Punjabi et al. performed a multicenter, randomized controlled trial comparing a 0.005% mixture of solasodine glycoside cream to vehicle cream (both applied twice daily under occlusion for 8 weeks) in the treatment of BCCs [134]. The authors found that treatment efficacy based on intention-to-treat analysis was statistically significantly higher ($p < 0.001$) in the solasodine glycoalkaloid group (66%, 41/62) compared to the placebo group (25%, 8/32) [134].

Additionally, there are a number of other agents with limited efficacy reported in the literature such as topical retinoids and topical calcitriol [135–137]. Overall, the rates of tumor clearance reported with different topical retinoids for the treatment of BCCs are lower than those for other topical therapies, such as topical imiquimod and topical 5-FU [135–137]. In in vitro and in vivo murine studies, vitamin D3 and its metabolite calcitriol have been shown to have antitumor activity in BCCs through the inhibition of the hedgehog signaling pathway [138–140]. However, in a phase II randomized controlled trial by Brinkhuizen et al., topical calcitriol 3 μg/g ointment alone was not found to have a statistically significantly higher histologic tumor CR than the control group for the treatment of superficial and nodular BCCs [141].

Finally, there are new emerging topical treatments, which require further study including topical diclofenac, cidofovir, calcium dobesilate, and trichloroacetic acid [141–146].

## Combination Therapies

A number of topical agents, such as imiquimod, have been described in the literature in combination with other treatment modalities such as CT, ST, PDT, and ED&C (see below). Additionally, topical 5-FU plus other treatment modalities including CT and LT has also been studied (see below and subsection "5-Fluorouracil" in section "Efficacy").

### *Imiquimod Plus CT*

Treatment with CT during treatment with topical imiquimod, termed immunocryosurgery, has been described in the treatment of BCC. A randomized prospective trial by Gaitanis et al. compared the timing of CT during imiquimod treatment

(immunocryosurgery) versus prior to imiquimod treatment (adjuvant imiquimod) in the treatment of primary, non-superficial BCCs [147]. In both groups, patients were treated with 5% imiquimod cream once daily for 5 weeks, and CT was performed either 2 weeks into treatment with imiquimod or prior to the start of imiquimod treatment [147]. They found that the immunocryosurgery group had a statistically significantly higher CR of 10/10 compared to 3/7 in the adjuvant imiquimod group ($p = 0.0147$), and further, the overall treatment efficacy at both 6-month and 18-month follow-up was 9/10 in the immunocryosurgery group compared to 2/7 in the adjuvant imiquimod group ($p = 0.0345$) [147].

### *Imiquimod Plus PDT*

Imiquimod has also been studied in combination with PDT in the treatment of BCCs. Osiecka et al. performed a randomized controlled trial comparing treatment with aminolevulinic acid (ALA)-PDT plus imiquimod to ALA-PDT plus vehicle cream for recurrent, biopsy-proven facial BCCs [148]. In both groups ALA-PDT was performed with a 4-hour incubation, 30-minute irradiation total (15 minutes then repeated 48 hours later), 100 J/cm$^2$, and a 635 ± 20 nm light source [148]. Either imiquimod or vehicle cream was applied 72 hours after the completion of PDT irradiation and then twice weekly for 5 weeks [148]. They reported increased local skin reactions such as burning, edema, and erosions in the ALA-PDT plus imiquimod group compared to the ALA-PDT plus vehicle cream group [148]. The authors also reported a higher complete CR of 75% (18/24) and significant reduction rate of 25% (6/24) in the ALA-PDT plus imiquimod group compared to a complete CR of 60% (6/10) and significant reduction rate of 40% (4/10) in the ALA-PDT plus vehicle cream group and concluded that treatment with ALA-PDT followed by imiquimod cream has higher efficacy in the treatment of recurrent BCCs than ALA-PDT alone [148].

### *Imiquimod Plus Curettage*

Imiquimod in combination with either curettage without electrodesiccation or with ED&C has been described in the literature with higher CRs reported than those reported by many studies with ED&C (efficacy rates reported vary greatly; see section "Electrodesiccation and Curettage" in Chap. 6) or imiquimod alone. For example, a non-comparative, prospective, pilot study by Wu et al. included 34 primary, nodular BCCs located on the trunk and extremities treated with curettage followed by treatment with 5% imiquimod cream (applied once daily for 6–10 weeks) [149]. At 3 months after treatment completion, they found a 94% (32/34) histologic CR with 14/17 patients rating the CO as excellent or good [149]. Curettage followed by imiquimod as an effective treatment option was further

supported by other studies. A non-randomized, prospective study included 57 superficial and nodular BCCs curetted (without electrodesiccation) followed by treatment with 5% imiquimod cream (applied once daily, 5 times per week, for 6 weeks) [150]. The authors reported a 1-year RR of 0% [150]. A study of 17 nodular BCCs treated with ED&C followed by treatment with 5% imiquimod cream (applied once daily, 5 times per week, for 6 weeks) found a histologic CR of 100% (17/17) [151, 152].

A double-blinded, randomized, vehicle-controlled pilot study compared ED&C (3 cycles) followed by adjunctive therapy with either 5% imiquimod cream or vehicle cream (applied once daily for 1 month in both groups) for the treatment of nodular BCCs [153]. At 8-week post-treatment, they found significantly lower rates of residual tumor in the ED&C plus adjunctive imiquimod groups of 10% (1/10) compared to a residual tumor rate of 40% (4/10) in the ED&C plus adjunctive vehicle cream group [153]. This further supported that imiquimod in combination with ED&C is more effective than ED&C alone.

### *Imiquimod Plus MMS*

Treatment with imiquimod 5% cream prior to treatment with MMS has been studied for the treatment of facial nodular BCCs in an effort to decrease the tumor burden, defect size, and number of Mohs stages required. There have been mixed results. Butler et al. performed a randomized controlled trial comparing imiquimod (daily under occlusion for 6 weeks) followed by MMS 4 weeks later to vehicle cream (daily under occlusion for 6 weeks) followed by MMS 4 weeks later in the treatment of primary, nodular, nasal BCCs [154]. They found no statistically significant difference in the number of Mohs stages, defect sizes, or cost between the imiquimod and MMS group versus vehicle cream plus MMS group [154]. They found that only 42% (5/12) of patients had no histologic evidence of residual tumor at the time of MMS [154]. The authors concluded that the study may have failed to show a difference between the two groups given its small sample size and nasal BCCs may be less responsive to imiquimod compared to other sites [154]. They recommended histologic evaluation for clearance following imiquimod treatment for facial nodular BCCs [154]. A larger randomized controlled trial of primary, nodular BCCs on the face compared a 4-week course of imiquimod 5% cream prior to MMS to MMS alone [155]. They found a lower number of Mohs stages, statistically significant shorter time of reconstruction ($p = 0.01$), and lower median percentage of increase between baseline tumor area and post-MMS defect area ($p < 0.001$) in the imiquimod plus MMS group compared to the MMS alone group [155]. They concluded that pretreatment with imiquimod prior to MMS decreases tumor size, defect size, and time of reconstruction in the treatment of facial nodular BCCs [155].

### *5-FU Combination Therapy*

More recently topical 5-FU cream in combination with other treatment modalities such as CT and LT has been described in the treatment of BCC. There are non-randomized studies describing 5-FU in combination with CT and 5-FU in combination with LT to increase 5-FU tissue penetration.

For example, Soong and Keeling performed a retrospective review of patients with biopsy-proven superficial BCC and SCC in situ treated with a 3-week course of topical 5% 5-FU cream plus CT who had been clinically assessed for evidence of recurrence at 6-month follow-up [156]. The study included 34 superficial BCCs [156]. They reported that at 6-month follow-up 30/34 patients with superficial BCCs assessed had no evidence of recurrence and the 6-month clinical CR including patients lost to follow-up was 73% for superficial BCCs treated with a 3-week course of 5% 5-FU cream and CT [156].

Further, Nguyen et al. performed a prospective non-randomized study of 14 superficial BCCs (trunk and extremities, <2 cm in diameter) and 16 SCC in situs to evaluate the efficacy of topical 5% 5-FU cream (applied immediately after LT, 1 application, under occlusion for 7 days) and ablative fractional laser (carbon dioxide laser, 1 pass, 0.12 mm spot size, 10 mJ/pulse, 1 pulse, 5% density) [93]. The authors found a histologic clearance rate of 71% (10/14) for superficial BCCs treated with 5-FU cream and ablative fractional laser [93]. They reported localized skin reactions at 1 week after treatment (mild erythema in 57%, moderate erythema in 40%, erosion of the epidermis in 50%, erosion of the superficial dermis in 30%, infection in 0%) and no major adverse events [93]. The CO was good at 1–2 months after treatment with a Vancouver Scar Scale score (1–13) of 1.6 ± 1.1, residual pinkness in 74% (22/30), dyspigmentation in 30% (9/30), and patient-reported scores of "better than before treatment" in 76% (23/30) and "same as before" in 24% (7/30) [93, 157]. The authors concluded that topical 5-FU in combination with ablative fractional laser had efficacy similar to that reported with 5-FU alone [93]. A follow-up study by the same group found an overall treatment success rate of 67% (8/12) for superficial BCCs considering initial treatment failures and tumors followed for at least 9 months, with neither tumor size ($p = 0.87$) or tumor location ($p + 0.96$) predicting treatment failure [158]. Treatment with 5-FU cream in combination with ablative fractional laser may be a good treatment option in those in whom topical therapy would be considered (where ST and RT are contraindicated or inappropriate) but in whom there is concern regarding patient compliance or tolerability [93].

However, more long-term follow-up data to evaluate long-term efficacy and comparative studies to allow comparison of safety and efficacy of these combination therapies to other treatment modalities in the treatment of BCC are still needed (see section "Comparative Studies").

## Discussion and Conclusions

Topical agents including imiquimod cream, 5-FU cream, and ingenol mebutate have been studied in the treatment of BCCs and are appropriate treatment considerations in primary, superficial, low-risk BCCs where ST or RT are contraindicated or not appropriate. Generally, advantages of topical therapy include that they are tissue sparing and cost-effective (especially 5-FU cream) with good COs. The disadvantages of topical therapy include that in general these treatments rely on patient compliance, have limited tissue depth of penetration and efficacy, and do not allow histologic evaluation of clear margins. Imiquimod in a recently published study has been shown to be superior to both MAL-PDT and 5-FU cream for the treatment of superficial BCCs (except in older patient with superficial BCCs on the lower legs based on the published subgroup analysis) [69, 129]. Additionally, there are a number of new topical treatment modalities on the horizon for the treatment of BCCs including a number of new topical agents as well as the combination of agents such as imiquimod or 5-FU cream with other treatment modalities such as CT, curettage, ST, or LT (see section "Emerging Topical Treatments and Combination Therapies"). These newer modalities are promising but require further investigation of their efficacy and safety compared to standard treatments in order to determine their appropriate use in the treatment of BCCs.

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# Chapter 5
# Local Immunotherapy for Basal Cell Carcinoma with Interferon


**Hung Q. Doan and Stephen B. Tucker**

## Introduction

Basal cell carcinoma (BCC) is the most common nonmelanoma skin cancer (NMSC) in the United States, accounting for 80% of (NMSC) [1]. Treatment options include local destruction such as curettage with or without electrodesiccation, cryosurgery, radiation, and surgical interventions including Mohs micrographic surgery (MMS) and excisional surgery with 4 mm margins. In many instances these methods can give a complete response rate (CRR) of 90–99%. Along with consideration of CRR, the choice of intervention used to eliminate BCC should include patient preference. This may encompass factors including the patient's age and health, cost, the original tumor size and type, location, potential for postoperative anatomic dysfunction, and posttreatment cosmesis as well as efficacy.

The aim of this chapter is to review and discuss immunostimulatory (ISRX) treatment for BCC and the techniques involved for choosing and administering this treatment. Because of the large number of BCC that dermatologists and dermatologic surgeons encounter in myriad locations and clinical situations, an alternative treatment to destruction might be useful.

H. Q. Doan
The University of Texas MD Anderson Cancer Center, Department of Dermatology, Division of Internal Medicine, Houston, TX, USA

S. B. Tucker (✉)
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA
e-mail: stmd@sbcglobal.net



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_5

## Background

### *Role of the Immune System*

Immune surveillance is vital to maintaining homeostasis. Immune dysregulation and immunosuppression have both been associated with a higher risk of developing cutaneous malignancies. Organ transplant patients have a greatly enhanced risk of developing NMSC including BCC [2]. Moreover, chronically immunosuppressed patients are at a higher risk for developing other cancers [3, 4]. This suggests that the overall immune system may function to both eliminate cancer cells and suppress their growth, but when immune functions are inhibited, these cancers become apparent. Since immunosuppression is associated with a greatly increased risk of BCC, immunostimulation would reasonably be expected to have the opposite effect of eliminating them.

Imiquimod (IMIQ) and interferon (IFN), both with immunostimulatory properties, have been investigated in the treatment of cutaneous BCC. We will focus on these two agents for the remainder of the chapter. The use of IMIQ alone will not be discussed as it is an FDA-approved therapy for the treatment of superficial basal cell carcinoma. However, with IMIQ treatment intense redness and ulceration as well as posttreatment hypopigmentation are common. Both of these effects can be avoided by using interferon injections alone or in combination with IMIQ as described in this chapter. The use of the term ISRX in this chapter refers to intradermal injections of interferon-α-2b and/or the combination of IMIQ and IFN. These treatments increase local tissue levels of IFN when injected or applied.

### *Treatment with Immunostimulatory Agents (ISRX)*

Immunostimulatory treatment of BCC has shown efficacy in clinical trials and in practice for over 30 years. However this method of treatment is not commonly used or taught, with surgical removal and other destructive methods comprising the overwhelmingly most common forms of treatment. The following is a list of possible specific advantages of ISRX to be considered when choosing options for BCC treatment:

1. Efficacy.
2. Low recurrence rate.
3. Cosmesis.
4. Preservation of function.
5. No wound.
6. All other therapeutic modalities remain open if ISRX is ineffective.

## Efficacy

The initial studies of ISRX using intradermal injections of IFN alone include the pilot study in 1986, where all eight patients in the trial had a complete response (CR) after nine treatments with intradermal injection of IFN at a dose of 1.5 million units per injection. Clearance of BCC was verified by excisional biopsy 2 months following the last injection [5]. A variety of regimens and doses were investigated with none of them showing the complete efficacy of the regimen of nine treatments at 1.5 million units of IFN injected intradermally over 3 weeks. A subsequent multicenter placebo-controlled trial of 172 patients, using this regimen, demonstrated a CRR of 81% of BCC treated. At the 1 year posttreatment follow-up, the entire tumor area was excised and evaluated with step sectioning examining for histologic evidence of BCC. The criteria for CR were based on these findings. Importantly, no histologic evidence of BCC was found at sites of treatment which clinically showed no evidence of tumor [6]. Intralesional injections of IFN, in contrast to perilesional injections, were used in both studies mentioned above.

The efficacy rate with any method of removal is dependent on the skill and techniques of the operator administering the treatment. For example, in the large multicenter study described above, one institution, with the highest number of enrolled subjects, had a 94% CRR. At that site, all injections were given by one investigator with years of experience giving intradermal injections of IFN. This suggests that the much lower CRR seen in the multicenter trial might be explained by injection technique (see section on IFN injections).

## Low Recurrence Rate

Recurrence rates reflect tumors that seem to be clinically resolved but recur at the same site at a later date. This suggests that subclinical tumor was still present after treatment but was not clinically seen. The recurrence rate for BCC is known to increase with each subsequent year after treatment [7]. Initial studies of IFN injections for BCC had shortened follow-up periods due to excisional removals of the area for histologic examination. The longest clinical follow-up study of BCC treated with IFN/ISRX included 67 BCCs followed for a mean of 10.5 years (median 12.5 years). All tumors showing clinical resolution on exam at 6 months posttreatment remained clear at the end of follow-up. A nodular BCC on the lip was noted at 4 months posttreatment and was retreated with IFN/ISRX and remained clear 10 years later. A possible exception to this observation was a superficial BCC which was documented near the site of a nodular BCC treated 12 years previously [8].

### Normal Skin Markings

Normal skin markings are seen at the site of BCC resolution at 3–6 months post-treatment follow-up. This is best observed by pinching the skin to evaluate skin markings. On sebaceous skin the equivalent to normal skin markings is seen as normal follicular openings. If these findings are not seen, a biopsy should be performed. This finding of normalized skin markings provides an advantage for determining clinical recurrence over evaluation of sites where destructive methods have been used with accompanying scars and other skin changes. The ease by which recurrence can be noted on clinical follow-up and the findings of absent subclinical tumor at sites where clinical evaluation showed resolution, as was noted in the multicenter study, allows clinical follow-up to be reliable after ISRX.

### Cosmesis

Before and after photographs in previous publications have shown excellent cosmesis with the use of ISRX [6, 8–10]. Figures 5.1, 5.2, and 5.3 show some of the typical cosmetic results with this treatment for various patients, skin types, and tumor locations. If the tumor is large and deep, or marked inflammation occurs during the treatment, post-inflammatory hypopigmentation will result (Fig. 5.4a, b).

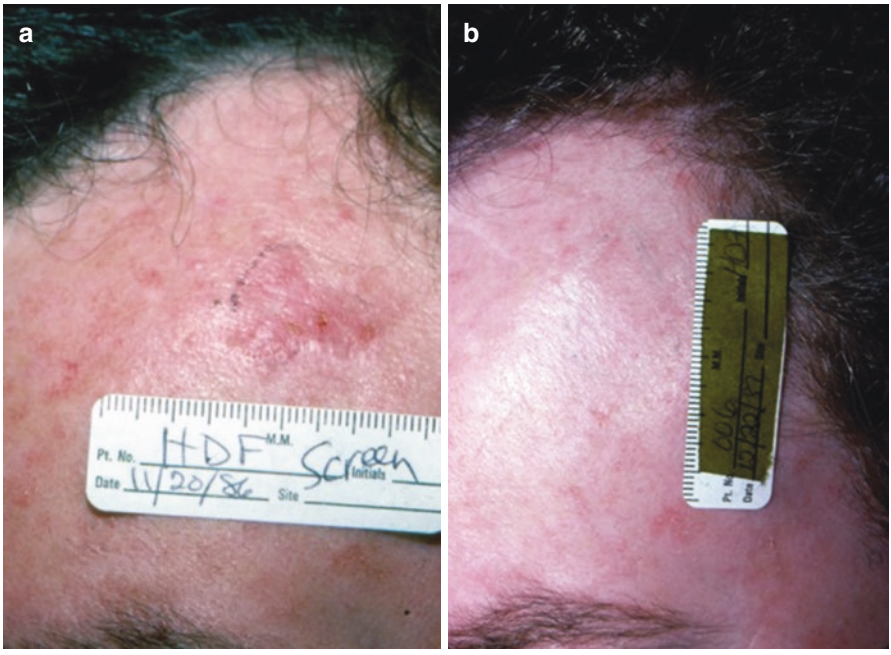


**Fig. 5.1** Before (**a**) and after (**b**) ISRX of superficial BCC on forehead

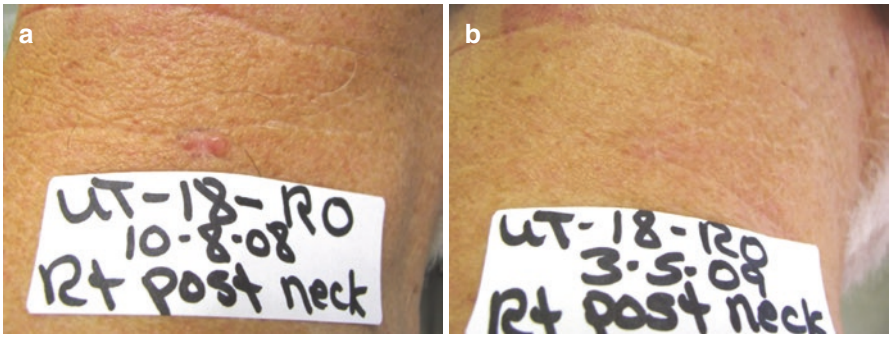


**Fig. 5.2** Before (**a**) and after (**b**) ISRX of nodular BCC on neck

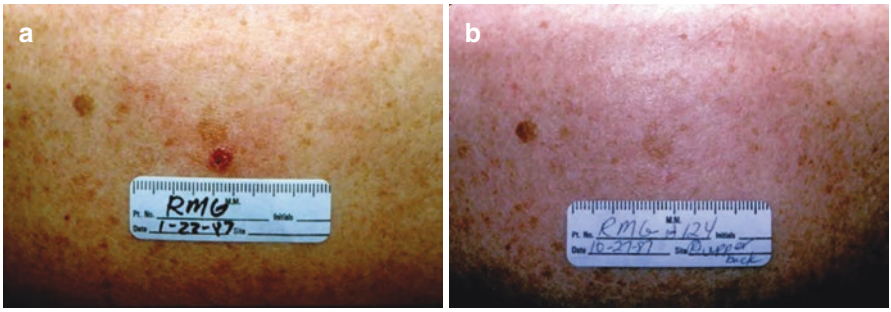


**Fig. 5.3** Before (**a**) and after (**b**) ISRX on back. Please note clearing of tumor with no effect on benign seborrheic keratosis in the treatment field. Benign lesions are not affected by ISRX

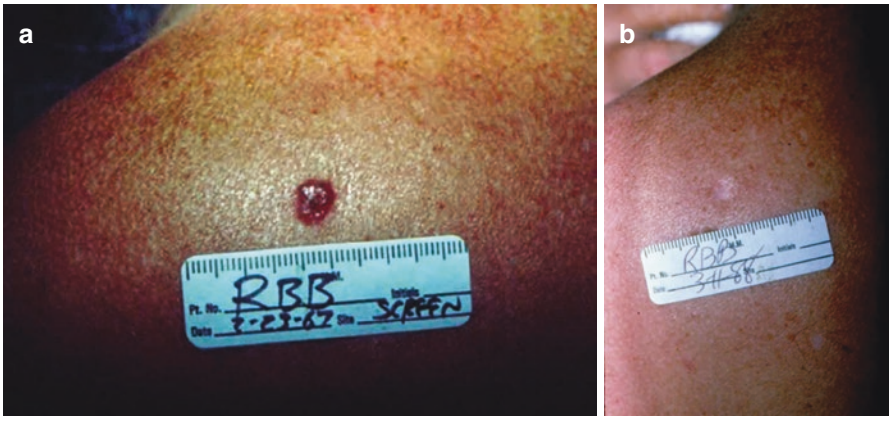


**Fig. 5.4** Before (**a**) and after (**b**) ISRX of nodular BCC with deep dermal destruction. Resolution of tumor with delling of skin and hypopigmentation at follow-up

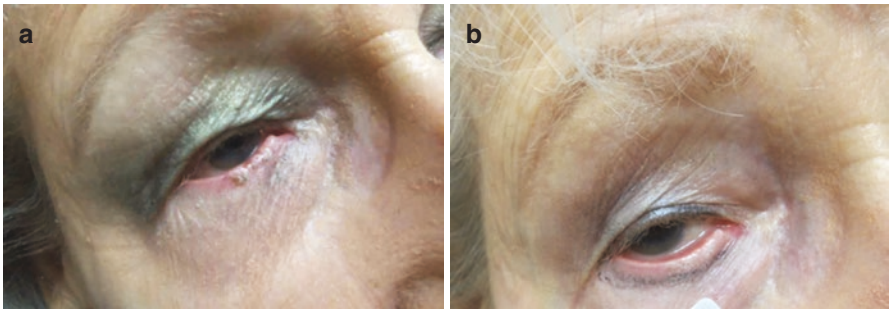


**Fig. 5.5** Before (**a**) and after (**b**) ISRX with complete resolution of eyelid margin BCC involving the tear duct. Five-year follow-up showed no recurrence

### Preservation of Function

In certain unusual tumors, ISRX has been used for preservation of function. These include tumors around the eye (Fig. 5.5a, b), very large lesions (Fig. 5.6a–c), or tumors blocking nostrils. However the histology of these tumors is not typically nodular or superficial, and lower efficacy rates can be expected (Fig. 5.7) (see Fig. 5.8 paradigm for tumor selection).

### No Wound

After injection of IFN, which typically takes approximately 5 minutes, the patient walks out of the office simply applying pressure to the injection site. There is no bandage, and the only visible sign of the treatment is mild-to-moderate erythema at the site of the tumor while treatment is ongoing.

### All Other Therapeutic Options Remain Open

Since there is no destruction at the site of the tumor such as that with radiotherapy or surgery, all other options for destructive treatment are available if ISRX does not result in a complete response. Additionally there are examples of partial regression which reduce the tumor size for subsequent surgical or destructive methods as seen in Fig. 5.6a, b, which required subsequent destruction seen in Fig. 5.6c.

## *Disadvantages of ISRX*

Multiple visits for the injections are required which necessitate coordination between the patient's and practitioner's schedules. Since the time required for injection is minimal, insertion of the treatments into a busy practitioner's schedule

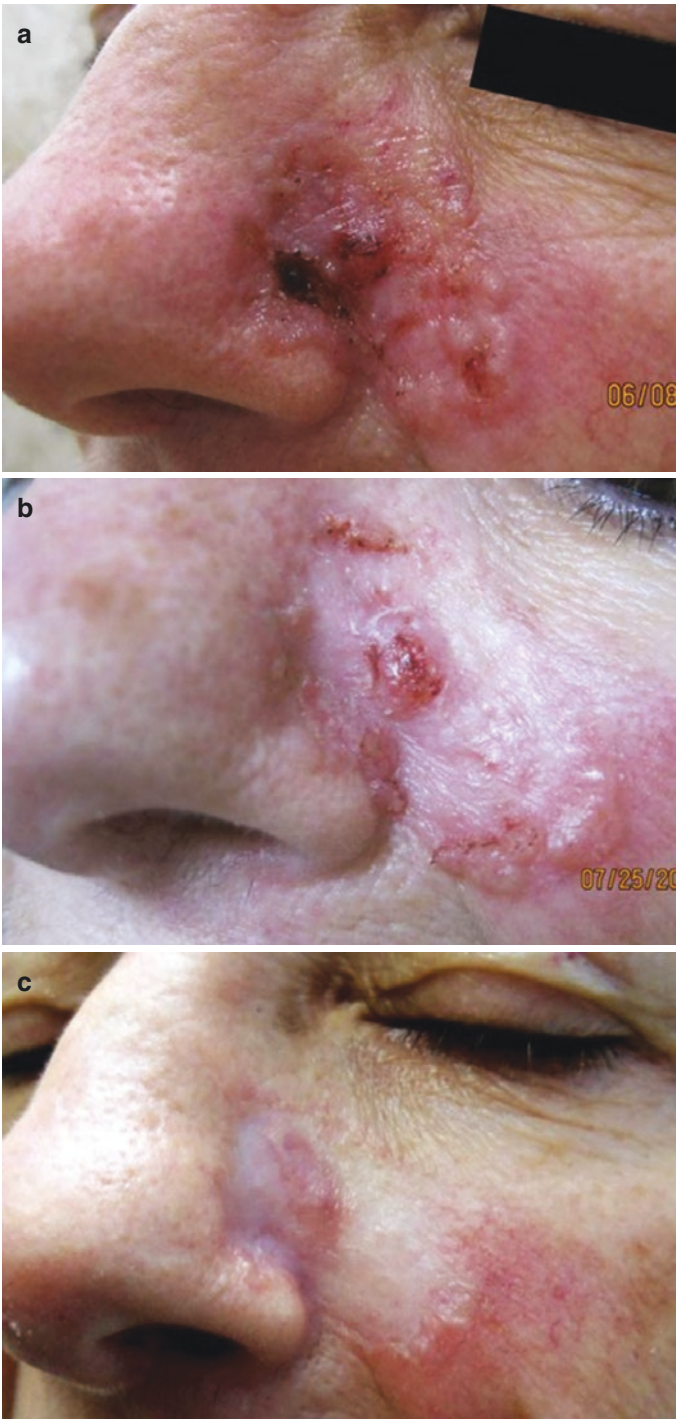


**Fig. 5.6** Before (**a**), during (**b**), and after (**c**) ISRX of the left nasal sidewall with dermal destruction and hypopigmentation

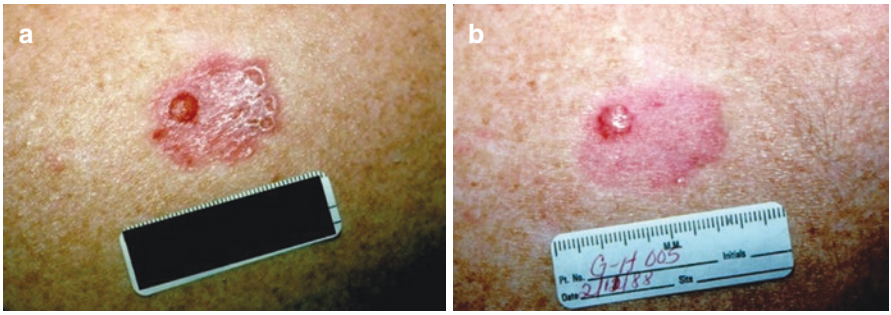


**Fig. 5.7** Before (**a**) and after (**b**) ISRX with partial resolution of nodular BCC. The much smaller unresolved tumor was curetted with complete resolution

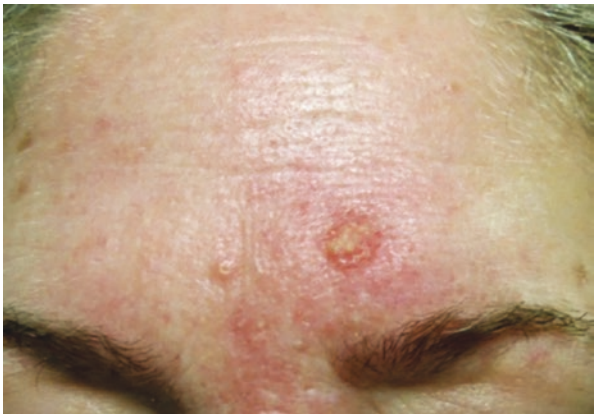

**Fig. 5.8** Mound of cysts following ISRX of nodular BCC. These uniformly resolve and are residual keratotic scaffolding of BCC from tumoral FasL secreted into the tumor (see text)

is usually not difficult. The schedule for treatment requires 10–13 weeks which includes pre- and postinjection IMIQ application. The site of the tumor usually becomes erythematous but typically not to the extent that a cosmetic concealer cannot cover the area. Also, flu-like symptoms can occur. This can be mitigated by taking acetaminophen or ibuprofen immediately before each injection and then again after injection (please see the section on side effects for a recommended prophylaxis schedule). Finally, it should be noted that this treatment is not FDA approved. Therefore the patient typically must pay for the interferon which is not usually covered by insurance.

## Mechanism of Action of ISRX

Ultraviolet (UV) radiation accounts for the major mechanism by which BCC's develop. UV radiation promotes DNA damage that, if left unchecked, can lead to the accumulation of mutations rendering a cell susceptible to carcinogenesis. The major mechanism to prevent carcinogenesis is the tumor suppressor gene complex

p53 (referred to as the "guardian of the genome"). This gene complex has functions as a transcription factor to prevent carcinogenesis by activating proteins involved in DNA damage repair and by promoting checkpoints during the cell cycle to allow for DNA repair. If a cell sustains DNA damage beyond repair, p53-associated genes promote apoptosis or senescence. The p53 protein plays a central role in protecting organisms from carcinogenesis. Most human cancers have been shown to have a mutation in TP53, the gene for the p53 protein, with mutation rates ranging from 5% to almost 100% in serous ovarian cancer [11].

However, once the *TP53* gene or p53 pathway components are mutated, cells may accumulate further mutations because they are not appropriately eliminated by normally functioning p53. As a result these accumulating mutations may cause abnormal signaling of cell cycle proteins allowing unrestricted growth, promoting cancer development.

When p53 function is abrogated, the immune system becomes the predominant anticancer mechanism at eliminating abnormal cells. The immune system is usually in a homeostatic functional mode, recognizing and eliminating tumor cells by their expression of abnormal cell surface antigens. Immune cells accomplish this by promoting tumor cell death through lymphocyte-mediated and cytokine-mediated apoptosis [12–14]. However when repair of cells in a tissue is the priority, for example, in a wound, there are alterations in the tissue microenvironment which promotes a proliferative state. This change is accomplished by alterations in gene expression which promotes a proliferative/repair mode resulting in a more rapid turnover of cells. This proliferative/repair mode may be described as proinflammatory. The functions of lymphocytes in this mode (proinflammatory) are different than lymphocyte behavior in the homeostatic (immune) mode. Inflammation has been found to be a significant part, if not a necessary part, of carcinogenesis and is considered a hallmark of cancer [15].

In BCC, the most common mutations are those associated with the sonic hedgehog pathway (Shh). Specifically, mutations in human *PTCH* and *SMO* account for up to 70% of all BCC mutations [16]. There has been an association between aberrant Shh-pathway activation and immune evasion by blunting the anticancer mechanisms of intrinsic IFN-γ-mediated cytokine production [17]. These activities within tumor cells and the surrounding stroma promote the immune response toward a carcinogenic proliferative pathway. Formation of BCC usually occurs when the proliferative (proinflammatory) mode is activated by abnormal signaling of cell cycle genes downstream of Shh signaling. This constant signaling turns the BCC intracellular environment into the proliferative (inflammatory) mode. While the mechanisms are not entirely clear, in BCC tumors, it has been shown that tumoral tissue has increased secretion of proinflammatory cytokines IL-6, IL-17, and IL-22 [18–21]. Immune cells have likewise been shown to express a similar cytokine profile with enhanced macrophage expression of IL-6 and IL-17 in p53-deficient mice [22–24]. Other studies have suggested an inverse relationship between p53 activity and proinflammatory NF-κB activity, providing yet another means for inflammation-associated tumorigenesis [25, 26].

This shift to the proliferative mode prevents cell death by normal lymphocytes in the homeostatic (immune) mode. These mechanisms involve Fas receptor (FasR)-/Fas ligand (FasL)-mediated initiation of the extrinsic pathway for apoptosis activation

via activation of the death complex. Buechner et al. showed that BCC tumor cells expressed FasL but not FasR, whereas IFN-treated BCC tumor cells had detectable FasR which increased apoptosis in those BCC cells [27].

A subsequent study by Li and colleagues demonstrated that this IFN-α-mediated upregulation of cell-surface FasR was mediated through the MEK-ERK pathway [28]. It has also been observed that the large numbers of lymphocytes in the tumor microenvironment express both FasR and FasL on their surface as well as secreting soluble FasL into the microenvironment. Presumably because of the relative downregulation of FasR on the cell surface of BCC tumor cells, there is a relative abundance of FasL in the tumor stroma which leads to lymphocyte apoptosis since FasR is expressed on the lymphocyte cell surface, in turn further dampening an immune response [29]. The dying lymphocytes essentially promote the persistence of this proliferative pro-inflammatory environment. From this, we can conclude that IFN works by increasing the expression of FasR on BCC tumors rendering BCCs more sensitive to Fas-mediated apoptosis [28].

Rising IFN levels in the tumor microenvironment have been shown to reverse the proliferative (inflammatory) state which has been preventing FasR expression on the tumor cell surface [28]. Specifically IFN blocks MEK/ERK signaling by inhibiting ERK phosphorylation thereby upregulating FasR expression on the BCC cell membrane, restoring homeostasis.

Another effect of increased IFN is recruitment of more CD4- and CD8-positive lymphocytes within the vicinity of the tumor [30]. This leads to more tumor-infiltrating lymphocytes present with the ability to activate BCC cell death which has restored FasR surface expression. As previously mentioned these activated T lymphocytes express FasL on their own surfaces and can bind to FasR on the BCC cell surface to activate the death complex. They also secrete FasL into the tumor microenvironment. This secreted FasL itself promotes BCC apoptosis within the tumor even when no T lymphocytes are present. This mechanism can lead to widespread regression of the BCC but with the tumor site having the formation of numerous tiny cysts (Fig. 5.9). Both IFN and IMIQ treatment have been associated with this finding [31]. These cysts have always resolved over weeks.

## *Patient/Tumor Selection*

High efficacy has been documented for superficial and nodular BCC with ISRX. However this treatment has been used for other types of BCC in which efficacy of ISRX is decreased. These tumors include:

- Basal cell carcinomas which are not nodular or superficial with histological features showing morpheaform, metatypical (adnexal), sclerosing, and infiltrative features.

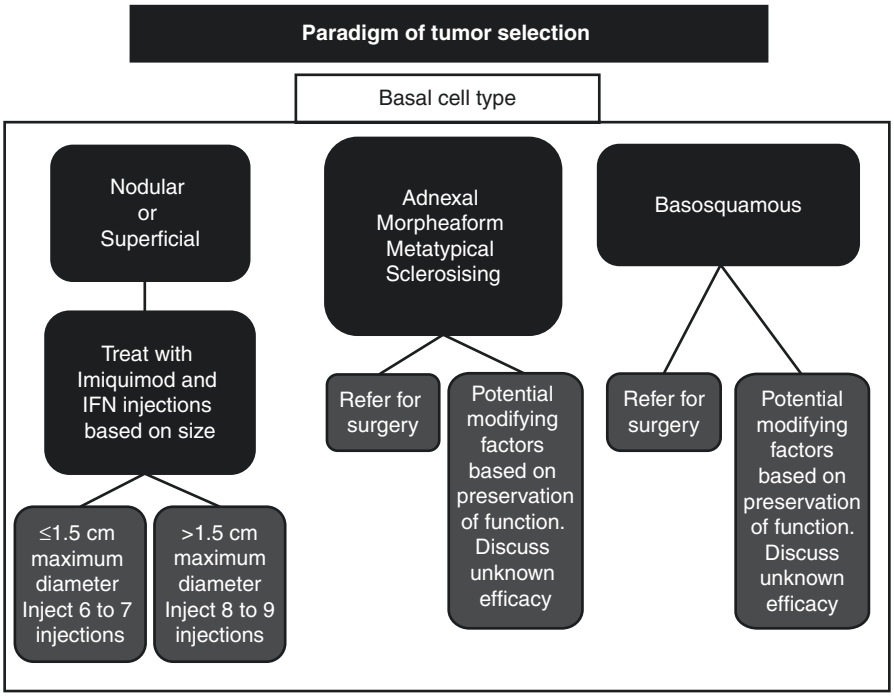


**Fig. 5.9** Paradigm used for choosing tumors that are candidates for ISRX

- Basal cell carcinomas which show no signs of response such as redness or swelling when treated with ISRX for 2–3 weeks.
- Basal cell carcinomas with spindle cell histology (crosstalk tumors) exhibiting both epidermal and dermal components.
- Basal cell carcinomas on immunosuppressed individuals. These include individuals with organ transplants and hematologic malignancies such as CLL.

Aggressive types of BCC have been successfully treated but may require a prolonged regimen or more than one series of ISRX [32]. If the tumor shows redness and swelling and areas of regression with one completed course of ISRX, a complete response can be achieved with prolonged treatment or more than one course of treatment. However, because of the time and effort needed for ISRX therapy, a switch to other methods may be preferred by the patient, and the treatment advantage of a smaller tumor is maintained. If there is no response to ISRX, destructive methods should be used [33].

## *Interferon Injections*

### Preparation of IFN for Injection

Interferon typically comes lyophilized and is accompanied with a diluent bottle. Because of inevitable loss of fluid that occurs when transferring the solution from the bottle into syringes and then again lost when injecting, we dilute the lyophilized IFN with bacteriostatic saline to make 10% more solution than would otherwise be necessary. For example a 10-million-unit vial of IFN would be reconstituted with 2.2 mL of bacteriostatic saline which will give a concentration of approximately 0.5 million units per 0.1 mL. We have not found diminution of efficacy using bacteriostatic saline in place of the accompanying diluent. This dilution has been found to be optimal for the recommended regimen. For very large tumors, the dilution can be even greater, up to two times, to allow for injection into the larger area occupied by the tumor. The optimum syringes to be used for injections are 1 milliliter syringes with plungers (NORM – JECT).

### Injection Technique

Perhaps the most important aspect of ISRX is the injection technique. The following guidelines are essential for obtaining maximal efficacy:

1. The injection must be placed intradermally which can be verified by swelling, blanching, and induration of the skin (Fig. 5.10). Prior to inserting the needle into the dermis, ice wrapped in gauze is placed at the injection site for 5–10 seconds which considerably lessens the discomfort of the needle prick. Incorrect placement of IFN is obvious by leakage of the solution from the injection site or spurting from follicles on sebaceous skin. In these situations an adjustment of the needle is necessary both in location and pressure of injection. If there is no

**Fig. 5.10** Properly placed injection site is above (cephalad) the tumor causing swelling and blanching of the entire upper portion of the tumor

sign of swelling, blanching, or induration, this indicates a subcutaneous rather than intradermal location of injection. The injection should be done slowly with necessary adjustments of both the needle placement and pressure of injection based on leakage of solution from the site.
2. The injection is placed above the tumor (cephalad) just as is the correct application of IMIQ. Injections along the upper sides of the tumor may be done to ensure that the entire tumor is being treated. Swelling, blanching, and induration of the skin should be noted along the entire upper portion of the tumor with this technique. The immune response comes from the surrounding normal skin and is placed cephalad since lymphocytes are affected by gravity and will move caudad into the tumor. They will not move in the opposite direction.
3. Perilesional location of injection is of great importance. Basal cell carcinomas have disrupted intercellular cellular junctions as demonstrated by their easy friability and bleeding. Intralesional injections have a much greater incidence of leaking of the interferon solution for these reasons [9]. If IFN solution is seen leaking out of the skin at the injection site, this fluid should be aspirated back into the syringe and delivered perilesionally with the needle located where the solution stays within the skin. It is critical for maximum efficacy to deliver the entire dose of IFN at the correct location.

### Dosage of IFN

The concentration of ISRX with IFN injections alone is 1.5 million units given 3 times weekly over 3–9 weeks. Treatment with ISRX has been more effective when given over a longer period of time, giving the immune system more time for killing the tumor cells. However a 3-week course of three injections per week, with at least 1 day in between each injection, is the shortest regimen documented to have good efficacy. Spreading the injections out over even longer periods than weekly has no loss of efficacy and allows for flexibility with patient schedules.

### Combination of IFN with IMIQ

In addition to injectable IFN, the IMIQ is also a known potent immune response stimulator. Several studies have shown efficacy in its use for the treatment of BCC leading to its approval as a single agent for superficial BCC [34, 35]. One proposed mechanism is that IMIQ stimulates the immune response by increasing the presence of IFN, as well as other potent cytokines, at the site of application [36]. A potential drawback to the use of this agent alone is its stimulation of the innate immune system through its agonist effect on Toll-like receptor seven, which can lead to attack on bacteria in hair follicles and the skin surface leading to an excessive inflammatory response.

A synergistic effect, with the use of these two agents combined, was noted by one of the authors (SBT) when IMIQ was applied to the tumor area every other

day for 2 weeks prior to beginning IFN injections. The combination caused more swelling and longer induration at the site than the use of either one of the agents alone. The potential additive effect of these two agents may be due to the immune compartments stimulated. IMIQ is applied topically and is highly efficacious in causing resolution of superficial BCC. However, its usefulness as a single agent for BCC is mitigated by instances of the finding of a normal-appearing epidermis with histology showing persistent tumor cells in the dermis. In contrast, injections of IFN are into the dermis. Very little epidermal inflammation is noted with these injections even though a significant dermal lymphocytic response occurs [37]. IFN appears to mainly stimulate the dermal portion of the skin immune system, whereas IMIQ stimulates the epidermal portion of the skin immune system. The combination shows synergism in treating BCC. Because of this noted synergism and the desire for less post-inflammatory hypopigmentation, the combination treatment of ISRX has been used for treating BCC in our clinic for the last 15 years. Successful use of treatment with this combination ISRX in an aggressive basal cell tumor has been reported [38]. An exception to the use of this combination for treating BCC includes lesions on the eyelid where IFN-only injections are performed.

A study at our institution of truncal BCC was performed to evaluate if IMIQ application could be closely monitored in order to allow decrease in the inflammatory response, and thereby post-inflammatory hypopigmentation, and allow fewer IFN injections and amounts of IFN to be used without sacrificing efficacy. Forty subjects were recruited with biopsy-proven nodular and superficial BCC of the trunk (excluding face and scalp). The subjects were instructed to apply IMIQ to just above the site of the tumor for 2 weeks prior to initiating IFN injections. IFN was injected at a dose of 1.25 million units per injection once weekly for 5 weeks. Once the injections were started, the tumor was evaluated for redness or ulceration. A total of five weekly injections were given. At each injection visit, the investigator informed the patient as to how many applications of IMIQ would be used the following week to prevent excessive redness or ulceration. This sometimes involved no application of IMIQ for some weeks. Following the last injection of IFN, at week 7 of the treatment regimen, IMIQ was used for an additional 2 weeks with the instructions as noted before. This study of truncal BCC, with approximately equal numbers of superficial and nodular BCC, showed a CRR of 85% at the final clinical follow-up visit 2 years posttreatment. A higher CRR, however, was expected, and therefore it was concluded that the number of injections and the amount of IFN was not sufficient (unpublished data).

Our current regimen for combination treatment is 6–7 injections of 1.5 million units IFN for BCC based on the size of the tumor (up to 1.5 cm diameter) and the type of BCC. For BCCs that are not nodular or superficial and are larger than 1.5 cm, 8–9 injections are usually given. Application of IMIQ is as described above including 2 weeks preinjection and then again 2 weeks postinjection. The regimen for IMIQ applications below the neck is 5 nights of applications/week and every other night for BCC above the neck. At each injection visit, the schedule for IMIQ application for the subsequent week is given to the patient. Each

time, it is emphasized that there should never be ulceration of the area or redness such that the area cannot be covered with a cosmetic concealer.

All patients on this regimen are seen after 2 weeks of applying IMIQ alone before starting IFN injections. If erythema is not present, the interferon injections are held until erythema is seen. It rarely takes longer than 2 weeks to see a response to IMIQ applications. Please refer to Fig. 5.11 for the timeline of IFN and IMIQ treatments.

This erythema may even begin prior to the 2-week visit. Patients are told at the initial visit when instructions for ISRX are given to stop IMIQ applications even prior to the visit for the first injection if intense erythema is seen at the application site. It is explained that this redness is the sign of BCC cell death, the result of which is erythema. This is similar to the sunburn reaction. With a sunburn there is such extensive DNA damage that the p53 gene complex is unable to repair the damaged DNA of many keratinocytes. As long as the p53 gene of the UV-damaged cells is not mutated or inhibited, apoptotic cell death of sunburn cells is p53-dependent. Similarly, with ISRX, the erythema produced is a sign of the stimulated immune system eliminating BCC cells by apoptosis.

Intradermal IFN injections cause very little apparent epidermal inflammation but typically cause some swelling and mild erythema below the tumor. The tumor may seem to grow when injected with IFN. IFN when used with IMIQ in the combination treatment appears to provide synergism which allows complete responses of BCCs with the added benefit of fewer injections of IFN, fewer applications of IMIQ, and less post-inflammatory hypopigmentation.

## Side Effects

Injection of IFN typically produces a mild flu-like syndrome on the day of injection. Prophylaxis is always recommended for patients consisting of acetaminophen (325 mg) or ibuprofen (200 mg) 1 hour prior to injection, 3 hours postinjection (the time when symptoms most typically occur), the evening of the injection, and the following morning. Using this regimen routinely for prophylaxis of flu-like symptoms typically eliminates their occurrence.

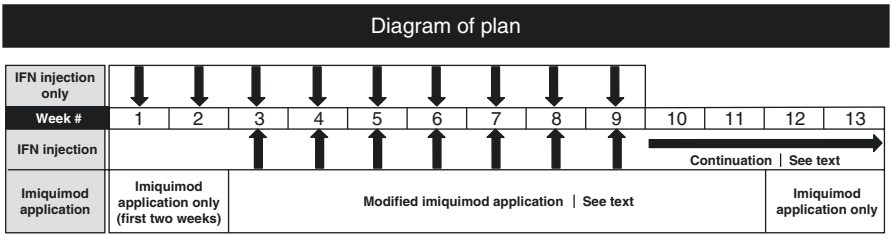


**Fig. 5.11** Schematic showing ISRX regimens for IFN only (top portion) and combination with IMIQ and IFN (bottom portion).Please see text for directions and dosing of IFN only and combination ISRX

### Recommended Follow-Up for BCC Treated with ISRX

Follow-up after treatment is usually done after 3 months. It should be noted that with ISRX, little to no regression of the BCC is observed during the actual treatment itself. The tumor must be clinically evaluated 3 months posttreatment. If skin lines are normal and clearly visualized and/or follicular openings are normal, repeat visits are scheduled for 6 months posttreatment and then annually thereafter. This is our routine surveillance regimen after the treatment of basal cell carcinoma no matter the method of intervention. The patient is informed that long-term follow-up studies have shown an extremely low incidence of recurrence if the tumor has been cleared with ISRX.

## Conclusion

Under certain circumstances surgical methods or destruction are not appropriate or desired by the patient for treatment of BCC. In these cases, consideration of IFN with or without IMIQ can be an option for the patient. The use of ISRX can be highly effective, may allow certain unique advantages over surgical and destructive methods, and result in high patient satisfaction.

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# Chapter 6
# Cryotherapy and Electrodesiccation & Curettage for Basal Cell Carcinoma


**Natalie Kash and Sirunya Silapunt**

## Introduction

Surgical therapy (ST) including surgical excision (SE) and Mohs micrographic surgery (MMS) are generally the preferred treatment options for the treatment of basal cell carcinoma (BCC) in those who can tolerate surgery given that ST allows the posttreatment histologic confirmation of tumor clearance and has been shown to have higher efficacy and lower recurrence rates (RRs) compared to nonsurgical treatment modalities. The National Comprehensive Cancer Network (NCCN) 2018 Clinical Practice Guidelines in Oncology for BCC recommendations on treatment vary based on tumor risk stratification [1]. For the primary treatment of low-risk BCCs, the NCCN recommends electrodesiccation and curettage (ED&C) in non-hair-bearing areas, standard excision with 4 mm clinical margins with postoperative margin assessment, or radiotherapy (RT) for nonsurgical candidates [1]. However, there are individual patient factors such as comorbidities, patient preferences, tumor features, risks of treatment, cosmesis, and function that should be considered in deciding a treatment modality for BCC that is appropriate for the tumor and patient being treated. In those who are not ideal surgical candidates, there are a number of nonsurgical treatment options. The NCCN recommends that topical therapies, cryotherapy (CT), and photodynamic therapy (PDT) be considered in cases of low-risk, superficial BCCs in patients where ST and RT are contraindicated or impractical [1]. This chapter will cover CT and ED&C. Additional nonsurgical treatment options including topical therapy, PDT, laser therapy (LT), RT, intralesional therapy, and systemic therapy such as targeted therapy and immunotherapy will be discussed in other chapters (see Chaps. 4, 11, 12, 10, 5, 13, and 14).

N. Kash · S. Silapunt (✉)
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA
e-mail: Sirunya.Silapunt@uth.tmc.edu



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_6

## Cryotherapy

### *Background*

Cold has been used as a medical therapy for thousands of years, by the ancient Egyptians and in Greece by Hippocrates, for its analgesic and anti-inflammatory properties [2]. However, in more recent times, cold has been used in focal areas to cause localized tissue destruction, which has been termed CT or cryosurgery (CS). This was first reportedly accomplished by the English physician, James Arnott, in the mid-nineteenth century by using a mixture of salt and crushed ice to cause localized destruction for the palliation of tumors including skin cancers [2]. In the late nineteenth century and early twentieth century, refrigerated liquid air, refrigerated liquid oxygen, and carbon dioxide snow gained popularity [2].

However these methods of CS fell out of favor with the development of liquid nitrogen spray by Douglas Torre in 1965 [2]. Shortly after in 1967, Setrag Zacarian developed a handheld device, Kryospray, and copper probes which allowed freezing of tissue to a depth of 7 mm [2, 3]. The liquid nitrogen handheld device allowed the operator to spray using one hand, and its relative ease of use quickly made this device popular in dermatology for the treatment of a number of benign skin lesions, precancerous actinic keratosis, and select skin cancers, including low-risk BCCs [2].

### *Mechanism of Action*

Cryotherapy uses liquid nitrogen to create freeze-thaw cycles in order to destroy tumor cells. Normal cells may also be destroyed. The mechanism of cellular injury in CT has been well studied and is multifactorial. There is rapid transfer of heat from the skin to a heat sink as the liquid nitrogen boils upon contact with warmer tissue. Cryotherapy leads to extracellular ice formation, which on its own is insufficient to cause lethal damage to cells [4]. However, extracellular ice formation has downstream effects including hypertonic damage as extracellular water decreases causing shifts in fluid and electrolytes and disrupting cell membranes [4]. The rapid electrolyte exchange brought about by shifts in temperature during freezing and thawing is thought to damage cell proteins and enzymes [4].

Additionally, there is intracellular ice formation with rapid freezing which is thought to lead to cellular death and damage to organelles including the mitochondria and endoplasmic reticulum [4]. Recrystallization of ice during slow thawing also leads to cell damage, explaining the known increase in tissue damage with slower thawing. In addition to direct cellular injury, there is also vascular occlusion and ischemia. Initially, arteriospasm leads to decreased blood flow. About 30 seconds after freezing is completed, the rewarming process begins as arterial blood flow resumes. However, there are venular and capillary dilatation, fluid leakage out

of vessels leading to skin edema, hemoconcentration, and red blood cell sludging leading to a continued decrease in tissue perfusion for hours and even days with the development of blood vessel necrosis and tissue gangrene in severe cases [4].

Low temperatures affect different tissue components in different ways, and there are varying degrees of sensitivity to cold among different cell types. After freezing, collagen fibers in the lamina propria have been noted to appear disoriented, while dermal collagen networks appear to remain intact [4, 5]. This preservation of dermal collagen explains the low risk of atrophic or contracted scars with this treatment modality. In peripheral nerves, CT has been shown to lead to axonal degeneration, but intact collagen within the perineurium is thought to allow regrowth along the original neural networks and eventual restoration of normal neuronal function [4, 6].

In regard to differences among cell types, melanocytes are more sensitive to cool temperatures than other cells and only require a temperature of −5 °C for destruction explaining hypopigmentation in treated areas following CT. Epithelial cells such as keratinocytes have been shown to be more sensitive to injury with low temperatures than fibroblasts [4]. A temperature of −50 °C is needed for adequate destruction of keratinocytes, correlating with the recommendation to achieve a temperature of −50 °C to −60 °C or lower for CT in the treatment of malignant skin cancers, such as BCCs [4]. Rapid thaws have been shown to lead to decreased fibroblast collagen production which has led to the use of rapid thaws in situations where decreased collagen production is desirable including in the treatment of benign lesions in scar-prone areas and for keloidal scars [7]. However, the increased tissue destruction associated with slow thaws makes this method preferred in the use of CT for the treatment of malignant lesions.

## *Efficacy*

The efficacy and RR of CT in the treatment of primary and recurrent BCC reported in the literature vary greatly among individual studies. This may reflect variability in user technique, patient characteristics, tumor characteristics, and study design.

Some of the lowest RRs for CT have been published by single clinicians including by Kuflik. In his report on his 30-year experience with CS for skin cancer in 2004, he selected cases of BCC with well-defined borders, unrestricted location, primary and select recurrent tumors, and size ranging from 2 to 100 mm with the majority being 5–20 mm in diameter to be treated with CT [8]. He included 4406 new and recurrent skin cancers including 3937 BCCs, 446 squamous cell carcinomas, and 23 basosquamous carcinomas between 1971 and 2001 and reported a 30-year cure rate (CR) of 98.6% with a RR of 1.4% (62/4406) with similar RRs noted between different locations [8]. He also reported a more recent 5-year CR of 98.8% (or RR of 1.2%) in 415 BCCs from 1990 to 1996 [8]. There were 5 recurrences among the 415 BCCs, and 4 of the 5 were previously treated (recurrent) tumors [8].

A systematic review and meta-analysis by Rowe et al. included 14 studies on CT published between 1972 and 1984 [9]. Thirteen of these studies reported RRs at <5 years which ranged from 0% to 12.9% [9]. The average RR at <5 years from all included studies weighted by the number of lesions was reported as 3.7% (90/2462) [9]. The review found only a single study which provided a RR at 5 years for CT, which found a 5-year RR of 7.5% (20/269) for CS in the treatment of eyelid BCCs [9, 10]. Rowe et al. called for studies with longer periods of follow-up. The weighted average RRs at <5 years and 5 years were compared to the weighted average RRs for other treatment modalities including SE, ED&C, RT, and MMS. The short-term (<5 year) and long-term (5-year) weighted average RRs for CT were 3.7% and 7.5%, respectively [9]. The short-term weighted average RR of CT was higher than the reported weighted average RRs for SE and MMS which were 2.8% and 1.4%, respectively, and was lower than the reported weighted average RRs for ED&C and RT which were 4.7% and 5.3%, respectively [9]. The long-term weighted average RR of CT was higher than the reported weighted average RRs for MMS which was 1.0% and lower than the reported weighted average RRs for SE, ED&C, and RT which were 10.1%, 7.7%, and 8.7%, respectively [9].

In a systematic review by Thissen et al., 4 patient series on CT were included with a total of 796 BCCs located exclusively on either the nose in Nordin et al. or on the eyelid in Lindgren and Larko, Anders et al., and Fraunfelder et al. [10–14] The raw RR[1] ranged from 0% to 11.4% among the four studies with a mean of 3.0% (24/798) [11]. The strict RR[2] ranged from 0% to 20.4% with a mean of 4.3% (24/556) [11]. The cumulative 5-year rate was not available from the Nordin et al. study and ranged from 0% to 16.5% in the remaining three studies [11]. There was no calculable mean cumulative 5-year rate for the four studies given the lack of data in the Nordin et al. study [11].

## *Safety*

Risks of CT are primarily localized. Short-term risks include pain, discomfort, bleeding, discharge, edema, blister formation, and tissue necrosis in the treated and surrounding areas. Scarring and a poor cosmetic outcome (CO) are also risks. Scars following CT typically have a central area of hypopigmentation with a peripheral rim of hyperpigmentation. The hypopigmentation generally persists for months to years. Hypopigmentation is common with CT for BCC given the low temperatures required for adequate treatment and the high sensitivity of melanocytes to low temperature injury. Milia have also been described in the treated area following CT.

[1] Raw rate: absolute number of patients with recurrence divided by the number of patients at study start [11].

[2] Strict rate: absolute number of patients with recurrence divided by the number of patients observed for at least 5 years [11].

## *Comparative Studies*

Compared to alternative treatment modalities for BCC, CT is relatively fast and cost-effective. However, disadvantages of CT include great variability in technique, operator dependence, and inability to histopathologically evaluate tumor margins. Additionally, there are a number of comparative studies that show poorer COs associated with CT compared to SE and PDT.

A prospective randomized study compared CS (with initial curettage, two freeze-thaw cycles, 20-second freeze time, thaw time of 60 seconds, and 5 mm margins) to SE (with 3 mm margins) for the treatment of primary, histopathologically proven, uncomplicated, nodular, and superficial BCCs of the head and neck [15]. Exclusion criteria included size ≥20 mm, recurrent BCC, patients with five or more BCCs, life expectancy <1 year, and contraindication to surgery or CS such as cold intolerance [15]. There were 48 BCCs in each group [15]. Patients were followed for 12 months after treatment [15]. Cosmetic outcomes were graded on a scale of 1 (very bad) to 10 (excellent) and as good, fair, or bad by the patient and graded as either good, fair, or bad by a group of professionals not involved in treatment who were blinded to the treatment modality (a beautician, a male dermatologist, a female dermatologist/Mohs surgeon, a plastic surgeon, and a nurse from the department of dermatology) based on photographs taken 1 year after treatment [15]. Cosmetic outcomes graded by the clinical professionals were significantly better for the SE group compared to the CT group [15]. There was no statistically significant difference in the COs graded by beauticians between the two groups [15]. The COs graded by the male dermatologist were poorer for tumors located on the cheek, periauricular, and neck area regardless of which therapy was given with no statistically significant difference in COs between the CS and SE groups [15]. There was a statistically significant difference in COs graded by patients between the groups with better COs with the SE group compared to the CS group, independent of tumor size and location [15]. There were three recurrences within 1 year from treatment in the CS group and none in the SE group [15]. The authors concluded that CS should be reserved for patients with contraindications to surgery or for small superficial or nodular BCCs on the eyelid, inner eye angle, and helix where preservation of important underlying structures is desired [15].

Wang et al. performed a non-blinded, prospective randomized phase III clinical trial comparing δ-aminolevulinic acid (ALA) PDT to CS in the treatment of histopathologically verified nodular or superficial BCCs [16]. Twenty percent weight-based ALA/water-in-oil cream was applied to the lesion and a 10-mm-wide surrounding zone, covered with a thin occlusive dressing, and then treated 6 hours after application with a frequency doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) laser as a light source tuned to 635 nm wavelength, quasicontinuous mode, 5 kHz repetition rate, and 100 ns pulse width [16]. In the CS group, two 25–30-second freeze-thaw cycles were performed by a dermatologist experienced with CS with a thawing period of 2–4 minutes [16]. Patient was assessed for clinical

evidence of residual tumor at 1, 4, and 8 weeks and 3 months and for recurrence at 12 months after treatment [16]. Biopsies were performed to assess for residual tumor growth at 3 months and for recurrence at 12 months [16]. If there was histologic evidence of BCC at 3 months, then patients in the PDT group were retreated with PDT [16]. However, in the CS group, those with histologic evidence of BCC at 3 months were only retreated with CS if there was clinical evidence of recurrence [16]. This is a notable difference in the treatment strategy of the two groups, and 30% of lesions (13/44) were retreated in the PDT group, while only 3% (1/39) were retreated in the CS group [16]. The RR based on biopsy at 12 months was 25% in the PDT group and 15% in the CS group, but the difference was not statistically significant [16]. Pain and discomfort were self-reported by patients and were overall low with both treatment modalities with no statistically significant difference between the two groups [16]. At 1 week, there was significantly less leakage and edema in the PDT group but no significant difference in erythema between the two groups [16]. At 4 weeks, there was significantly less leakage in the PDT group compared to the CS group [16]. In terms of crust formation and necrosis, at 1 week, there was significantly more necrotic crust in the CS group versus the PDT group (12/39 vs. 6/44) [16]. There was no statistically significant difference in crust and necrotic crust formation at 4 weeks after treatment [16]. The CO including hypopigmentation, hyperpigmentation, scarring, tissue defect, and overall judgment was significantly better in the PDT group compared to the CS group [16]. This study has been used to support consideration of ALA-PDT in the treatment of large and superficial lesions especially in locations and situations where function, healing, and CO are particularly important [16].

These findings of comparable RRs with poorer COs with CT when compared to PDT were further supported by a multicenter, prospective randomized study published in 2008 by Basset-Seguin et al. which notably followed patients for 5 years [17]. They compared methyl aminolaevulinate (MAL) PDT (160 mg/g MAL cream applied for 3 hours before illumination, 570–670 nm, 75 J/cm$^2$) to CT (two freeze-thaw cycles) in the treatment of superficial BCCs and found no statistically significant difference in the 5-year RR (22% in the MAL-PDT group versus 20% in the CT group, $p = 0.86$) [17]. All patients with an incomplete response at 3 months received two further MAL-PDT (20/114) sessions or repeat CT (16/105) [17]. Cosmetic outcome was graded, and there was a significantly higher percentage of patients in the MAL-PDT group with excellent COs compared to the CT group (60% vs. 16%, $p = 0.00078$) further supporting consideration of treatment with PDT, including MAL-PDT, in cases of superficial BCCs where CO is important and close follow-up is feasible [17].

Of note, a prospective randomized trial of 93 patients by Hall et al. comparing CT and RT in the treatment of BCC reported the risk of recurrence at 2-year follow-up to be 39% in the CT group compared to 4% in the RT group [18]. At 2-year follow-up, 39% (17/44) of the CT group was noted to have histologically proven recurrence, while 4% (2/49) of the RT group was noted to have histologically proven recurrence [18]. The CO and localized complications were noted to

be similar between the two groups. Clinical appearance was graded from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = very bad) in three areas including atrophy, scarring, and pigmentary change. The scores were comparable between CT and RT with a score of 0.94 for RT and 0.88 for CT, 0.31 for RT and 0.54 for CT, and 1.00 for RT and 1.03 for CT in the areas of atrophy, scarring, and pigmentary change, respectively, with overall photograph score of 1.35 for RT and 1.43 for CT [18]. The rates of necrosis and severe localized pain, swelling, and discharge were comparable between the two groups [18]. Hypopigmentation occurred more frequently (in 88% of the CT group and 81% of the RT group) than hyperpigmentation in both groups [18]. Five patients in the CT group (11%) developed milia which disappeared within 1 year [18]. This study was excluded from the Rowe et al. study as the RR in the CT group was three times higher than the RR reported in any other study [9]. The Rowe et al. authors felt that the authors' background as radiotherapists may have provided a bias against CT and limited the degree of experience with proper CT technique. Some, including Hall et al., have used this study to argue that CT is not a satisfactory alternative to RT in the treatment of BCC.

Additionally, a prospective randomized trial by Mallon et al. compared one freeze-thaw cycle to two freeze-thaw cycles in the treatment of facial BCCs [19]. There were 84 facial BCCs randomized to receive either a single 30-second ($N = 36$) or double 30-second freeze-thaw cycle ($N = 48$) [19]. Of note, the diagnosis of BCC was made clinically in the majority of cases in this study, and biopsy was only performed to confirm the diagnosis in cases where diagnosis was not clear based on clinical grounds alone [19]. The follow-up period ranged from 1.2 to 6.1 years for the two freeze-thaw cycle group and from 10 months to 7.1 years for the one freeze-thaw cycle group. The RR for CT for the treatment of facial BCCs was 4.7% in the two freeze-thaw cycle group and 20.6% in the one freeze-thaw cycle group [19]. The study concluded that two freeze-thaw cycles should be performed in CT for the treatment of facial BCCs given the decreased RR in the two freeze-thaw cycle group compared to the one freeze-thaw cycle group. Additionally, the study looked at a single group of 29 superficial BCCs on the trunk with a maximum diameter of 20 mm treated with one 30-second freeze-thaw cycle and followed patients between 2.1 and 4.1 years. The RR was found to be 4.5% [19]. This study concluded that one freeze-thaw cycle was adequate for treatment of truncal BCCs, but other authors have advocated for two freeze-thaw cycles independent of location to lower the RR.

## *Discussion*

Careful review of studies with the highest and lowest RRs reveals differences in study design including follow-up time and case selection as well as significant differences in user technique. For example, in the Hall et al. study, the authors reported

reaching recorded temperatures of only −25 °C to −30 °C beneath tumors [18], while some of the lowest RRs are from studies by single experienced clinicians, such as Dr. Emanuel G. Kuflik [8, 20]. In his report of his 30-year experience with CS referenced above, he reports a 30-year CR of 98.6% [8]. Kuflik utilized careful CT technique including open spray technique, freeze time of 40–90 seconds for 10–15 mm lesions, at least 3–5 mm margins, tissue temperate at the base of the tumor of −50 °C to −60 °C, slow and spontaneous thaws, and a repeated freeze-thaw cycle and additionally reported using preliminary curettage in the majority of cases [8].

For increased efficacy and to avoid tumor recurrence, many experienced operators recommend to freeze malignant skin lesions including BCCs using a temperature of at least −50 °C to −60 °C, cooling velocity of more than −100 °C/min, slow thaw, freeze time of at least 30 seconds after iceball formation, margin of at least 3–5 mm of normal surrounding tissue, and at least two repetitions of the freeze-thaw cycle [2, 4, 19]. Cryotherapy is dependent on the skill of the operator and requires sufficient operator education on correct technique. Thus, appropriate education on CT technique for the treatment of BCC is vital for efficacy in these cases, and variation in technique may to some degree explain variability of efficacy and RRs reported in the literature.

## Electrodesiccation and Curettage

### *Background*

Electrodesiccation and curettage is an option for the treatment of BCC that is appropriate for primary, low-risk tumors. The technique of ED&C initially described involved tumor removal and destruction by alternating three cycles of scraping with a curette to remove tumor with denaturation using electrodesiccation. In recent years there has been a shift by many clinicians from the traditional technique described above to three cycles of curettage followed by one cycle of electrodesiccation based on studies showing RRs of curettage alone comparable to those of traditional ED&C (see Fig. 6.1 and section "Efficacy"). This method of treatment requires the ability of the clinician to feel the difference while curetting between soft tumor and firm dermis to allow selective and complete tumor removal. Thus, if subcutaneous tissue is reached, numerous authors and the NCCN recommend converting to SE as the ability to differentiate tumor from normal tissue is lost given that both tumor and adipose tissue are soft [1]. Of note, terminal hair-bearing areas such as the scalp, pubic area, axillary area, or beard in males should be avoided as tumor may track down follicular structures in these regions, and ED&C will not allow treatment depth to adequately treat tumor with follicular extension [1].

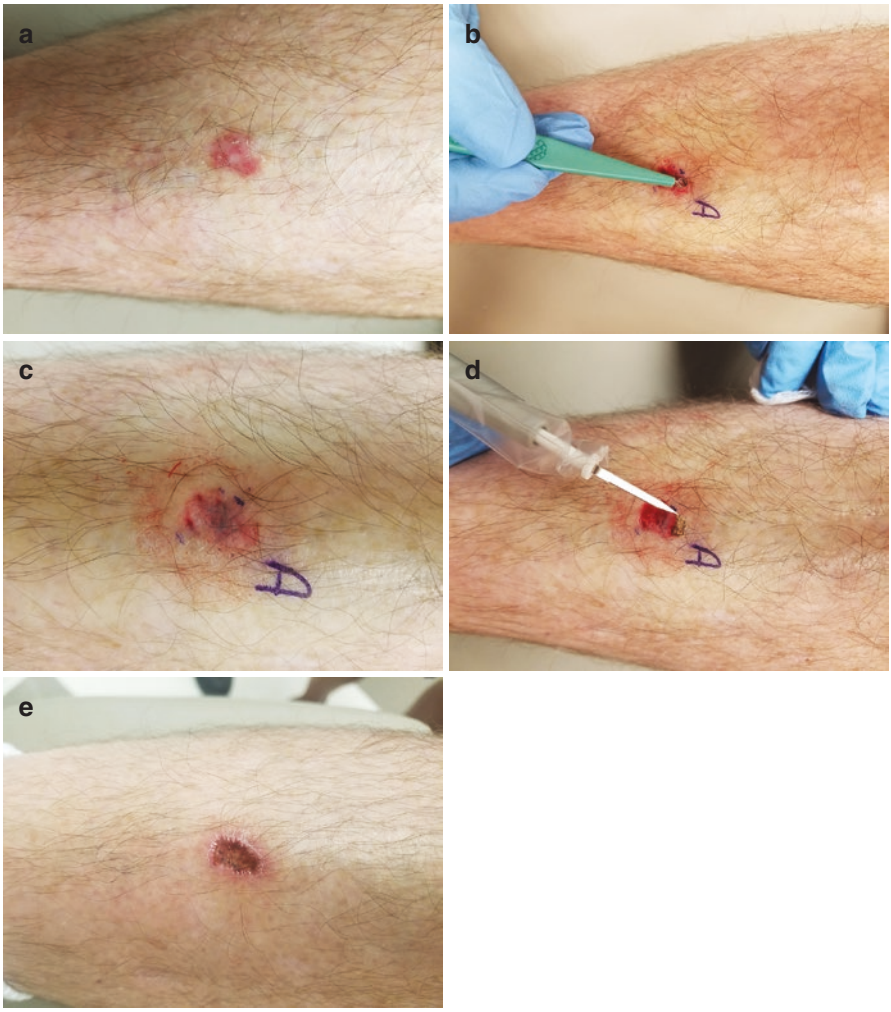


**Fig. 6.1** A 62-year-old white male with a nodular BCC on right shin (**a**); curettage was performed (**b**); immediately after three passes of curettage in three different directions were performed (**c**); electrodesiccation was performed (**d**); 1 week after treatment (**e**)

## *Mechanism of Action*

There is direct removal of tumor by scraping away tumor with the curette. Tumor is scraped away until the clinician feels firm normal dermis rather than soft tumor. In addition, electrodesiccation is thought to allow denaturation of the area; however, observational and retrospective studies have shown similar efficacy between ED&C and curettage alone (see section "Efficacy").

## *Efficacy*

The CRs and RRs reported in observational studies, retrospective studies, and systematic reviews vary based on a number of factors including technique used by the operator, study design, and case selection including tumor characteristics such as size, location, and histologic subtype.

The systematic review and meta-analysis by Rowe et al. included 12 studies from 1950 to 1981 reporting short-term (<5 year) RRs which ranged from 1.8% (17/948) by Knox et al. in 1967 to 25.0% (16/64) by Ward and Hendrick in 1950 [9, 21, 22]. The weighted average RR based on the 12 studies reporting RRs at <5 years was 4.7% (173/3664) [9]. This was higher than the weighted average short-term RR reported for SE, CT, and MMS which were 2.8% (157/5560), 3.7% (90/2462), and 1.4% (5/367), respectively [9]. This was lower than the 5.3% (318/6072) short-term weighted average RR reported for RT. Rowe et al. found 10 studies between 1963 and 1985 which reported long-term (5-year) RRs which ranged from 1.3% (4/315) by Knox et al. in 1967 to 18.8% (112/597) by Kopf et al. in 1977, with an overall weighted average RR of 7.7% (274/3573) [9, 21, 23]. The weighted average RR for ED&C of 7.7% was higher than the long-term weighted average RR reported for CT and MMS which were 7.5% (20/269) and 1.0% (73/7670), respectively, and lower than those for SE and RT, which were 10.1% (264/2606) and 8.7% (410/4695), respectively [9].

Thissen et al. included six studies on ED&C and reported raw RRs for five studies ranging from 3.8% to 18.1% [23–25], strict RR for one study of 8.5% [25], and cumulative 5-year RR for four studies ranging from 5.7% to 18.8% [11, 23, 26]. No weighted average RR could be calculated to allow comparison between treatment modalities given non-standardized design between studies.

There is clearly great variation in 5-year CRs of ED&C in the treatment of BCC reported in the literature, ranging from 81.2% to 98.7% [9]. A number of factors may explain the variability in RRs and CRs including differences in follow-up time, methods of calculating RR and CR, operator technique, and characteristics of tumors included in different studies.

One factor is variability in calculation of RR as strict, raw, or 5-year cumulative based on life table analysis. For example, a study by Dubin and Kopf demonstrated a strict RR of 26% for ED&C in the treatment of BCC performed at their institution between 1955 and 1969; however, the same group in a later paper by Silverman et al. felt that this was an overestimate likely reflecting the calculation of RR as a strict RR and reported lower RRs using 5-year cumulative RRs (17.0% for those performed between 1955 and 1963) [26, 27].

A number of studies support the association of longer follow-up time with higher RRs, and most advocate for at least 5-year follow-up with Rowe et al. advocating for lifetime follow-up given the known slow growth rate of BCCs and reports of BCC recurrences greater than 10 years after treatment [9, 28–30]. Additionally, studies by the same authors following a single group of patients over time and calculating RRs at different time points clearly demonstrate this. For example,

Reymann followed the same group of 178 patients with 338 BCCs treated with curettage alone for 1 year, 38 months, and 5 years and found RRs of 3.6%, 8.4%, and 10.1%, respectively [31–33].

## *Operator Dependence and Technique*

Additionally, operator technique and experience also seem to play a role and may to some degree explain some of the variability seen in RRs reported with ED&C in treatment of BCC.

Williamson and Jackson first demonstrated operator dependence in ED&C for the treatment of BCC. In 1962 they reported an overall RR of 7.7% for ED&C in the treatment of biopsy-proven BCC [34]. Of note, there were substantial differences in the RRs between the four doctors performing the procedure. They noted that the RR for ED&Cs performed by Doctor A, who had interest and training in ED&C, was 2.6%, while the RR for ED&Cs performed by Doctors B, C, and D who were resident physicians with no prior experience with ED&C was 10.8% [34].

Kopf et al. compared 5-year cumulative RRs for ED&C in the treatment of BCC among three groups: Group A (597 BCCs treated from 1958 to 1962 at the Skin and Cancer Unit at New York University Medical Center), Group B (91 BCCs treated in 1970 at the Skin and Cancer Unit), and Group C (210 BCCs treated from 1962 to 1973 in private practice) [23]. Dermatology residents treated many of the tumors in the Skin and Cancer Unit in both Groups A and B, while they were not involved in the treatment of BCCs in the private practice setting of Group C. The 5-year cumulative RRs for Groups A, B, and C were 18.8%, 9.6%, and 5.7%, respectively [23]. There were thought to be multiple explanations for this difference. The higher percentage of tumors located on the head and neck in Groups A (83%) and B (67%) compared to C (52%) were thought to contribute [23]. However, operator experience was also thought to contribute given the significant improvement in the 5-year cumulative RR between Groups A and B after implementation of efforts to improve resident training and supervision in performing ED&Cs in the late 1960s [23]. Silverman et al. provided additional data in 1991 from the Skin and Cancer Unit and included 2314 primary BCCs treated with ED&C between 1955 and 1982 [26]. Their multivariate analysis showed treatment during the time span of 1955–1982, prior to increased efforts to provide adequate resident supervision and training in ED&C technique, to be associated with increased risk of recurrence. The 5-year RRs for ED&Cs performed during the time periods of 1955–1963, 1964–1972, and 1973–1982 were 17.0%, 12.3%, and 7.3%, respectively [26].

Spiller and Spiller performed a retrospective review of 233 biopsy-proven BCCs treated with ED&C and followed for ≥5 years and reported an overall CR of 97.0% [35]. When they excluded tumors >20 mm and tumors located on the high-risk nose or nasolabial area, they found a CR of 99.4% (171/172) [35]. They also noted good COs with no hypertrophic scarring in the study group [35]. They attributed their higher CR, lower RR, and improved COs compared to other studies to high rates of

follow-up and operator experience and technique [35]. They reported adjusting the number of ED&C cycles to the individual patient and tumor [35]. For example, if a tumor was <10 mm and there was no residual tumor felt after one pass, they would not perform additional passes to minimize scarring [35]. They reported obtaining 2–4 mm peripheral margins with curettage like many other studies but reported using electrodesiccation only in order to achieve hemostasis and obtain a minimal safety margin [35].

More recently in 2002, a retrospective review by Werlinger et al. included 102 BCCs treated with ED&C (with 3 cycles and 2–5 mm margins) and 90 BCCs treated with SE (2–4 mm margins) with a mean follow-up time of 4.1 years in the private practice setting and demonstrated a 5-year cumulative RR of 3.7% for ED&C and 1.7% for SE for the treatment of BCC [36]. The procedures were performed by two dermatologists, one with 24 years of experience and one with 3 years of experience [36]. The majority of BCCs were located on the head and neck, and tumors up to 20 mm were included [36]. There was no statistically significant difference in the RRs between ED&C and SE or between the two clinicians [36]. However, the RR reported for ED&C was significantly lower than those previously published, and the authors concluded that one explanation is the increased experienced of the private practice clinicians compared to the clinicians, often dermatology residents, performing the procedure at academic institutions [36]. This highlights the importance of clinical education, proper technique, and experience in the performance of ED&C for the treatment of BCC to ensure an adequate CR.

Adequate training and supervision of the inexperienced practitioner is vital in order to allow development of the meticulous, detail-oriented technique and the ability to differentiate tumor from normal tissue required to ensure adequate CRs with ED&C. The curette should be firmly passed along the base of the entire tumor with at least 2–5 mm peripheral margins. For the best CR, ED&C should include multiple passes in three different directions; however, some authors such as Spiller and Spiller advocate for a single pass in certain cases, such as small tumors in which there is no identifiable residual tumor after one pass, to improve COs [35]. The base should be wiped between passes to allow for better visualization of any evidence of residual tumor such as dermal irregularity, friability, grittiness, and pooling of blood [37]. Any prominent follicular ostia should be treated with subsequent curettage with a smaller curette when needed [38, 39]. Normal dermis is described as firm and regular with pinpoint bleeding [37]. The use of magnifying loupes is described in the methods of many studies and advocated for by many authors to allow for more detailed inspection of the base and identification of tumor features versus normal dermis.

Additionally, a variation in technique with curettage alone has been shown to have CRs and RRs comparable to those reported for ED&C. The 1971, 1973, and 1985 Reymann studies (see above) reported 1-year, 38-month, and 5-year RRs of 3.6%, 8.4%, and 10.1% with curettage alone for the treatment of BCCs which are within range of reported RRs with ED&C [31–33]. Reymann later went on to treat 1057 BCCs total in patients with multiple BCCs (581 BCCs at study initia-

tion) with curettage alone with a mean follow-up time of 30.8 months and reported a RR for curettage alone of 2.8% (16/581) similar to those reported for ED&C [40]. Later in 1983, McDaniel reported a group of 644 BCCs treated with curettage alone [25]. Curettage alone was performed with 3–4 mm peripheral margins [25]. He noted 28 recurrences with a CR of 91.5%, comparable to previously reported CRs with ED&C [25]. He did note that COs with curettage alone were better than the COs expected with ED&C. He also noted additional advantages of curettage alone including simplicity, ease, less time required, and lower associated cost [25]. More recently, in 2006 Barlow et al. conducted a retrospective review of patients with biopsy-proven BCC treated with curettage alone with a minimum of 5-year follow-up [41]. In the majority of cases, curettage alone was performed in at least three directions with 2–5 mm peripheral margins immediately after shave biopsy [41]. Tumors that extended to subcutaneous tissue or were found on pathology to have micronodular, infiltrative, or morpheaform features were typically sent for SE or MMS [41]. The only tumors included in the study which on histopathologic exam were found to have aggressive features were in patients that preferred to be observed following curettage at the time of biopsy rather than undergo further treatment with SE or MMS [41]. Patients were followed for at least 5 years. Biopsy was performed only if there was clinical suspicion for recurrence, and recurrence was based on histopathologic findings [41]. The 5-year RR was 3.97% of individual tumors and 4.97% of tumors available for follow-up (with CRs of 96.03% and 95.03%, respectively) [41]. The CR was noted to be comparable to those published for ED&C [41]. The CR of 95.03% of tumors available for follow-up was noted to be near identical to that reported by McDaniel which used life table analysis to adjust for patients lost to follow-up [25, 41].

## *Tumor Characteristics*

The variation in CRs and RRs reported for ED&C in the literature is also thought to reflect variability in case selection including tumor characteristics such as size, location, and histologic grade. A number of studies have demonstrated higher CRs and lower RRs for ED&C in the treatment of smaller BCCs compared to those reported with larger BCCs. Additionally a number of high-risk areas have been identified including the head and neck compared to the trunk and extremities, specifically the nose, nasolabial area, eyelids, medial canthi, ears, and lips [26, 35, 41, 42].

For example, Spiller and Spiller in their retrospective review of 233 biopsy-proven BCCs treated with ED&C with 5-year follow-up (see above) reported RRs of 1.23% (2/163), 2.22% (1/45), and 16% (4/25) for tumors that were ≤10 mm, 10–20 mm, and >20 mm, respectively [35]. More recently, a study by Julian et al. studying the 5-year CR of ED&C in 405 BCCs further demonstrated higher CRs among smaller tumors compared to larger tumors [43]. They reported 5-year CRs of 80% for lesions <10 mm and 88% for those <5 mm [43].

Additionally, in a multivariate analysis by Dubin and Kopf, risk factors found to be associated with a higher risk of recurrence in cases of BCC treated with ED&C included increasing tumor diameter and location on the face specifically the nose, ears, and forehead [27]. The 1991 study by Silverman et al. from the same group which included 2314 primary BCCs treated with ED&C performed a multivariate analysis showing increased diameter, location on a high-risk site (including the nose, paranasal area, nasolabial groove, ear, chin, mandibular area, perioral area, and periocular area), and location on a middle-risk site (including the scalp, forehead, preauricular area, postauricular area, and malar area) to be associated with increased risk of recurrence [26]. The analysis found that age, sex, and lesion duration did not affect RR [26]. For the most recent time span (1973–1982), the 5-year RR for BCCs of all sizes on low-risk sites (neck, trunk, and extremities) was 3.3% [26]. For middle-risk sites (as defined above), the 5-year RR was 5.3% for tumors <10 mm and 22.7% for tumors ≥10 mm [26]. The 5-year RR for BCCs located on high-risk sites was 4.5% for tumors <6 mm and 17.6% for tumors ≥6 mm [26]. The authors concluded that ED&C is a reasonable treatment consideration in BCCs <6 mm regardless of site including high-risk sites and in larger tumors depending on their location [26].

Salasche performed a prospective study on 100 biopsy-proven, primary, nodular BCCs that were ≤10 mm in size comparing the percentage of tumors with residual lesion present after ED&C between tumors located on the nose or nasolabial fold and non-nose regions of the head and neck [42]. He included 50 BCCs on the nose or nasolabial fold and 50 on the non-nose head and neck [42]. After ED&C was completed, one-stage MMS was performed to allow for assessment of any residual tumor cells [42]. The nose and nasolabial fold group was noted to have a significantly higher rate of residual tumor (30%) compared to the non-nose head and neck group (12%) [42].

Additionally, Spiller and Spiller not only reported higher RRs in larger lesions but also identified high-risk sites on the head and neck, in particular the nose and nasolabial area [35]. Among the 163 tumors that were ≤10 mm, there were 2 recurrences both of which were on the nose with a RR of 6.45% (2/31) for tumors ≤10 mm located on the nose and RR of 0% (0/132) for tumors ≤10 mm located in a location other than the nose [35]. They also found a CR of 99.4% (171/172) for BCCs <20 mm in size and not located on the nose or nasolabial area [35].

Filho et al. and Suhge d'Aubermont and Bennett studied the percentage of BCCs with evidence of residual tumor on histopathologic evaluation following ED&C [44, 45]. Filho et al. found histologic evidence of persistent tumor in 25% (5/20) of BCCs treated with 2 cycles of ED&C [44]. Suhge d'Aubermont and Bennett found histologic evidence of residual tumor in 33.3% (23/69) of BCCs treated with 3 cycles of ED&C [45]. Of note, they also demonstrated a statistically significant difference in the rates of histologic evidence of persistent tumor following ED&C between BCCs located on the head (46.6%) and trunk and extremities (8.3%). The preoperative and postoperative sizes were comparable between the two groups [45]. However, it is important to note that histologic evidence of residual tumor immediately after treatment with ED&C is not equivalent to clinical recurrence, and these

rates of histologic evidence of residual tumor immediately following ED&C cannot be interpreted as RRs as the process of healing and scar formation is thought to destroy residual tumor cells [46, 47].

Higher RRs than those typically reported in the literature, 19%–27%, were found in studies where BCCs in high-risk locations and high-risk histologic subtypes were treated with ED&C [43, 48]. In regard to high-risk histologic subtypes, Blixt et al. performed a retrospective study on 37 primary BCCs with either an infiltrative, desmoplastic, morpheaform, or micronodular pattern on histology and found a 27% RR (10 had recurred at 3.3 years) with median follow-up time of 6.5 years [48, 49]. Given the demonstration of higher RRs associated with ED&C performed by inexperienced operators and in the treatment of BCCs with high-risk features, including high-risk locations, aggressive histologic subtypes, and large size, many sources including the NCCN recommend consideration of ED&C as a treatment modality only in appropriately selected cases of primary, superficial or nodular, low-risk BCCs with an experienced operator.

## *Safety*

Risks of ED&C primarily include poor COs including hypopigmentation, hypertrophic scar formation, atrophy, and persistent erythema (see Figs. 6.2, 6.3, and 6.4) [23]. The main complication of curettage alone described is hypopigmentation [25]. Electrodesiccation has been associated with increased postoperative hypopigmentation, hypertrophic scarring and keloid formation, interaction with implanted cardiac devices, and delayed wound healing [25, 50–52]. Additional risks with the use of electrocoagulation devices include demonstration of viral particles and potential carcinogens in the associated smoke plumes [53–55].

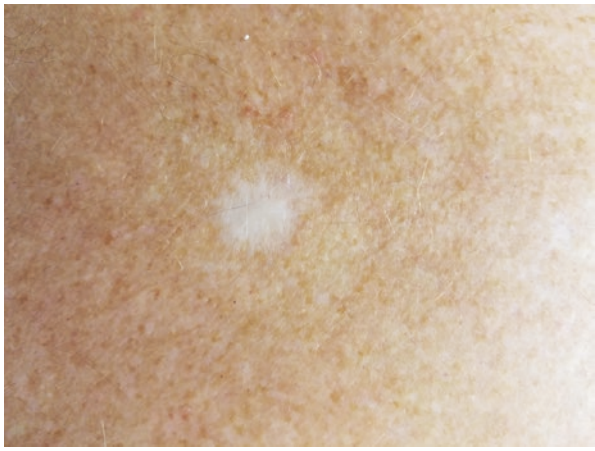

**Fig. 6.2** Hypopigmented scar at 5 years following ED&C for a superficial BCC on the right back

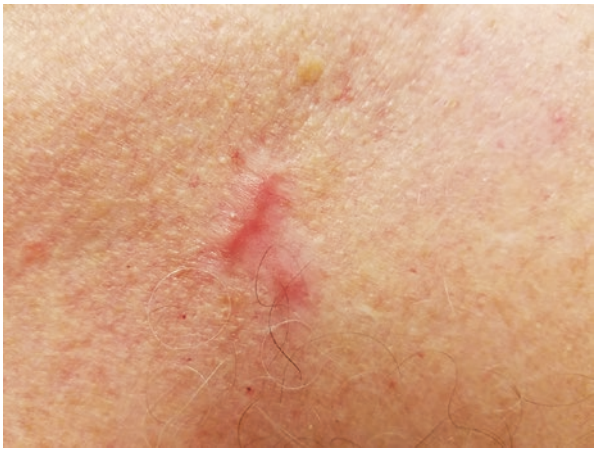

**Fig. 6.3** Hypertrophic scar on the left chest at 6 months after ED&C

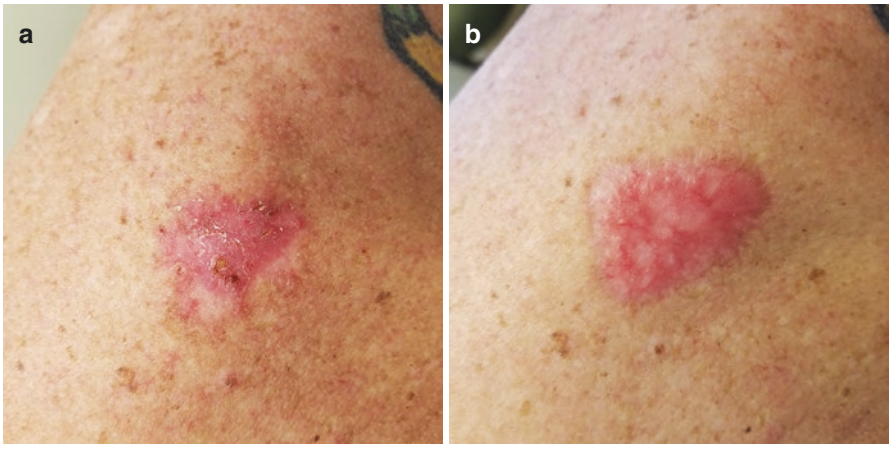


**Fig. 6.4** A 62-year-old white male with a biopsy-proven nodular BCC on the right upper back before treatment (**a**) and with persistent erythema at 2 months after ED&C requiring future clinical monitoring (**b**)

## *Comparative Studies*

Comparative studies, including prospective randomized trials, comparing ED&C to other treatment modalities for the treatment of BCC are lacking. One prospective, randomized trial by Julian et al. compared disposable curettes to non-disposable curettes and found no statistically significant difference between the two groups [43]. Most of what is known regarding ED&C in the treatment of BCC is based on the observations by and experience of clinicians over many years, observational studies, retrospective studies, and systematic reviews (see section "Efficacy").

Randomized trials comparing ED&C to other treatment modalities, including curettage alone, for low-risk BCC are needed in the future to allow more direct comparison of efficacy and COs between ED&C, curettage alone, and other treatment modalities.

### *Discussion*

Generally, advantages of ED&C include a fast, tissue-sparing, relatively well-tolerated, and cost-effective procedure [1, 56]. However, limitations include operator dependence, risk of hypopigmented scar, inability to histopathologically evaluate tumor margins, and need for careful clinical monitoring for evidence of tumor persistence or recurrence [1, 56].

The literature is lacking on prospective randomized trials comparing ED&C to other treatment modalities. However, based on observational studies, retrospective analyses, and systematic reviews, ED&C has been shown to be an effective treatment of superficial and nodular, low-risk BCCs. Curettage alone has also been shown by observational and retrospective studies to have RRs comparable to published RRs for ED&C with better COs observed; however, again randomized prospective studies are lacking.

## Conclusions

For both CT and ED&C, case selection is key in their consideration as treatment modalities for BCC. According to the NCCN recommendations, first-line treatment options for low-risk BCCs include SE with 4 mm clinical margins, ED&C in select cases (see below), and RT for nonsurgical candidates. They state that ED&C is an appropriate treatment option for low-risk BCCs in nonterminal hair-bearing areas with the following stipulations: conversion to SE if adipose tissue is reached and confirmation of clinical suspicion of the diagnosis of a low-risk BCCs with pathologic examination in cases without prior histopathological confirmation [1].

In low-risk, superficial BCCs on low-risk sites on the trunk and limbs in patients in which ST and RT are contraindicated, not appropriate, or not practical based on patient-specific factors such as patient preference, the NCCN Recommendations list alternative therapies, including CT, as first-line treatment options [1]. Cryotherapy is generally not recommended in the treatment of high-risk BCCs given decreased efficacy compared to SE and MMS. However, there may be cases of high-risk BCC where consideration of CT may be reasonable such as when other treatment modalities, including MMS, SE, and RT, are contraindicated or not appropriate based on individual patient factors, the operator is highly experienced, and tissue temperatures are measured to ensure that adequate temperature cooling is achieved [8, 56].

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# Chapter 7
# Mohs Micrographic Surgery for the Treatment of Basal Cell Carcinoma


**Leon Chen and Tri H. Nguyen**

## Historical Perspective of Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) is a surgical method developed by Dr. Frederic Mohs while he was still a trainee at the University of Wisconsin in the 1930s. Dr. Mohs utilized zinc chloride paste for tissue fixation in vivo, in combination with stibnite and bloodroot powder, so that the cytological features of the excised specimen were preserved for histologic evaluation [1]. Because chemical fixation was utilized, he named it "chemosurgery." One day after tissue fixation, Dr. Mohs would excise the tumor with narrow margins and manipulate the tissue so that the deep and peripheral margins of the specimen were sectioned in a single horizontal plane. If the deep or peripheral margin demonstrated residual tumor, zinc chloride was reapplied overnight prior to excision of another saucer-shaped specimen. This process was repeated until all margins were cleared of any residual tumor. However, due to the amount of time required to complete each surgical layer (typically 1 day), Dr. Mohs and his colleagues later introduced the idea of using local anesthetics in conjunction with frozen section processing to improve the efficiency. The fresh tissue fixation technique allows most tumors to be removed and cleared within a day while maintaining a cure rate comparable to the chemosurgery. In 1985, the official name of his procedure was changed to Mohs micrographic surgery to reflect the change from chemical tissue fixation to frozen section processing.

The goal of MMS is to achieve complete microscopic control of the tumor margins, thus providing the highest cure rate. Conventional surgical excision specimens

L. Chen
The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

T. H. Nguyen (✉)
Texas Surgical Dermatology PA, Spring, TX, USA



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_7

are typically "bread-loafed," that is, sectioned at 2–4 mm intervals like slicing a loaf of bread (Fig. 7.1). In this method the tumor margins are inadequately examined, with reportedly less than 1% of the margins visualized [2]. The 5-year cure rate for primary basal cell carcinoma (BCC) is 93% when treated by conventional excision, compared with 99% when treated by MMS [3]. For recurrent basal cell carcinoma, the 5-year cure rate reaches 95% when treated by MMS, compared with 80% by conventional excision [4]. Because it offers a superior cure rate, MMS is often indicated when a tumor recurs after conventional excision or other nonsurgical treatment modalities; exhibits more aggressive histologic features (such as morpheaform basal cell carcinoma) or indistinct clinical margins; or is located in anatomic regions (face, particularly in the H zone) where maximal tissue preservation and a superior cosmetic outcome are desired. MMS can also be most helpful in functional areas such as digits and genitalia to spare unnecessary removal of the tissue.

In 2012, the American Academy of Dermatology in collaboration with the American College of Mohs Surgery, the American Society for Dermatologic Surgery, and the American Society for Mohs Surgery developed appropriate use criteria for 270 scenarios for which MMS is indicated based on areas of the body (area H vs. area M vs. area L), tumor characteristics (positive margin on recent excision), aggressive features, and patient characteristics (immunocompetent vs. immunocompromised vs. those with genetic syndromes) [5]. The authors used a scoring system with a 9-point scale that divides the use of MMS in three categories: appropriate (score 7–9), uncertain (score 4–6), and inappropriate (score 1–3). The guidelines include many different skin cancer types; those for basal cell carcinoma will be outlined in Table 7.1. In general, all types of BCCs in area H ("mask area" of the face, genitalia, hands, feet, nail units, ankles, and areola) in all patient populations are deemed appropriate for MMS. All types of BCCs in area M (cheeks, forehead, scalp, neck, jawline, pretibial surface) are appropriate for MMS except for a primary superficial BCC that is ≤0.5 cm in healthy patients, which is deemed "uncertain." In area L (trunk and extremities), the only scenarios

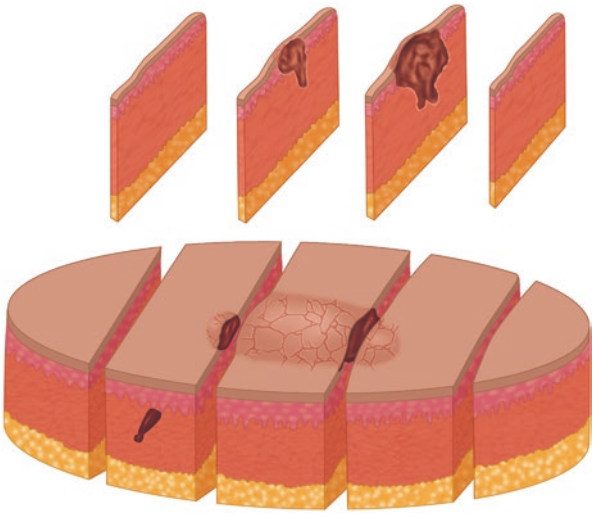

**Fig. 7.1** Conventional surgical excision specimens are typically "bread-loafed." In this method the tumor margins are inadequately examined, as demonstrated here by the tumor extension on the lower left, which is not captured

**Table 7.1** Appropriate use criteria for Mohs micrographic surgery on basal cell carcinoma

| | Appropriate | Uncertain | Inappropriate |
|---|---|---|---|
| Area H | Primary or recurrent<br>Aggressive<br>Nodular<br>Superficial | | |
| Area M | Primary or recurrent<br>Aggressive<br>Nodular<br>Superficial<br>(immunocompromised)<br>Primary<br>Superficial ≥0.6 cm | Primary<br>Superficial ≤0.5 cm | |
| Area L | Recurrent<br>Aggressive<br>Nodular<br>Primary<br>Aggressive ≥0.6 cm<br>Nodular >2 cm<br>Nodular<br>(immunocompromised)<br>≥ 1.1 cm | Primary<br>Aggressive ≤0.5 cm<br>Nodular 1.1–2 cm<br>Nodular<br>(immunocompromised)<br>0.6–1 cm<br>Superficial<br>(immunocompromised)<br>≥ 1.1 cm | Recurrent<br>Superficial<br>Primary<br>Nodular ≤1 cm<br>Nodular<br>(immunocompromised)<br>≤ 0.5 cm<br>Superficial<br>Superficial<br>(immunocompromised)<br>≤ 1 cm |

Adapted from Ref. [5]
Area H: "Mask areas" of face (central face, eyelids [including inner/outer canthi], eyebrows, nose, lips [cutaneous/mucosal/vermillion], chin, ear and periauricular skin/sulci, temple), genitalia (including perineal and perianal), hands, feet, nail units, ankles, and nipples/areola
Area M: Cheeks, forehead, scalp, neck, jawline, pretibial surface
Area L: Trunk and extremities (excluding pretibial surface, hands, feet, nail units, and ankles)

where MMS is considered appropriate are recurrent BCCs that are either aggressive or nodular, primary aggressive BCC that is >0.5 cm, and primary nodular BCC that is >2 cm in healthy patients or > 1 cm in immunosuppressed individuals. Figure 7.2 outlines the steps involved in Mohs micrographic surgery.

## Preoperative Evaluation

Like any surgical procedure, preoperative evaluation in MMS is critical. This includes identification of tumors; confirmation of pathology; documentation of the patient's overall health condition and comorbidities; smoking history; confirmation of the presence of any pacemakers or automatic implantable cardioverter-defibrillators (AICDs); review of the patient's medication list and allergies, with particular focus on the use of antiplatelet and anticoagulant agents; and assessment of the need for antibiotic prophylaxis, as all of the above factors can impact the outcome of the surgery.

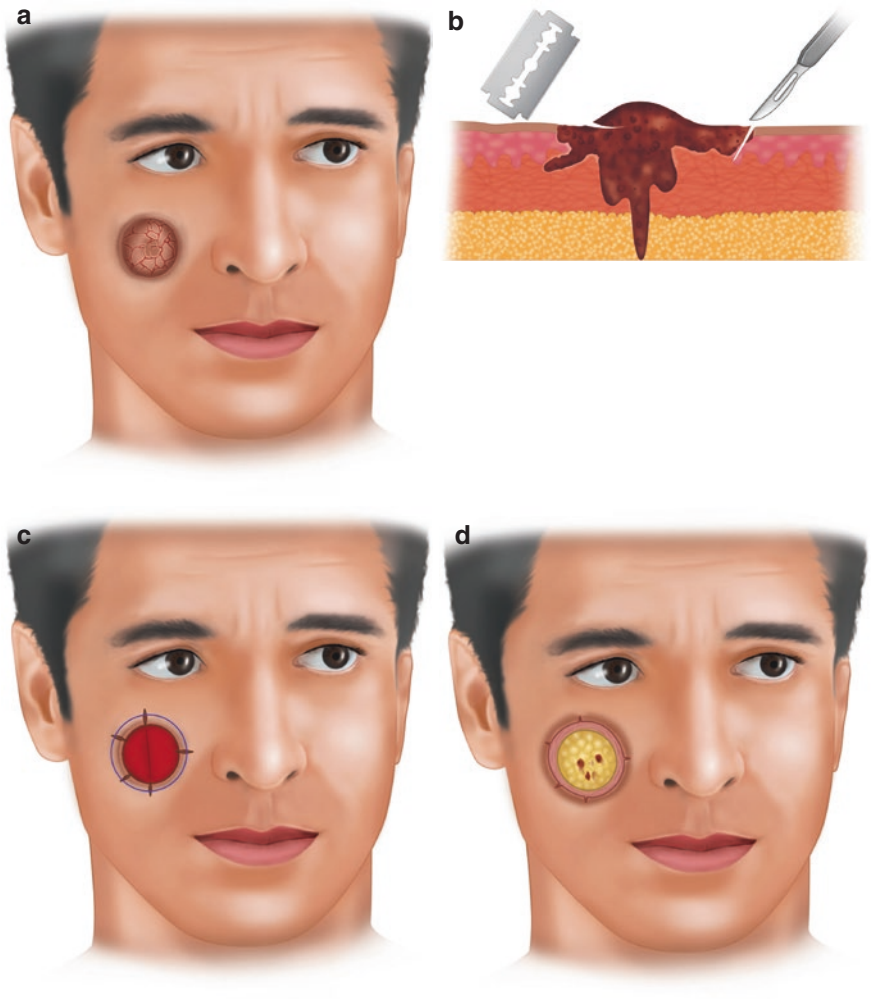


**Fig. 7.2** (**a**) After reviewing the pathology of the biopsy, proper identification of the lesion is critical to prevent wrong site surgery. (**b**) The tumor is first debulked, followed by incision at a beveling angle. (**c**) Nicking and intraoperative relaxation is done prior to removal. (**d**) After the first Mohs layer is excised, hemostasis is achieved. (**e**) The removed specimen with a beveling angle at the edges. (**f**) The epidermal edges of the specimen are flattened so that the true superficial and deep margins are in the same plane. Section A represents the true margin, furthest away from the tumor. (**g**) The Mohs map is appropriately labeled and accurately drawn, and the tissue is inked accordingly to preserve the orientation. (**h**) Slide A is the true margin, demonstrating residual tumors in both superficial and deep margins. (**i**) The positive areas are marked on the Mohs map to facilitate tumor identification prior to taking the second stage. (**j**) The corresponding site for residual tumor is marked, involving both superficial and deep margins. (**k**) Successful removal of the second layer and hemostasis are achieved. (**l**) The specimen is inked on the non-epidermal side, and the Mohs map is accurately drawn to reflect the orientation. (**m**) Both C and B showed trace residual tumors; however, slide A, which represents the true margin, is free of tumor cells

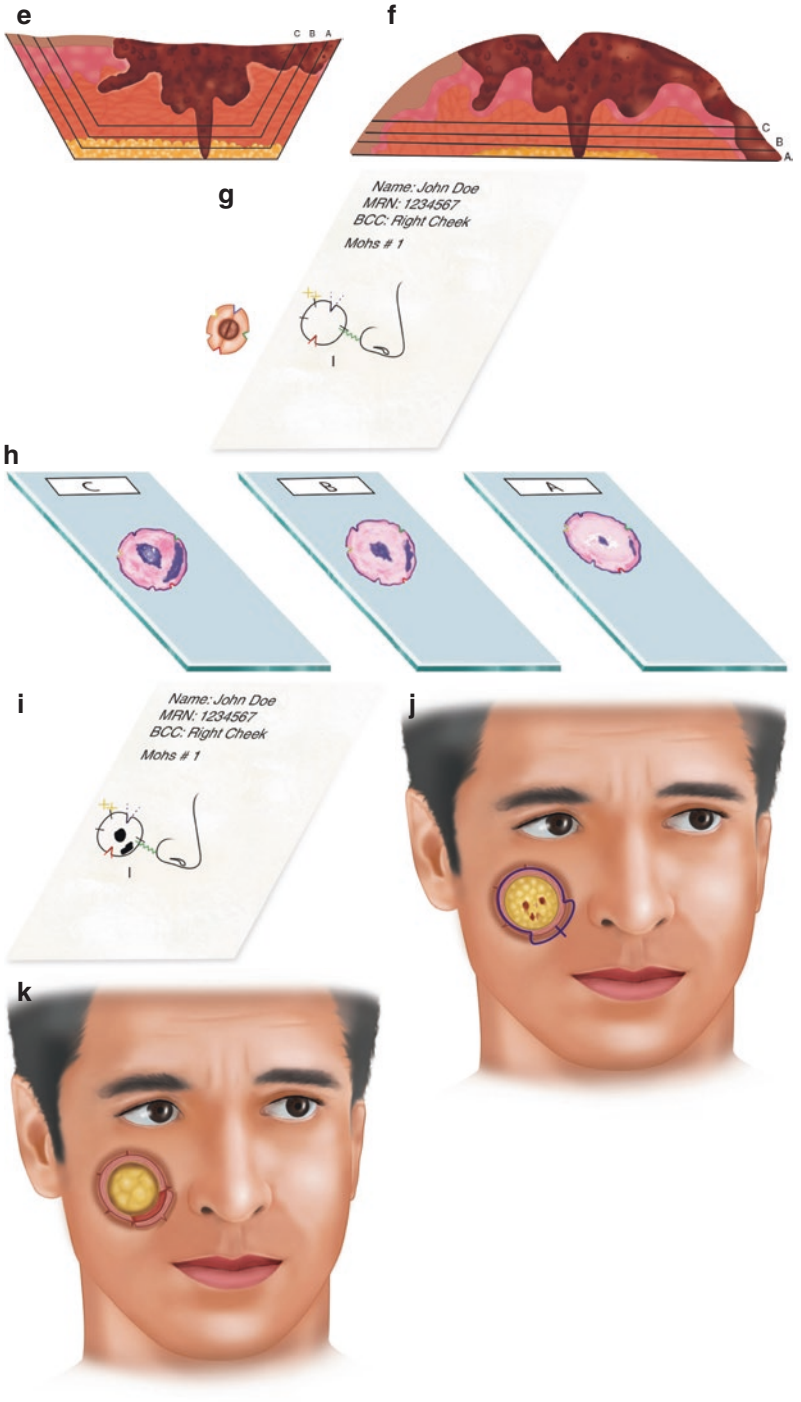


**Fig. 7.2** (continued)

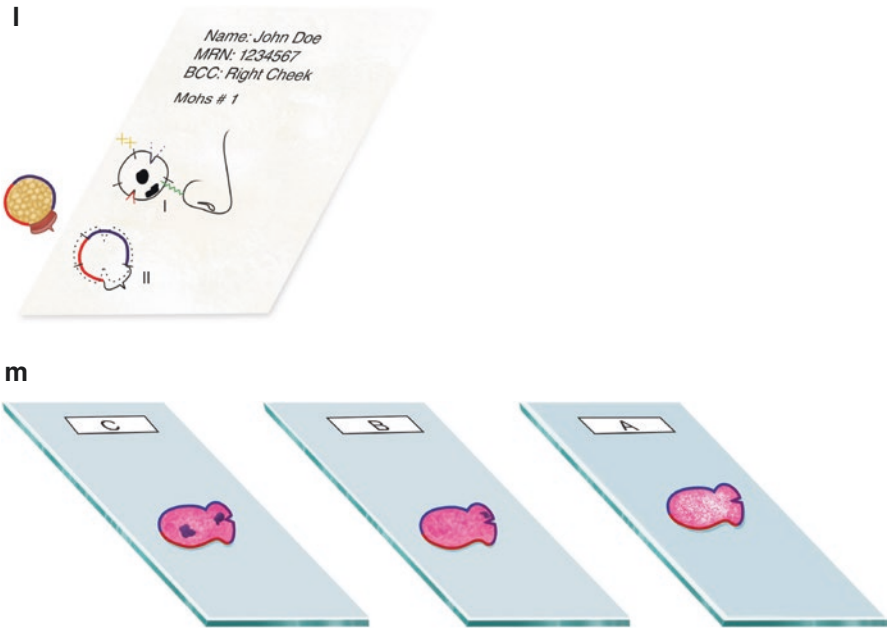


**Fig. 7.2** (continued)

## Site Identification

After reviewing the pathology of the biopsy, localization of the lesion is critical to prevent wrong site surgery. In a survey of 722 Mohs surgeons, 71% reported that more than 5% of their patients failed to identify their surgical site correctly [6]. In two other studies, 29% and 16% of patients were unable to identify their surgical sites correctly, and 12% and 4% of surgical sites were incorrectly identified by both the patients and the physicians, respectively, in the same studies [7, 8]. The factors that contribute to challenge in site identification include time lapse after biopsy, diffuse background actinic damage, recent cryotherapy or 5-fluorouracil topical application in the vicinity, pre-existing scars, or ambiguous descriptive terms used to name the biopsy sites. Although no practice guidelines currently exist regarding the documentation of a biopsy site, a clearly labeled preoperative photography that encompasses skin topography as well as anatomic landmarks is considered the gold standard by many dermatologic surgeons [9]. Some clinicians also document the distances of lesions from certain fixed anatomic landmarks such as medial/lateral canthus or oral commissure to help identifying the biopsy sites in the future [10]. Dermatoscopy can be useful in lesion identification by visualizing basal cell carcinoma remnants, scar tissue, and hypopigmented borders that separate scar patch from the surrounding skin [11]. In a prospective cohort study published in 2015, the authors tattooed the biopsy sites with ultraviolet fluorescent ink and found that the physician could confidently identify the site in 100% of the cases ($n$ = 51) in

comparison to 93% of the cases without the aid of ultraviolet illumination [12]. Another prospective study demonstrated a simple, cost-effective, and readily available means to identify skin biopsy site. This requires the physicians to circle the lesion with a marking pen and take photographs with the patient's personal digital device (cellphone, personal digital assistant [PDA], smartphone, etc.). When compared to the gold standard medical photography, the lesions were correctly identified in 100% of the cases ($n = 53$) [13].

## Anticoagulant and Antiplatelet Use

Reviewing the patient's medical history can facilitate surgical planning. One important aspect of history-taking is to check the status of anticoagulant and antiplatelet use. In the past, the acceptable approach was to discontinue any antithrombotic medication several days prior to cutaneous surgery; however, recent literature suggests that the relatively low risk of bleeding complication does not justify the potential life-threatening thromboembolic events.

Discontinuation of warfarin for cutaneous surgery is not recommended, as serious thromboembolic events and stroke have been reported after cessation of warfarin [14, 15]. However, the patient should inform the clinic prescribing the warfarin regarding upcoming procedures so that an international normalized ratio (INR) can be controlled to less than 3.5, with the understanding of a higher postoperative bleeding risk, particularly if the surgery site involves the eyes or ears or if the repair utilizes a skin flap or graft [16]. Antiplatelet therapy with aspirin should be continued prior to cutaneous surgery in high-risk patients with a history of cerebrovascular disease, cardiac surgery, unstable angina, or recent placement of coronary artery stents. However, if antiplatelet therapy is being taken for prophylaxis or pain, then it should be held at least 7–10 days prior to surgery. Clopidogrel is another commonly used antiplatelet agent that prolongs bleeding time and delays clot formation by irreversible blockade of the adenosine diphosphate (ADP) receptor on platelets. Although data is scarce, many believe clopidogrel should be continued for high-risk patients and withdrawn in low-risk patients while continuing aspirin or with the addition of an NSAID in patients not already on aspirin [17]. For newer antithrombotic medications, patients should consult with their prescribers to discuss the benefits and risks of discontinuing their medication(s).

## Indication for Prophylactic Antibiotic Use

Antibiotic prophylaxis for dermatologic surgery remains a controversial topic due to the paucity of data and the lack of large-scale randomized controlled trials. Studies have suggested that dermatologic surgeons tend to overuse antibiotic prophylaxis [18, 19]. To reflect updated prophylactic antibiotic guidelines published by the

American Heart Association (AHA) in 2007, the *Journal of the American Academy of Dermatology* Advisory Statement has also updated the indications for antibiotic prophylaxis in dermatologic surgery, focusing on prevention for the following three categories: (1) infective endocarditis, (2) hematogenous total joint infection, and (3) surgical site infection [20].

Because of the relatively low incidence of intraoperative bacteremia during dermatologic surgical procedures, the consensus has shifted away from routine administration of prophylactic antibiotics for MMS. High-risk cardiac patients include those with prosthetic cardiac valves, a prior history of infective endocarditis or congenital heart disease, and cardiac transplantation recipients who develop cardiac valvulopathy. In general, when operating on infected skin or the oral mucosal surface, prophylactic antibiotics for *Streptococcus viridans* are indicated to prevent infective endocarditis in high-risk cardiac patients. The only exception is when high-risk cardiac individuals undergo procedures on non-infected skin without breaching the oral mucosa. Routine antibiotic prophylaxis is not normally given to patients with pacemakers, defibrillators, peripheral vascular stents, vascular grafts, coronary artery stents, breast implants, penile prostheses, or central nervous system shunts.

Hematogenous spread due to bacteremia can potentially lead to total joint infection. The American Dental Association (ADA), in conjunction with the American Academy of Orthopaedic Surgeons (AAOS), identified patients with prosthetics as being at high risk for total joint infections from bacteremia. Patients considered at increased risk of prosthetic joint infection include those who are in their first 2 years following joint placement; have had previous prosthetic joint infections; are immunocompromised or immunosuppressed; have a history of insulin-dependent type I diabetes, HIV infection, or concurrent malignancy; are malnourished; or have hemophilia. Similar to the recommendation from the *Journal of the American Academy of Dermatology* Advisory Statement for infective endocarditis prophylaxis, prophylactic antibiotics are indicated when the dermatologic procedure involves the infected site or oral mucosa. On non-oral mucosal surfaces and non-infected sites, no antibiotic prophylaxis is indicated even with high-risk individuals with prosthetic joints. Patients with orthopedic pins, plates, or screws also do not need prophylactic antibiotic administration.

Antibiotic prophylaxis for surgical site infection is recommended when the procedure location is on the lower extremities, groin, lips, or ears. Additionally, in cases where skin flaps are needed for defects on the nose, skin grafting is involved, or patients have extensive inflammatory skin disease, then antibiotic prophylaxis is also warranted.

In general, the first-line prophylactic antibiotic for patients without penicillin allergies is cephalexin 2 gm when the surgical site does not involve oral mucosa. For procedures that breach the oral mucosa, amoxicillin 2 gm is usually given when patient has no known penicillin allergy. The recommended alternative for patients with penicillin allergy is clindamycin 600 mg for both oral and non-oral sites.

MMS is customarily performed as a “clean” procedure due to possible breaks in sterility. Nevertheless, although counterintuitive, most recent evidence suggests

that there is no significant difference in the rate of postoperative surgical site infection (SSI) between outpatient surgeries performed with sterile versus non-sterile gloves [21–23].

## Pacemaker and AICD

Electrosurgery is an integral part of dermatologic surgery to achieve hemostasis; however, it may cause malfunction of pacemakers or automatic implantable cardioverter-defibrillators (AICDs) secondary to interference. Pacemakers can be either single-chamber or dual-chamber and are often indicated in patients with symptomatic bradycardia as a result of sinus node dysfunction or atrial ventricular block. Pacemakers can be further categorized into unipolar or bipolar, with bipolar being the most common type and more resistant to electromagnetic interference [24]. Further interrogation by the surgeon is needed to determine whether the patient is pacemaker-dependent, as they will be at higher risk of having inadequate cardiac output if the pacemaker function is interrupted. On the other hand, AICDs are less common than pacemakers and are often indicated in patients with a high risk of severe ventricular arrhythmia. AICDs function to correct any arrhythmias by delivering bursts of high-energy electric shocks to defibrillate the heart. AICDs which are at risk of reprogramming or actual damage during electrosurgery also require particular attention. Although less effective at achieving hemostasis compared to electrofulguration (e.g., hyfrecator) or electrocoagulation, electrocautery typically is considered safe for patients with pacemakers or AICDs due to the absence of alternating current and the fact that the current does not pass through the patient. If electrosurgery must be used, a bipolar configuration should be used whenever possible [25]. Other recommended precautions include (1) avoiding the use of electrosurgery in proximity to the device near the chest area or within 15 cm of the device for possible direct damage; (2) using electrosurgery in moderation, with the lowest power possible and short, intermittent bursts to reduce the risk of prolonged interference; and (3) placing the grounding pad as far from the device as possible [26].

## Imaging

Basal cell carcinoma is primarily a localized disease with a metastatic rate of 0.0028–0.55% [27, 28]. When locally advanced disease or metastatic disease is suspected, imaging is often needed to assess the extent of tumor involvement. Some indications for imaging prior to surgery include a deeply ulcerated BCC near the calvarium, as locally advanced BCC has an estimated incidence of 0.03% for intracranial invasion; when the BCC is near the orbit, to rule out orbital spread; when the pathology shows perineural invasion; when the patient demonstrates peripheral

neurologic deficit near tumor location; when the tumor appears to be fixed and bound down to the underlying structure; and when regional lymph nodes are palpable on the physical exam.

## Consultation

Multidisciplinary consultation is indicated based on oncologic and reconstructive factors. If there is suspicion of deep invasion (based on clinical or radiologic features), such that resection may not be comfortably done under local anesthesia, then consultation with head and neck surgery or oculoplastic surgery is appropriate. In these situations, the Mohs surgeon may clear the peripheral margins first under local anesthesia, followed by the deep central excision under general anesthesia by another specialty. Similarly, if the anticipated defect is beyond what the Mohs surgeon can repair, or repair comfortably under local anesthesia, then preoperative consultation is critical. Whenever possible, the discussion should occur before MMS to adequately prepare both patients and colleagues.

## Smoking

It has been well-documented that cigarette smoking can contribute to full-thickness graft necrosis. One study demonstrated that current heavy smokers (one or more packs per day) develop necrosis three times more frequently than nonsmokers, low-level smokers (<one pack per day), or former smokers [29]. Other literature also demonstrates an increased risk of mastectomy flap necrosis and abdominal flap necrosis in active smokers when compared with nonsmokers or former smokers [30]. Furthermore, an animal study suggests that smoking irreversibly increases the risk of flap necrosis in a random flap pattern, while pure axial flaps are unaffected [31].

## The Mohs Micrographic Surgery Procedure

The tumor and a 1–2 mm margin is typically marked with a surgical marker, and the patient is instructed to hold a mirror to confirm the location (Fig. 7.3). The surgical site is then cleaned, typically with chloroxylenol, chlorhexidine, or povidone-iodine (Betadine). Chlorhexidine is a highly effective antiseptic that provides 24-hour bactericidal action after a 2-minute application [32]. Although not specific for dermatologic surgery, a randomized controlled trial showed preoperative cleansing with chlorhexidine is superior to cleansing with povidone-iodine for prevention of surgical site infection [32]. Care must be taken when applying chlorhexidine around the

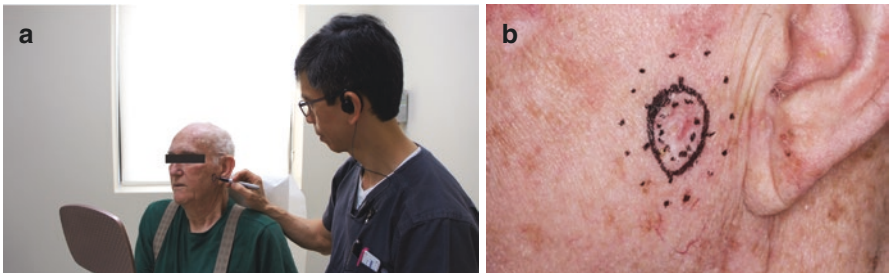


**Fig. 7.3** (**a**) The lesion and a 1–2 mm margin are marked with a surgical marker, and the patient is instructed to confirm the surgical site. (**b**) The tumor and a 1–2 mm margin are drawn. The nicking locations are also marked. The outer dotted line reflects the area to be anesthetized

eyes or ears, as keratitis and otologic toxicity secondary to chlorhexidine has been well-documented [33]. Chloroxylenol may be safely used for facial surgery, as it is not toxic to the eyes or inner ear.

After the surgical area has been fully prepped and cleaned, a local anesthetic, most commonly 0.5–1% lidocaine with epinephrine 1:100,000 or 1:200,000, is administered. An "allergy" to lidocaine should be investigated as it often represents a tachycardia from epinephrine. If the patient is truly allergic to epinephrine, which has vasoconstrictive effects and also prolongs the duration of anesthesia, then plain lidocaine may be used. If the patient is also allergic to lidocaine or other amide or ester local anesthetics, alternatives include benzoyl alcohol, normal saline solution, or diphenhydramine hydrochloride (DPH) 1% solution [34]. DPH 1% local injection provides adequate anesthesia for 80% of patients within 5 minutes, and the effects last between 15 minutes and 3 hours [35]; however, being a first-generation antihistamine, it should be remembered that a dose-related sedating effect can also occur.

The patient is then properly positioned to minimize their discomfort and enhance the ergonomics for the surgeon. A good mnemonic to remember the sequence of MMS is D-I-R-E-C-T, which stands for *d*ebulking, *i*ncising, *r*etracting, *e*xcising, *c*oagulating, and *t*ying (*t*issue processing).

## Debulking

Debulking of the tumor allows better visual delineation of tumor tissue from normal tissue, as well as decreasing the thickness of the specimen. Excavating the central part of the tissue facilitates tissue flattening, an essential element in Mohs horizontal processing. Furthermore, debulking reduces the risk of floaters or false-positive margins. Tumor debulking is typically performed with a curette or razor blade, as skin cancer often produces a friable texture (Fig. 7.4). When the tumor is exophytic, a scalpel or scissors can aid in removal of the tumor tissue.

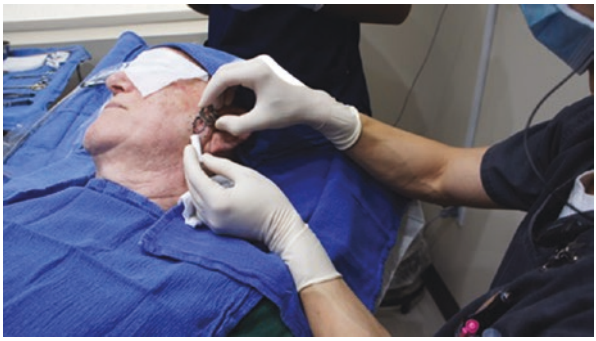

**Fig. 7.4** Debulking of the tumor allows better visual delineation of tumor tissue from normal tissue, as well as decreasing the thickness of the specimen

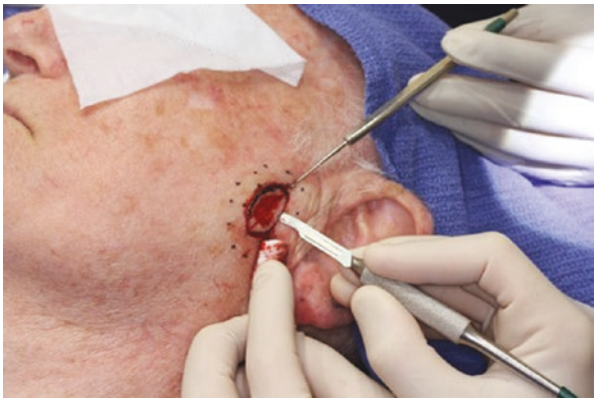

**Fig. 7.5** The Mohs layer is incised with a beveling angle. This picture also shows the nicks and intraoperative vertical relaxation line

## Incision

The initial layer is carefully incised with a 1–2 mm margin around the tumor, while the scalpel is kept at an angle so that the skin edge is beveled (Fig. 7.5). Larger margins (3–4 mm) are appropriate if the lesion is associated with inflammation or scarring. The blade angle can range between 45 and 90 degrees. An angle closer to 45 creates greater beveling and enables easier tissue flattening. There is a greater likelihood, however, of encountering a positive margin with a beveled edge. A 90-degree angle makes tissue flattening more challenging, and more relaxing incisions or more tissue division is needed. However, margins are more likely to be clear, and debeveling is not necessary during reconstruction. From a tissue flattening perspective, 45-degree angles are best for thicker tissue (fibrous ala, nasal tip, scalp, back, or cartilage), and 90-degree is better for thinner tissue. Whenever possible, a slightly oval specimen is better for orientation than a perfect circle.

In order to preserve the orientation of the specimen with respect to the patient, several critical steps are needed to ensure Mohs mapping integrity. Orientation techniques include the use of sutures, staples, gentian violet, methylene blue, or tissue nicking (TN). This senior author recently proposed superficial tissue nicking at 12,

3, 6, and 9 o'clock, with one extra nick placed equidistant between 12 and 9 o'clock to create asymmetry in case of potential flipping or rotating during tissue transfer or processing. The nicks must be superficial, as otherwise floaters can be introduced. Nicking from the outside margin into the tumor may also reduce the risk of floaters. A relaxing incision can also be made in vivo by scoring from 12 to 6 o'clock. This longitudinal incision is essential for orientation if the specimen is more like a circle than an oval. The shape of the Mohs specimen can be used to optimize accuracy. Whenever two Mohs specimens are excised from the same patient, especially if they are close in proximity, then the senior author excises one site as an oval and the other site as a rhomboid. The shape distinction reduces the likelihood that the incorrect site will be excised should there be subsequent stages.

## Retraction

Retracting the normal tissue from the tumor creates a separation for better visualization of the excising plane, as well as providing gentle traction in the opposite direction. Retraction is best with a single skin hook in the lower field allowing gravity to gently pull on the skin edge and absorb drainage [36].

## Excision

The Mohs specimen may be excised using tissue scissors, Gillette blades, or scalpels by transecting the base of the tissue parallel to the tumor surface (Fig. 7.6). Care must be taken not to cut any deeper than necessary to avoid transecting important underlying vasculature or nerves. When operating in danger zones such as temples

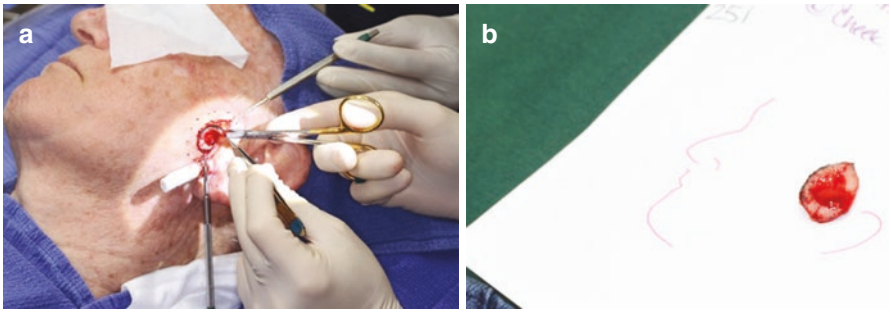


**Fig. 7.6** (**a**) The tumor and its margin are excised with tissue scissors. Please note the retraction that provides better visualization of the tissue plane as well as gentle traction in the opposite direction. The dental roll on the lower left prevents slippage of the retractor as well as absorbs excess blood. (**b**) The excised tissue specimen is placed on a transfer card. Note the correct orientation of the specimen in relation to the patient's head

or jawline, accurate identification of the tissue plane is crucial to avoid transecting motor nerves. Unless tumor invasion is suspected to be deep, then a dermal excision on the scalp may preserve hair follicles and allow for hair regrowth with second intention healing.

## Coagulation

After the tumor is completely detached from the surrounding tissue, hemostasis is most commonly achieved with electrodesiccation or electrofulguration (Fig. 7.7).

## Tissue Processing

The next step is to transfer the tissue to the Mohs laboratory; common methods of transfer include gauze pads, filter paper, petri dishes, glass slides, and Telfa paper. In the senior author's experience, a transfer card made of thick card stock will absorb the blood and adhere the tissue specimen. Proper labeling of the transfer card is important, and generally the case number, location, and current stage are written on the card.

The tissue is first dried and pressed down with gauze so that excess fluid is exuded. Subsequently, the nicks on the specimen are accentuated with a razor blade to create the space and visibility for inking, as well as to prevent inadvertent closure of the nicks during embedding (Fig. 7.8). Flattening the tissue so that the epidermal margin and the deep margin lie in the same plan permits a complete 360-degree margin evaluation. There are many approaches to achieve tissue relaxation including heat-extractor flattening in the cryostat, aerosol freezing, the Miami Method (sponge forceps with two attached copper plates and liquid nitrogen), or simply

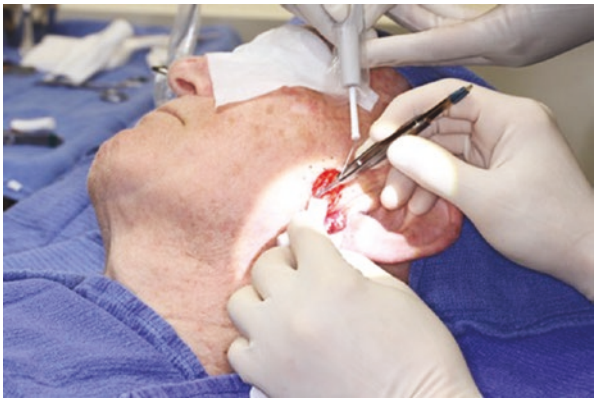

**Fig. 7.7** After the tumor is completely detached from the surrounding tissue, hemostasis is most commonly achieved with electrodessication or electrofulguration

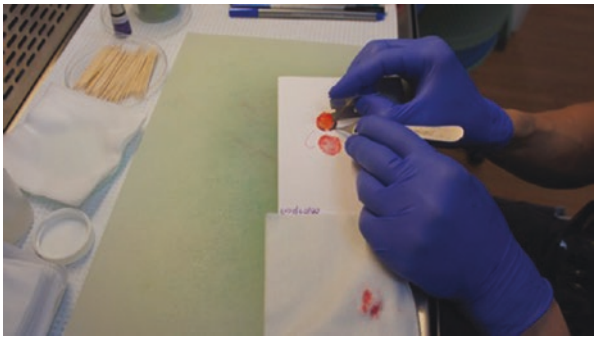

**Fig. 7.8** The nicks on the specimen are accentuated with a razor blade to create the space and visibility for inking. The epidermal edges of the tissue specimen are laid flat

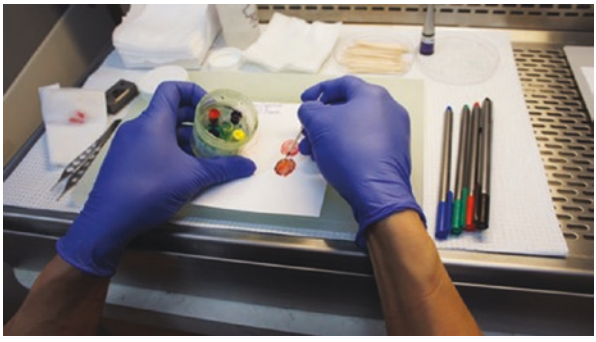

**Fig. 7.9** The purpose of inking is to maintain tissue orientation, as well as for tumor identification when the margins are involved. In our practice, we ink 3, 6, 9, and 12 o'clock and leave the extra nick (either between 12 and 3 o'clock or between 9 and 12 o'clock) uninked

utilizing various incision techniques to relax the tissue. The relaxation incision line can be placed more precisely in vivo because the field can be stabilized by stretching while the tumor is still attached to the surrounding skin. Another advantage of placing the relaxation incision in vivo is that the orientation is preserved prior to tissue removal. Care must be taken to avoid extending the incision too deeply in order to prevent unintended division of the sections. Wiping the blade after relaxing incisions should be considered to avoid inadvertent tumor transfer and floaters.

The next step is to ink the tissue, and many techniques have been described in the literature. The purpose of inking is to maintain tissue orientation, as well as for tumor identification when the margins are involved. Typically four colors – blue, red, green, and yellow – are used in most Mohs labs. In our practice, we ink 3, 6, 9, and 12 o'clock and leave the extra nick (either between 12 and 3 o'clock or between 9 and 12 o'clock) uninked (Fig. 7.9). The ink is applied with a sharp-ended toothpick in the nicks and underlying tissue transfer card. In cases where the pattern does not correlate with the Mohs map, the ink that remains on the tissue card can serve as an additional identifier (Fig. 7.10). When parts of the epidermis are missing, inking the entire 360 degrees with four different colors (one color in each quadrant) will provide clues to whether or not adequate amounts of true margins are assessed [37].

In instances when either the tissue cannot lie flat or the specimen is too large to be processed, then bisecting or cutting in multiple sections will be necessary. One survey indicates that the majority of Mohs surgeons (47.7%) processed the

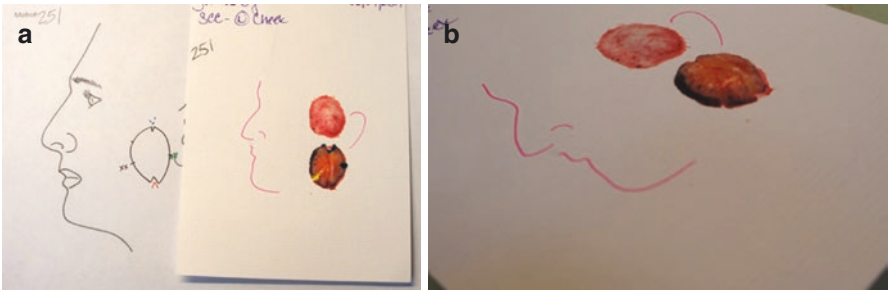


**Fig. 7.10** (**a**) The inking scheme corresponds to the Mohs map so that tissue orientation is maintained. (**b**) The epidermal edges of the tissue are flat and the tissue is ready to be embedded

first layer as two pieces [38]. Cutting the specimen into multiple sections allows the deeper portions of the tumor at the cutting edge to be on the same plane in continuity with the true surgical margin and thus could potentially introduce false positives during slide interpretation. Potential floaters from multiple cuts can also give a false-positive reading. Additionally, tissue loss as a result of cutting can also result in false negatives. A mathematical model was proposed to demonstrate that the inherent error rate increases as the number of divisions or the thickness goes up [39]. Multiple sections also require more complexity with specimen inking and Mohs map labeling, which can further contribute to errors. To simplify the subsequent processing and labeling, efforts should be made to keep a single section unless the first layer cannot lie flat or is too large to be processed.

## Tissue Embedding, Cutting, Staining, and Coverslipping

These steps are typically carried out by trained and certified histology technicians and are critical for accurate histologic interpretation. The tissue is first embedded on a slide in optical cutting temperature (OCT) or other similar compound and labeled with patient's name, date, slide sequence/accession number, and layer number to avoid any potential errors. The tissue is immediately frozen with tetrafluoroethyl chloride or liquid nitrogen before being mounted on a chuck holder within the cryostat, a device that maintains a very low temperature (−20 to −30 Celsius) (Fig. 7.11). The cryostat contains a microtome, which cuts both fresh and frozen tissues into very thin slices by advancing a fixed knife blade a preset distance with each turn of the rotating hand wheel. The first cut section, representing the truest margin, consists of both the peripheral and deep margins. Once the tissue is cut, camel-hair brushes may be used as the tissue has a tendency to curl at this point.

In most practices, slide staining is carried out with an automatic tissue stainer to save time and labor. Hematoxylin and eosin (H&E) is one of the most commonly used stains for Mohs specimens, including basal cell carcinoma. H&E staining gained its popularity because it provides superior histological detail, versatility

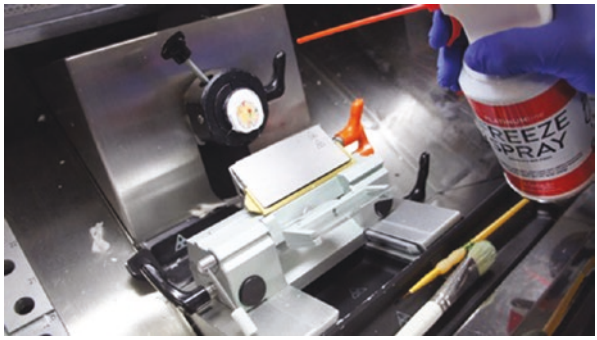


**Fig. 7.11** The tissue adhered to the chuck is now ready to be sectioned by the cryostat blade

to stain most cutaneous tumors, low cost, and fast staining time. One study found >99% sensitivity in identifying BCC stained with H&E on Mohs sections [40]. For basal cell carcinoma, some Mohs surgeons prefer toluidine blue instead, which is a basic thiazine metachromatic dye with a high affinity for acidic tissue components such as mucopolysaccharides and hyaluronic acid [41]. Toluidine blue stains BCC stroma-associated mucopolysaccharides magenta in color. One study showed toluidine blue took less staining time (less than 2.5 minutes) while still maintaining staining quality [42]. Ber-EP4 is a monoclonal antibody to two glycopolypeptides found in most human epithelial cells [43]. This marker has been shown to aid in differentiating basal cell from squamous cell carcinoma and microcystic adnexal carcinoma, as well as reliably staining all subtypes of BCCs, BCCs masked by inflammation, and rare metastatic BCC [44–47].

## Histologic Interpretation

Before trying to identify the tumor, there is an accuracy checklist that should be reviewed. (1) Do I have the correct patient map? (2) Do the slides belong to this patient (slide mislabeling can result in interpreting the wrong patient slides)? (3) If there are more than one section, then confirm that the correct section is being examined. (4) Review the slide for intact epidermis, no large gaps in the fat or dermis, and minimal folding. Recuts should be immediately ordered if tissue integrity is compromised. Basal cell carcinoma shows histologic features of nests of round basaloid tumor cells budding from the epidermis or follicles with palisading nuclei in the periphery. Stromal retraction artifact around the tumor can be seen as a result of stroma separating from the tumor lobules. Although BCC can have cytologic atypia and mitotic activity, abnormal mitoses are rarely seen.

There are several well-documented histologic subtypes of BCC, and in fact a single lesion can demonstrate features of more than one subtype. Nodular basal cell carcinoma is the most common subtype and consists of nodular aggregates of basaloid tumor arising from either the papillary or reticular dermis. It is sometimes accompanied by cystic degeneration [48, 49]. Other subtypes include superficial

BCC, infiltrating (sclerosing, morpheaform) BCC, micronodular BCC, pigmented BCC, basosquamous BCC, and keratinizing BCC. Occasionally, floaters generated from loose fragments of tissue can be seen as a result of curettage of friable tissue, nick accentuation, embedding, or sectioning. Minimizing floaters by meticulous tissue handling and distinguishing them from actual tumor on histologic grounds can reduce the false-positive rate.

One frequently encountered conundrum when interpreting slides is to differentiate BCC from hair follicles. Hair follicles lack stromal retraction, and the cells are usually monomorphic with more eosinophilic cytoplasm. Sometimes perifollicular fibrous sheaths and trichohyalin granules are present. Perineural invasion has been estimated to be between 0.178 and 1% in larger series [50, 51]. When BCC cells invade the perineural spaces of normal cutaneous nerves, oftentimes there is inflammation surrounding the nerve. The presence of perineural invasion is thought to correlate with tumor aggressiveness. BCC with perineural invasion requires more surgical stages (5.3 stages) compared to tumors without perineural invasions (2.2 stages) [52].

After carefully examining the histology slides, any residual tumor is marked on the corresponding location on the Mohs map. The residual tumor can involve the superficial margin, deep margin, or both. Based on the Mohs map drawn from the slide interpretation, any new margins for additional layers are marked with gentian violet on the tumor site. Because of the manipulation of the tissue with its periphery pressed down, sometimes the tumor is actually more lateral and closer to the epidermis than what appears under the microscope; therefore, additional epidermis is taken even if the superficial margin is clear. When taking additional stages, the area to be excised should be marked with gentian violet, especially the deep margin. This practice allows the surgeon to ensure that all necessary planes are removed for tumor clearance.

## Repair of Surgical Defect

The technical details of reconstruction are beyond the scope of this chapter. However, repair options should consider the aggressiveness of the cancer. Even with the high cure rate of MMS, a thick flap covering over a multiply recurrent, perineural BCC may not be appropriate unless function is at stake. A skin graft or skin substitute may be better options to achieve a window for monitoring recurrences.

Once complete tumor clearance is achieved, thorough evaluation of the surgical defect is needed before selecting appropriate repair methods. Size of the primary surgical defect, wound depth, anatomic location, cosmetic units involved, tension of the wound, proximity to free margins, skin thickness/laxity, smoking history, surrounding vascular supply, the need for cartilage support, aggressiveness of the tumor, and the patient's capability to perform wound care are all among the factors needed to be considered before proceeding with the repair.

In concave areas such as the temple, medial canthus, alar groove, and conchal bowl, granulation by second intention may be a great option [53–56]. In situations where tumor recurrence is more likely, flaps should be avoided as they may mask tumor growth. In these cases, secondary intention or split-thickness skin grafts allow better visualization of recurrent tumors. For a defect that is shallow and partial-thickness, second intention may also be an acceptable alternative. Second intention healing of larger wounds can also be achieved with an acellular xenograft such as Puracol (Medline) or PriMatrix (TEI Biosciences). Puracol is made of microscaffold type I bovine collagen, while PriMatrix is a type of fetal bovine dermal substitute composed of type I and type III collagen in its native non-denatured state [57]. Of note, PriMatrix has also demonstrated excellent long-term functional and cosmetic outcome in burn patients [58].

In most cases, debeveling and trimming of the previously beveled Mohs layer is necessary to ensure proper alignment of the wound edges. Tissue cones, sometimes referred to as "dog ears," will need to be removed to avoid puckering of the skin at either end. For primary closures, the best aesthetic result can be achieved when the direction of wound closure parallels the relaxed skin tension line and the future scar is concealed along the borders of cosmetic units (i.e., melolabial fold). M-plasty is sometimes utilized to shorten the length of incision, thus preventing scarring from crossing cosmetic units or extending into important functional structures such as eyes.

When the defect is too large or linear closure will distort the anatomy by pulling on the free margins, then flaps or grafts should be considered for better functional and cosmetic outcome. Flaps can be categorized based on either primary tissue movement (advancement flap, rotational flap, or transposition flap) or blood supply, such as an axial flap that contains a named artery, random pattern flap, or interpolation flap.

Advancement flaps do not change vector but rather redistribute the standing cones to a more favorable and cosmetically acceptable location. It is important to remember that an advancement flap does not lower the wound tension very much more than a side-to-side linear closure; therefore, a defect with good surrounding tissue laxity is a suitable candidate for this repair method. With an advancement flap, a length-width ratio of less than 3:1 is critical to ensure adequate perfusion of the distal flap and avoid potential ischemic necrosis of the flap. A special kind of advancement flap is called the island pedicle flap (IPF). An IPF retains a rich vascular supply from the underlying vessels and musculature that remained attached to the flap during advancement, so this type of flap is more likely to survive due to its protected blood supply. The upper cutaneous lip is one area that is suitable for IPF repair.

Rotational flaps provide the advantage of redirecting the tension vectors and utilizing tissue laxity in areas at a distance from the primary defect. Types of rotational flaps include bilateral rotation flaps (O-Z rotation flap) for scalp repair, dorsal nasal rotation flap (Rieger flap) and its variants for distal nose repair, and cheek rotational flap (Mustarde rotation flaps) for lower eyelid reconstruction.

Transposition flaps basically redistribute and redirect the wound tension by taking advantage of laxity from an adjacent area of the defect such that the high-tension wound can be closed with much less tension, therefore avoiding any potential anatomy distortion. The most common transposition flaps include the rhombic flap and its modified variations (DuFourmental and Webster), the bilobed flap, and the banner flap. Exquisite care with flap design before carrying out transposition flaps is critical to ensure minimal flap pivotal restraint and sufficient length. When the transposition flap is executed impeccably, the final geometric broken scar is less noticeable compared to a longer scar from linear closure.

Staged interpolation flaps utilize a named artery or its tributaries to provide a vascular pedicle and require more than one stage to complete, hence the name. This type of flap needs to be carried out with deliberate planning followed by precise execution. There are several types of staged interpolation flaps including the paramedian forehead flap (PFF), the cheek-to-nose interpolation flap (CNIF), and the Abbe (lip-switch) flap. PFF is best used to repair the distal sebaceous nose, which shares the same texture as the forehead skin, so that the convexity as well as projection of the nasal tip can be successfully recreated [59]. The named arteries supporting the pedicle are the supratrochlear artery and the dorsal nasal artery. Structural support with cartilage and mucosal lining is sometimes needed to prevent nasal valve collapse and alar rim contraction.

The first stage involves flap harvesting and flap inset, followed by donor site closure. The second stage for pedicle detachment typically takes place 3 weeks later but may be delayed for heavy smokers. Eyebrow realignment is essential in almost all cases after pedicle stump division. It is critical to monitor patient nasal airways throughout the process. If an additional stage of reconstruction is needed, then dermabrasion, shave sculpting, or laser treatment can be performed to improve the final cosmetic outcome.

CNIF can be best used to repair moderately sized defects located in the nasal ala, infratip, and columella. This particular flap has its pedicle based on tributaries and perforators from the angular artery, but not the artery itself. CNIF is known to preserve the alar groove while concealing the donor scar in the melolabial fold [60, 61]. The timeline for second-stage pedicle division is similar to that of PFF, being approximately 3 weeks.

The Abbe (lip-switch) flap is applicable for medium to large full-thickness lip defects when significant orbicularis oris muscle is lost. The inferior labial artery that branches off the facial artery is the named artery supplying the pedicle. Because one side of the inferior labial artery must be transected for mobilization of the flap, suction should be used to maintain visualization of the surgical field in this highly vascular area. Additional excision of all remaining lip layers including skin, muscle, and mucosa within the surgical defect is needed to accommodate the flap inset. The donor site is closed in the following order, mucosa, muscularis, subcutis, and cutaneous, while also precisely aligning the vermilion border. Pedicle division is performed after 3 weeks, and most patients can expect excellent neurovascular recovery 6 months to 1 year after surgery.

Skin grafts are usually reserved for situations where other repair methods are not optimal. There are two basic types of grafts: full-thickness skin grafts (FTSG) that consist of epidermis, dermis, and adnexal structure and split-thickness skin grafts (STSG) that only include epidermis and partial dermis without attached adnexal structures. FTSG typically gives better cosmetic results and has less wound contraction compared to STSG. FTSG demands higher nutritional requirements and a more robust blood supply compared to STSG and should therefore be avoided in avascular areas such as cartilage, perichondrium, or exposed bone. Patients with diabetes mellitus, nutritional deficiencies, or a long-standing smoking history have higher graft failure rates.

There are three phases of graft take. The first phase is the imbibition phase, which typically lasts 24–40 hours [62]. During this phase, the plasma exudate provides initial nutritional support via pass diffusion. Inosculation, the second stage, begins as early as 48–72 hours and lasts up to 10 days. It interconnects the vessels from the graft with those in the recipient bed [63]. The final stage, known as neovascularization, is the process of restoring blood flow to full circulation. Grafts may achieve comparable cosmetic and functional outcomes to the less invasive options in the right patient population, but they demand a robust vascular supply, meticulous wound care, and highly compliant individuals.

## Conclusion

Mohs micrographic surgery provides the highest cure rate possible for basal cell carcinomas. This elaborate procedure requires seamless collaboration and tremendous attention to detail among surgeons, nursing staff, and histotechnicians. Achieving cancer-free margins and preserving function should be the number one goal and supersede other priorities. The complexity of the surgical defect reconstruction can vary depending on the location, size of the defect, tissue laxity, and many other factors. When basal cell carcinoma becomes locally advanced or metastatic, alternative therapeutic options including hedgehog pathway inhibitor and immunotherapy should be considered; the abovementioned treatment modalities will be discussed in Chaps. 13 and 14.

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# Chapter 8
# Surgical Treatment for Basal Cell Carcinoma of the Head and Neck

**Sagar Kansara, Christopher M. K. L. Yao, and Neil D. Gross**

## Introduction and Epidemiology

Nonmelanoma skin cancer (NMSC) is the most common malignancy in the world, with over 5.4 million new cases diagnosed in the USA annually [1]. Basal cell carcinoma (BCC) comprises 70–75% of these cases, and up to 85% occur in the head and neck region [2]. Basal cell carcinoma is thus the most common cancer in the world and is reaching epidemic proportions, with an ever-rising incidence. This can be observed most strikingly in Australia, which has the highest prevalence of skin cancer in the world [2]. BCCs less commonly cause death, but if left alone can invade locally and cause significant functional loss and morbidity (Fig. 8.1).

Given its potential for causing local destruction, treatment of BCC is indicated. To date, there are numerous treatment strategies including electrodesiccation and curettage, surgical excision, Mohs micrographic surgery, topical and intralesional agents, radiation therapy, and photodynamic therapy. BCCs can be categorized by their potential for recurrence based on location, pathologic features, and patient factors. In addition to these factors, resource availability and costs of treatment may best guide the clinician in selecting the most appropriate therapy for reducing the likelihood of

S. Kansara
Baylor College of Medicine, Department of Otolaryngology, Houston, TX, USA

C. M. K. L. Yao · N. D. Gross (✉)
The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX, USA
e-mail: NGross@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_8

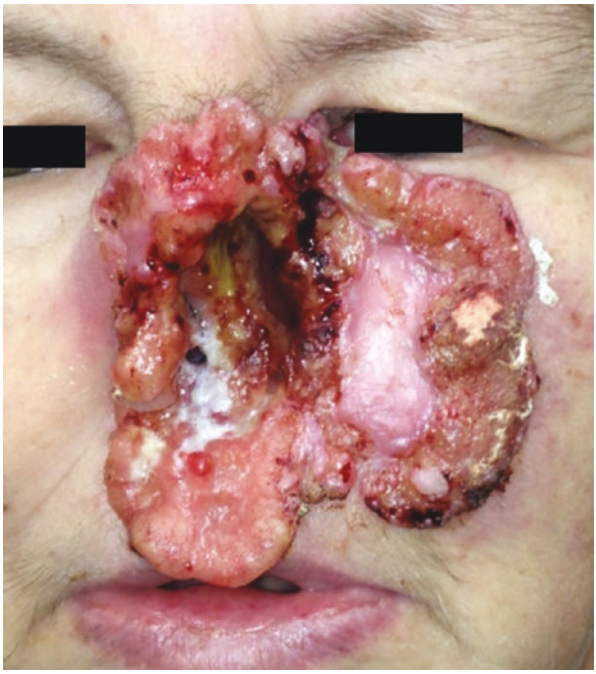

**Fig. 8.1** A large invasive, disfiguring basal cell carcinoma, with extension into the nasal cavity, maxillary sinus, and orbit

local recurrence as well as obtaining the best functional outcome. The focus of our chapter will be on the role of surgery for this disease entity in the head and neck.

In starting to understand the surgical treatment of BCCs of the head and neck, it is incumbent upon clinicians to have a thorough understanding of the predisposing factors of BCC, biology of the disease, and the extent of surgical excision necessary to obtain cure.

## Risk Factors and Pathogenesis

Basal cell carcinomas arise from the basal layer of the epidermis. Both environmental and genetic factors have been implicated as risk factors in the development of BCC. Exposure to ultraviolet (UV) radiation in sunlight is the most important, followed by other environmental exposures including arsenic, radiation, immunosuppression, and genetic factors.

## *Environmental Risk Factors*

The significance of sun exposure as a risk factor was initially proposed in the 1920s and has since been confirmed by a myriad studies [3]. Established tenets of risk stratification predict that BCC occurs more frequently in light-skinned sun-sensitive people, those with benign sun-related skin conditions, and occurs mainly on sun-exposed body sites [3, 4]. Multiple epidemiologic observations have shed light onto the association between sun exposure and the development of BCC, including the striking geographic variation (with states closer to the equator having twice the incidence of BCC compared with that of the Midwest United States) [5].

There remains considerable dispute regarding the exact nature of sun exposure that is required to cause pathogenic change. Some authors argue that the cumulative dose of ultraviolet UV radiation is the culprit, whereas Kricker and colleagues posited that frequent, intense periods of sun exposure significantly increase the risk of the development of BCC [6]. Some authors suggest that the intermittent versus continuous nature of sun exposure is irrelevant; rather, that sun exposure during childhood and adolescence predisposes these individuals to NMSC [7].

UV light exposure as a risk factor for BCC has also been described in relation to indoor tanning. A case control study from Yale revealed a 69% increased risk of early-onset BCC associated with tanning beds, especially among women, in a dose-dependent fashion [8]. Certain photosensitizing agents have been shown to increase the risk of NMSC, potentiating the carcinogenic effect of UV light. Robinson and colleagues showed a significantly increased risk of BCC, specifically early-onset BCC, in patients who have ever used photosensitizing antimicrobials such as tetracyclines [9]. The most common indications for tetracycline use in young patients include skin rashes and acne. These findings offer a word of caution to the use of these medications in younger patients. The authors also found a significant association between squamous cell carcinoma and ever use of thiazide diuretics, but this association could not be replicated in BCC [9].

A history of prior NMSC also significantly increases the risk of future BCC. There is a reported 45% 5-year risk of new BCC among patients with previous BCC, as opposed to 5% in the general population [10, 11]. This may be in part due to "field cancerization," a topic that has rapidly gained interest in head and neck oncology. Kanjilal and colleagues found multiple and distinct p53 mutations via DNA sequence analysis in tumor and adjacent nonmalignant skin samples in a cohort of patients with NMSC of the head and neck, confirming that field cancerization may play a role in the development of BCC [12].

Several other notable risk factors have been linked to the development of BCC. A recent prospective study revealed an almost twofold increase in the incidence of BCC in patients with a history of ionizing radiation compared to control patients [13]. Certain environmental exposures such as arsenic have also been linked to the development of BCC [14].

Immune modulation and suppression have been shown to be potent risk factors, which can be seen most strikingly in transplant patients. NMSC has been shown to

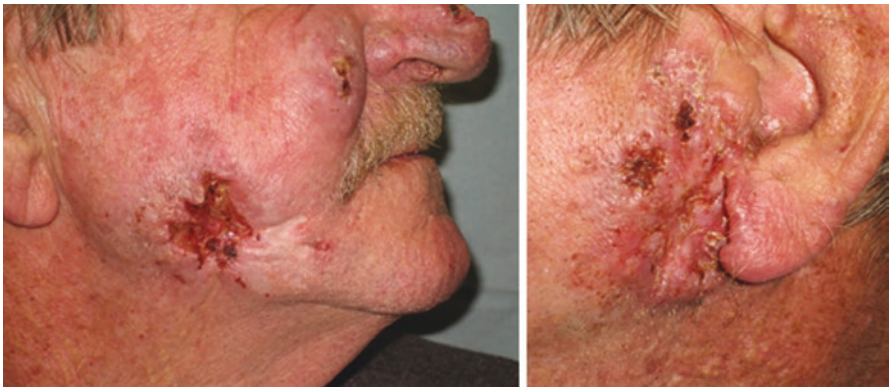

**Fig. 8.2** Transplant patient with multifocal basal cell carcinoma of the head and neck. This is a common but difficult problem to manage in this patient cohort

**Table 8.1** Risk factors for development of BCC

| Modifiable | Non-modifiable |
|---|---|
| UV radiation, ionizing radiation, sun exposure | Nevoid basal cell carcinoma syndrome |
| Use of tanning bed | Fair skinned individuals |
| Use of photosensitizing agents (thiazide, doxycycline) | History of prior benign skin conditions or prior nonmelanoma skin cancer |
| Immunosuppression: HIV, transplant population | |
| Arsenic exposure | |

Table depicting risk factors for basal cell carcinoma

develop at an alarming rate in this cohort; the cumulative incidence of NMSC in transplant patients was shown to be as high as 50% [15]. The risk of BCC in particular is increased tenfold in transplant recipients [16]. Figure 8.2 shows a transplant patient with multiple primary BCC of the head and neck, highlighting the scope of the problem in this patient population.

Interestingly, the incidence of NMSC increases in a linear fashion with the duration of immunosuppressive therapy. An Australian study reported an increase in skin cancer incidence from 7% at 1 year of immunosuppressive therapy to 82% at 20 years [17]. However, duration is not the only causative factor: the immunosuppressive regimen implemented also plays a significant role. For example, transplant patients who were placed on cyclosporine, azathioprine, and prednisolone were almost three times more likely to develop skin cancer when compared to patients on azathioprine and prednisolone alone [18]. Cyclosporine is a robust T-cell modulator.

Transplant patients treated with cyclosporine have been shown to have significantly lower CD4 counts compared to age-matched controls [19]. Similarly, HIV patients have been shown to have a significantly increased risk of BCC and SCC [20]. The significance of CD4 lymphocytopenia is discussed further below. Table 8.1 summarizes the known risk factors for BCC.

## *Molecular Pathogenesis*

The prevailing molecular theory for BCC involves the hedgehog pathway. It was first described in the context of nevoid basal cell carcinoma syndrome (NBCCS), an autosomal dominant disorder associated with multiple BCC, medulloblastoma, mandibular cysts, developmental disability, prominent forehead with broad nasal bridge, and pits on the soles of hands and feet [21]. The causative genetic alteration has previously been mapped to chromosome 9q22 [22]. Loss of heterozygosity at this locus was later confirmed to be an independent factor, found to be in 68% of BCC [23]. The locus codes for the protein Patched (PTCH), which is inhibited by sonic hedgehog (SHH) [24]. Loss of function PTCH mutations lead to downstream activation of smoothened (*smo*), B-cell lymphoma (*bcl*) 2, as well as glioma-associated oncogenes (*gli*) 1, 2, and 3 which have been found to be overexpressed in BCC mouse models and human cell lines, leading to oncogenesis [25, 26]. This pathway has provided several molecular targets for potential drug applications. Figure 8.3 summarizes the SHH pathway.

The p53 pathway has been extensively studied in cancer biology as a well-known tumor suppressor and more recently in BCC as well. In a study of 11 patients with BCC, DNA sequencing revealed a p53 mutation (or multiple p53 mutations) in every single sample studied [27]. Normal epithelium studied from these patients showed wild-type p53 in all but one sample [27]. Larger studies have revealed ultra-

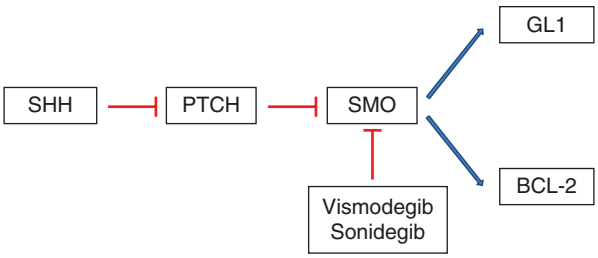


**Fig. 8.3** A schematic of the hedgehog pathway. Hedgehog pathway inhibitors vismodegib and sonidegib inhibit the smoothened of the hedgehog pathway. SHH, sonic hedgehog; PTCH, patched; SMO, smoothened; GL1, glioma-associated oncogene; BCL-2, B-cell lymphoma 2

violet light-induced point mutations in p53 in over half of all BCC, suggesting a correlation between the two [23].

Immune dysfunction has been shown to play a role in skin cancer as well, as evidenced by the NMSC epidemic in transplant and HIV patients. Significant dysregulation in the T-cell response has been shown in numerous studies. A 2017 study revealed a significant increase in the proportion of a subset of CD4+ cells, Treg cells, in BCC compared to control [28]. The author suggested that the crosstalk between T reg cells and basal keratinocytes may not only directly lead to carcinoma formation but also creates a microenvironment in which the tumor is allowed to flourish. The precise interplay between these factors has yet to be completely elucidated.

## Presentation and Work-Up

BCC usually presents as insidiously growing skin lesion, often with pearly appearance with potential ulceration, bleeding, or telangiectasias. There are various types of BCC such as nodular, cystic, superficial, micronodular, or pigmented [29]. As seen in Table 8.2, nodular, cystic, and superficial are low-risk subtypes, whereas morpheaform, micronodular, and basosquamous are high-risk subtypes [29].

Staging of BCC is performed according to the AJCC eighth edition TNM classification (Table 8.3) [30] and mirrors that used for cutaneous SCC. In stage 1 tumors, the tumor is smaller than 2 cm and does not invade any underlying structures. In stage 2, the tumor is larger than 2 cm and has likely invaded into the dermis, possibly surrounding neural structures. In stage 3 tumors, the cancer has spread to structures below the skin, such as the muscle, bone, cartilages, or lymph nodes. Lastly, in stage 4, the tumor may have spread toward the skull base or toward distant organs such as the lungs or brain [30].

**Table 8.2** Risk factors for recurrence of basal cell carcinoma

| History | Low risk | High risk |
|---|---|---|
| Location/size | Area H < 6 mm | Area H > 6 mm |
| Borders | Well defined | Poorly defined |
| Primary vs. recurrent | Primary | Recurrent |
| Immunosuppressed patient | – | + |
| Site of previous radiation | – | + |
| *Pathology* | | |
| Subtype | Nodular, superficial | Morpheaform, basosquamous, sclerosing, infiltrative, micronodular |
| Perineural invasion | – | + |

NCCN predictors for low- vs. high-risk basal cell carcinoma. (Adapted from Miller et al. [31])

**Table 8.3** AJCC eighth edition staging of head and neck BCC

| **T stage** | Criteria |
|---|---|
| Tx | Primary tumor cannot be assessed |
| Tis | Carcinoma in situ |
| T1 | Tumor <2 cm in greatest dimension |
| T2 | Tumor 2 cm or larger but smaller than 4 cm in greatest dimension |
| T3 | Tumor >4 cm in maximum dimension or minor bone erosion, perineural invasion, or deep invasion (>6 mm deep from stratum granulosum of the adjacent normal epidermis) |
| T4a | Tumor with gross bone/marrow invasion |
| T4b | Tumor with skull base invasion and/or skull base foramen involvement |
| **N stage** | |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Unilateral single cervical lymph node metastasis, 3 cm or less in greatest dimension without extranodal extension (ENE) |
| N2a | Metastasis in a single ipsilateral lymph node, more than 3 cm but less than 6 cm in greatest dimension, ENE (−) |
| N2b | Metastasis in multiple ipsilateral lymph nodes, less than 6 cm in greatest dimension, ENE (−) |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE (−) |
| N3a | Metastasis in a lymph node more than 6 cm in greatest dimension and ENE (−) |
| N3b | Metastasis in a single or multiple lymph nodes with clinical ENE |

Adapted from Amin et al. [30]

A biopsy is necessary for diagnosis, but wide local excision is often performed for small, suspicious lesions for diagnostic and therapeutic reasons.

For small lesions of the head and neck, imaging is not usually necessary. For extensive BCC of the head and neck, computed tomography (CT) is frequently the imaging modality of choice. CT allows evaluation of the extent of bony erosion (i.e., temporal bone, maxilla, zygoma, orbit, etc.) and also allows reasonable visualization of nodal basins. Figure 8.4 shows a representative example of bony erosion caused by BCC, which is optimally appreciated on CT scan. If clinical suspicion is high, magnetic resonance imaging (MRI) may be used to assess the extent of perineural invasion [29]. Due to the low rate of distant metastasis from BCC, positron emission tomography-CT (PET-CT) is generally not implemented, though may be of use to assess response to systemic therapy in locally advanced or metastatic BCC [29].

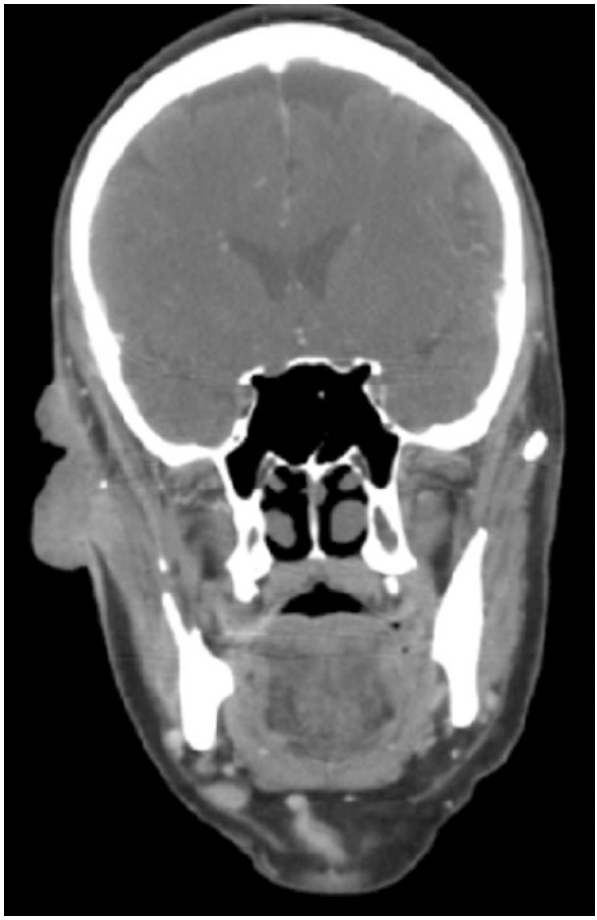

**Fig. 8.4** Coronal CT depicting bony erosion of the zygoma caused by locally invasive BCC

## Treatment

Largely due to the high incidence of BCC, clinicians of various subspecialties are involved in managing BCC. With more advanced BCCs, there is an increased need for a multidisciplinary evaluation. Head and neck surgeons, dermatologists, Mohs surgeons, and sometimes radiation oncologists and medical oncologists are involved in the care of patients with BCC. There are a variety of treatment options for BCC of the head and neck. The primary goal in treatment of BCC is always eradication of the disease. However in the head and neck, respect of anatomy and oncologic control must be balanced with the ablative defect and the form and function of the underlying structures. Locally invasive head and neck BCC can have debilitating effects on form and function, necessitating a thoughtful and thorough approach to treatment. The current standard of care and decision-making with regard to

treatment is heavily influenced by the risk stratification put forth by the National Comprehensive Cancer Network (NCCN) [31], as seen in Table 8.2**.** Determining the character of the BCC as low or high risk for recurrence is critical. The NCCN has identified features of head and neck BCC with lower likelihood for recurrence after treatment including BCC with less than 6 mm in diameter in high-risk areas (H-zone: central face, nose, lips, eyelids, eyebrows, periorbital), less than 10 mm in other areas of the head and neck, a nodular or superficial histopathologic growth pattern, lack of perineural invasion, primary lesion, well-defined clinical borders, lack of prior radiation, and immunocompetent patients [31].

In low-risk head and neck BCC, the treatment modalities of surgical excision, Mohs surgery, cryosurgery, curettage and electrodessication, radiation, and topical or intralesional agents can be utilized with various advantages and disadvantages. For the purposes of this chapter, we will focus on the role of surgery. In the head and neck, surgical excision offers significant advantages: allowing for margin-control, more precise control over tissues removed and preserved, and more deliberate preservation of critical structures. Generally accepted margins for surgical excision are established at 4–6 mm for small tumors, as excisions of lesions 2 cm or less in diameter have previously resulted in negative margins in more than 95% of cases [32–33].

Mohs micrographic surgery has also been shown to be a favorable treatment option in the appropriate tumors. In a randomized control trial of high-risk primary and recurrent facial BCC, 10-year recurrence rates were greater following surgical excision than Mohs micrographic surgery (12.2% vs. 4.4%, respectively), although at the time of the study, recommended margins were limited to 3 mm [34]. Importantly, Mohs micrographic surgery has been shown to create a median defect size 1.6 times smaller than that of surgical excision [35], which is ideal for lesions of the face and neck. Mohs micrographic surgery is relatively more costly a procedure and time intensive and therefore may not be feasible for all patients.

Head and neck BCC with high risk for recurrence after treatment include tumors greater or equal to 6 mm in high-risk areas, greater than 10 mm in diameter in other areas of the head and neck, aggressive histopathological subtypes (sclerosing, micronodular, basosquamous), recurrence, prior radiation, poorly defined borders, immunosuppression, or perineural invasion [31].

Within the head and neck, the basis for high-risk sites (so called H-zone) is defined embryologically. These locations represent embryological cleavage planes that offer little resistance to deeper tumor invasion. BCC arising in the H-zone displays a disproportionately high recurrence rate [36]. Given the density of critical structures and cosmetically sensitive areas within the head and neck, complete tumor removal without cosmetic or functional impairment becomes more difficult. In these settings, Mohs micrographic surgery, surgical excision, and radiation are the most effective treatments.

For locally advanced BCC of the head and neck, careful surgical planning is of utmost importance. Preoperative evaluation and imaging dictates the extent of surgery that is necessary. For extensive scalp BCC, neurosurgery involvement may be necessary for complete extirpation of disease. Similarly, for advanced orbit BCC,

ophthalmology or oculoplastic surgery can be helpful for complex orbit-sparing procedures. For extensive BCC involving the maxilla, oral oncology support may be helpful for potential dental extractions, radiation molds, and obturator placement for anticipated oral antral fistula. Pre- and postauricular lesions may dictate the need for parotidectomy and/or lateral temporal bone resection, necessitating a neuro-otologist. If the anticipated surgical defect is large or particularly complex, a microvascular reconstruction is often an ideal choice, especially if postoperative radiation is likely.

The incidence of metastasis of BCC is extremely low, approximately 0.003 percent to 0.1 percent of cases [37]. However, the presence of multiple primary tumors in the head and neck has been cited as a risk for the occurrence of metastasis. In fact, of the reported metastatic BCC cases, 85–90% were attributed to primary tumors in the head and neck [38, 39]. Thus, there is very little literature regarding the utility of sentinel lymph node biopsy and elective neck dissection in advanced BCC. While the potential utility of lymph node dissection is very low even in advanced head and neck BCC, there have been reports of sentinel lymph node biopsy in certain high-risk types of BCC, including basosquamous carcinoma [40].

Radiation therapy has been studied extensively in BCC. As a single modality, radiation therapy is effective for BCC not amenable to surgery, including BCC that if excised would lead to significant cosmetic deformity, or in patients too frail to undergo surgical excision [41]. Tumor size and location often dictate the course of radiation to be given. Doses and number of fractions are variable, but most head and neck BCC can be treated to a total of 40–50 Gy over 10–20 fractions [41]. Larger tumors often receive higher dose/fractions, whereas elderly, ill patients may be treated more palliatively with a lower dose over a shorter period of time [41]. Radiation as a single modality provides acceptable cure rates for small head and neck BCC, but is less efficacious with larger cancers. Head and neck BCC less than 2 cm treated with radiation alone have been shown to have 98% local control rate at 10 years. Conversely, BCC greater than 5 cm had only 53% local control at 8 years [42]. Further, advanced BCCs treated with radiation alone have an unacceptably high and cause-specific mortality [43], highlighting the need for multimodality therapy in this high-risk group of patients.

In the postoperative setting, radiation has been shown to be of benefit in select cases. Adjuvant radiation should be considered in patients with multiply recurrent disease, positive margins after multiple resections, perineural invasion, T4 disease with extensive soft tissue or bony invasion, or lymph node metastasis [44, 45].

Historically, there has been little use for systemic therapy in the treatment of BCC. However, in recent years, the Hedgehog pathway inhibitors for the treatment of BCC have emerged as a treatment option in the locally advanced or metastatic setting. Vismodegib and sonidegib are smoothened (smo) inhibitors (see Fig. 8.3), which have shown safety and efficacy in treating advanced BCC. Vismodegib was initially FDA approved for use in 2012, when a prospective study revealed a 30% response rate in patients with metastatic BCC and a 43% response rate in patients with locally advanced BCC [46]. Complete response was observed in 21% of

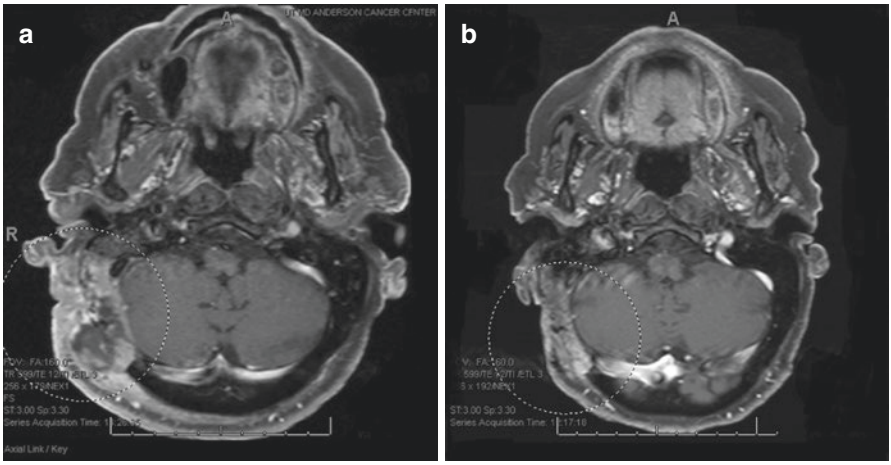


**Fig. 8.5** Axial T1 MRI sequence depicting a dramatic response of locally invasive BCC (with temporal bone and intracranial extension) before (**a**) and after (**b**) 3 months of neoadjuvant vismodegib. The patient had an excellent response to treatment and went on to definitive surgical resection

patients with locally advanced BCC [46]. Sonidegib was introduced in 2015 following a phase II randomized double-blinded study demonstrating a 12-month objective response rate of 57.6% in locally advanced BCC and 7.7% in metastatic BCC [47–49]. A recent meta-analysis of studies using vismodegib and sonidegib in advanced BCC confirmed these findings, showing similar overall response rates in locally advanced disease (69% vs. 57%, respectively), but significant complete response rates in only vismodegib (31% vs. 3%) [50]. However, such a comparison may be misleading. Although there has not been a cross-trial comparison, sonidegib and vismodegib were compared using a matching-adjusted indirect comparison to reduce confounding of treatment effects which could have occurred in an unadjusted indirect comparison. Patients from the sonidegib trial had an objective response rate (ORR) of 56.7% and progression-free survival (PFS) of 22.1 months, whereas patients from the vismodegib trial displayed an ORR of 47.6% and PFS of 9.5 months, thus indicating a slightly greater benefit with sonidegib therapy [51].

Vismodegib has been used in the neoadjuvant setting in locally advanced head and neck BCC, where early reports have shown very promising results in tumor reduction, allowing for more modest organ-sparing surgical excision or radiation treatment [52]. A dramatic example is shown in Fig. 8.5. Vismodegib may also have some applications in a concurrent treatment setting: a recent study revealed that vismodegib treated cell lines were more radiosensitive than control [53]. Thus, future applications of targeted systemic therapies will likely yield further evolution in the multidisciplinary management of advanced BCC.

## Conclusion

BCC is a ubiquitous disease entity with excellent treatment options. A variety of clinical subspecialties are involved in the care of patients with BCC of the head and neck, and understanding the populations at risk, molecular pathogenesis, and workup is key to managing BCC appropriately. Surgery is a cornerstone of BCC treatment and generally provides optimal outcomes with acceptable function and cosmesis. With the elucidation of the molecular pathogenesis of BCC, exciting novel therapies are now available and appear to be primed to change the paradigm of treating locally advanced and metastatic BCC. Most importantly, a multidisciplinary approach is crucial in patients with locally advanced or metastatic BCC of the head and neck.

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# Chapter 9
# Special Considerations for Periocular Basal Cell Carcinoma


**Oded Sagiv, Ho-Seok Sa, and Bita Esmaeli**

## Introduction

Basal cell carcinoma (BCC) of the periocular region presents unique challenges owing to the unique anatomic and functional implications of proximity of the cancer to the eye and the potential negative impact of treatments on both the visual function and aesthetic outcomes. This chapter will review the various treatment modalities and special considerations for the periocular BCC.

O. Sagiv
The University of Texas MD Anderson Cancer Center, Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, Houston, TX, USA

The Sheba Medical Center, The Goldschleger Eye Institute, Ramat Gan, Israel

H.-S. Sa
The University of Texas MD Anderson Cancer Center, Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, Houston, TX, USA

Asan Medical Center, University of Ulsan, Department of Ophthalmology, Seoul, South Korea

B. Esmaeli (✉)
The University of Texas MD Anderson Cancer Center, Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, Houston, TX, USA
e-mail: besmaeli@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_9

## Epidemiology

BCC is the most common eyelid malignancy and accounts for 90–95% of malignant eyelid tumors. It is found in the following locations in decreasing order of frequency: lower eyelid margin (50–60%), medial canthus (25–30%), upper eyelid (15%), and lateral canthus (5%), although some series have found the medial canthus to be more common than the lower eyelid [1, 2]. Risk factors, similar to BCC in other locations in the body, are fair skin, blue eyes, red or blond hair, and middle age to older Caucasians [1, 3]. Prolonged sun exposure during the first two decades of life and history of smoking are also risk factors. Patients with genetic predisposition, such as basal cell nevus syndrome (BCNS, also referred to as Gorlin syndrome) and xeroderma pigmentosum, were also found to be at increased risk for periocular BCC. The most common histologic subtype is nodular, followed by infiltrating, superficial, micronodular, morpheaform, and basosquamous [2].

## Surgical Excision

When diagnosis based on clinical grounds is uncertain, a 3–4 mm biopsy should be done to confirm the diagnosis prior to planning definitive surgery. Surgical excision with intraoperative frozen section control of margins is the treatment of choice for periocular BCC. It has been argued that for small nodular tumors, macroscopic assessment of the margins could be sufficient [4]. However, incomplete excision was found to result in a 27% local recurrence rate (a mean follow-up of 34.7 months) in a series of patients with periocular BCC, and thus it is advisable to aim for negative microscopic margins in all patients [5]. Simple wide local excision with 3 mm of clinical margins and no intraoperative control of margins was shown to result in incomplete excision in 25% of cases [6]. Additionally, sclerosing or recurrent BCC requires microscopic margin assessment since these are hard to determine macroscopically. Intraoperative frozen sections and Mohs micrographic surgery (MMS) are the two main methods used for control of resection margins for periocular BCC.

### *Wide Local Excision and Handling of Eyelid Specimens*

Tissue in the periocular area is the most precious due to the complex reconstruction required to protect the eye and to allow the eye to function properly. Therefore, surgical margins tend to be smaller than in other, more forgiving, parts of the body. Wide local excision of a BCC involving the eyelid margins is usually performed by a full-thickness wedge resection, from the skin to conjunctiva, including the eyelid margins (Fig. 9.1). The specimen is placed on a Telfa pad, and drawing of the eye, eyelids, and brow is added to assist with proper orientation for the pathologist

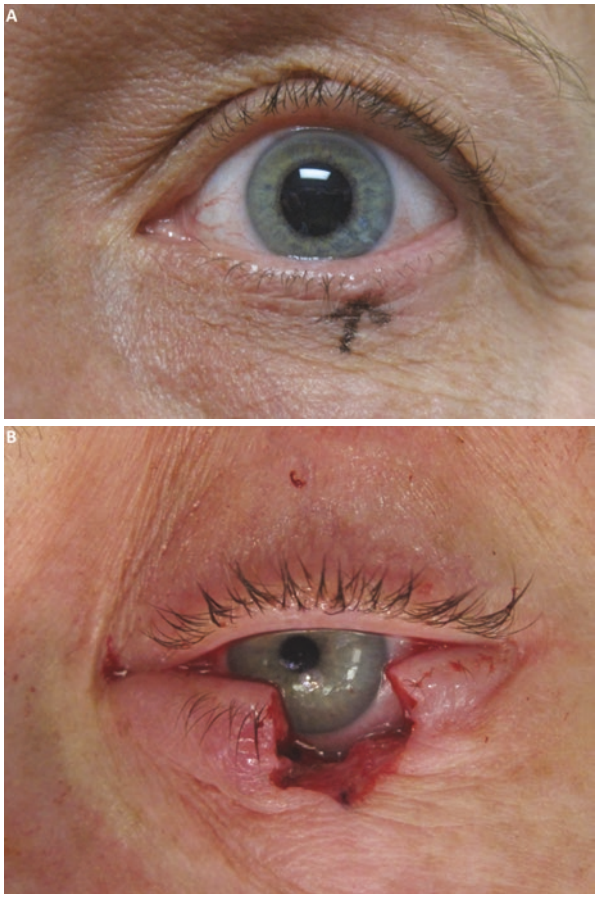


**Fig. 9.1** (**a**) Photograph of a typical small 4 mm BCC involving the lower eyelid margins. (**b**) Complete excision using a pentagonal wedge resection and evaluation of margins on frozen section using a "modified Mohs" technique to evaluate all adjacent en face margins

(Fig. 9.2). When eyelid margins are not included in the specimen, a suture can be added to it to help with the specimen orientation. Labels should specify laterality and whether the upper or lower eyelid or both are involved. Because, at bread-loaf sectioning, only about 2% of the margins are examined, additional dedicated en face margins of 1–2 mm thickness are sent for frozen section evaluation. Essentially a "modified Mohs" technique is used for eyelid margin and periocular BCC. Marking of the true margins of these specimens help the pathologist determine the margin of interest. For an eyelid margin carcinoma, these en face specimens are thin and contain both skin and tarsus/conjunctiva. The pathologist should be experienced with handling this type of specimens and be able to reliably report margins' status. The process of taking en face margins is repeated until clear margins are achieved all around the carcinoma. If the histologic diagnosis is unclear and also for a reminder of what the carcinoma looks like microscopically, the main tumor specimen can also be bread-loafed (thin sections) and analyzed intraoperatively on frozen section. All surgical specimens are also sent for paraffin fixation and further analysis. For

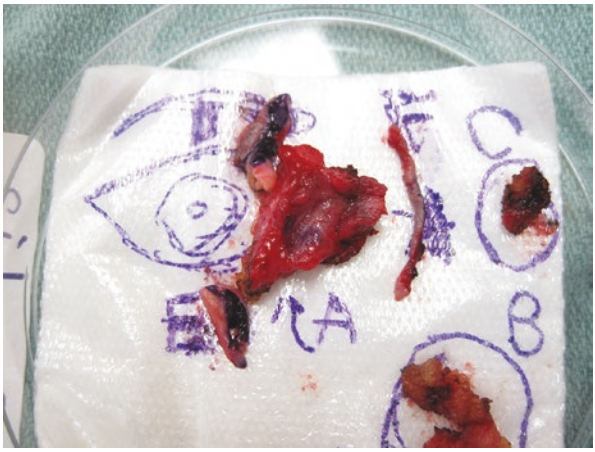


**Fig. 9.2** In this photo, the surgical specimen during resection of periocular BCC is shown. The main surgical specimen and additional dedicated en face margins are laid on a Telfa pad, on a drawing of the eye and eyelids to aid the pathologist with proper orientation of the specimen and margins of interest. True margins of the en face surgical specimens are inked and fully evaluated on frozen section. Labels should describe in detail the origin and location of each specimen

specimens that do not involve the eyelid margins, the depth and width of excision margins vary per surgeon's judgment but generally include the skin and orbicularis oculi muscle. Deep margins are also taken for en face analysis in cases of periocular BCC that do not involve the eyelid margin. Direct intraoperative communication with the pathologist is key in the success and reliability of frozen section evaluation of margins and is routinely practiced at our center.

## Mohs Micrographic Surgery

MMS has gained popularity for removal of periocular BCC for its reported advantage in minimizing the size of the defect that needs to be repaired compared with traditional wide excision surgery. This technique is performed by a board-certified dermatologist who has completed an additional fellowship training in Mohs micrographic surgery. Prior to excising the tumor, several orientation marks are made on both tumor specimen and on patient in order to maintain orientation after tumor removal. The marks on the specimen are then inked with different colors so that the orientation can be correctly identified under the microscope. After the specimen is processed by a histotechnician, the Mohs surgeons also perform histologic interpretation of the slides. If the specimen is positive for tumor at any particular edge, an additional layer of tissue is taken at this location. The process is repeated until all tumor margins are clear. This method spares uninvolved tissue while ensuring

complete removal of the tumor. The main difference between MMS versus traditional surgical excision is that MMS always examines 100% of the margins. Even with taking en face margin with excision, the degree and the number of sections can vary from case to case, and practices may vary among surgeons. In addition, MMS is performed in an outpatient setting with local anesthesia, while surgical excision is performed in the operating room and with some sedation but still in an outpatient setting. For more deeply infiltrative tumors of the orbit, Mohs micrographic surgery may not be appropriate, and general anesthesia is indicated. The start to finish time for MMS can vary and may be longer if multiple stages are needed to clear the tumor due to the time required to process the specimen. In cases where the surgical defect involves the lacrimal canaliculi, canthal tendons, or posterior lamellae of the eyelids, excision and reconstruction by oculoplastic surgeons are appropriate.

## Topical Imiquimod

Imiquimod is a non-nucleoside imidazoquinoline that acts as an agonist to Toll-like receptor 7, found on immune cells of the skin (Langerhans cells of the epidermis, dendritic cells, and monocytes). Through binding, it induces an immune response that destroys the cancer cells. Non-ocular studies have shown 6 weeks of topical therapy that resulted in clearance rates of 75–80%, with similar rates at 5 years of follow-up. Imiquimod 5% has been used in the periocular area as well. In a randomized trial, it was used to treat 15 patients and compared to a control group treated with radiation therapy. Treatment regimen was of 5 days/week for 6 weeks, and patients used an ophthalmic gel prior to application of the imiquimod cream. Patients were instructed to avoid contact with the eye surface during application in order to protect the cornea [7]. The authors reported that all tumors showed a complete remission within 3 months (verified histologically), and that was sustained in all patients over 24 months of follow-up. Ocular side effects included discomfort when blinking, significant conjunctival irritation in only two patients which was treated with topical steroids and antibiotic drops, and no other findings on ophthalmic examination. Another prospective study reported 24 patients with periocular BCC treated with topical imiquimod with histological clearance rates of 89% at 3 months and 84% at 39 months [8]. Ocular side effects were similar and only two patients were unable to tolerate therapy.

## Reconstructive Considerations in the Periocular Region

The goals of the reconstructive surgery in the periocular area are according to the following priorities: to preserve the eye, preserve vision, and provide the best possible aesthetic outcome. For the eye to stay intact, the main consideration is prevention of exposure by providing coverage for the cornea and ocular surface with the

eyelid that is lined with conjunctiva (the mucosal inner lining of the eyelid). Good apposition of the eyelid to the globe and blink mechanisms as normal as possible are also important to provide constant surface lubrication. If the cornea is exposed and not constantly lubricated by the blink mechanism, corneal abrasions, infection, melting, and perforation are serious risks that can cause loss of the globe. To provide the best potential for visual function, the visual axis (the central area of the cornea) should not be permanently covered by tissue.

The eyelids are one of the most delicate structures of the human body, and they protect the globe and vision and also play an important role in facial cosmesis. The general principles that guide eyelid reconstruction are as follows:

1. The eyelid consists of two components and both must be reconstructed. The anterior lamella is composed of the skin and orbicularis muscle, while the posterior lamella is formed by the tarsus and conjunctiva.
2. Grafts must not be used to reconstruct both lamellae (avoid graft on graft placement), and at least one of the lamellae should be repaired using a flap with intact blood supply.
3. Appropriate horizontal tension must be maintained to avoid postoperative eyelid malposition.
4. Careful attempt must be made to match "like" tissue to each lamella.

The anterior lamella can be best matched with the skin from the vertically opposite or contralateral upper eyelid. The posterior lamella substitutes should have a mucosal surface that will not irritate the ocular surface. Choices for posterior lamellar replacement include a tarsoconjunctival flap, a free composite tarsoconjunctival graft, or a hard palate graft.

An intimate knowledge of the eyelid anatomy and its functional implication is crucial for periocular reconstruction. The tarsus is a dense connective tissue providing structural integrity of the eyelid and measures about 1 mm in thickness and 29 mm horizontally by 7–10 mm vertically in the upper eyelid and 35 mm in the lower eyelid. The eyelids insert to the canthi medially and laterally, and the tarsoligamentous attachment to the bone provides the horizontal eyelid tension. The medial canthal ligament inserts to the anterior and posterior lacrimal crest, and the lateral canthal ligament attaches at Whitnall's tubercle, which is located posterior to the lateral orbital rim. The levator aponeurosis, the main retractor of the upper eyelid, inserts on the lower 7–8 mm of the anterior surface of tarsus and sends fibers through the orbicularis to the skin forming the upper eyelid crease. The lacrimal drainage system is located in the medial canthal region. The upper and lower puncta are 6–7 mm lateral to the medial canthus, and the canaliculi join to the lacrimal sac located below the medial canthal ligament. Regarding blood supply, the medial and lateral palpebral arteries anastomose to form a marginal arcade on the anterior tarsal surface 2–4 mm from each eyelid margin. The peripheral arcade is only found in the upper lid and located on the upper border of the tarsus between the levator aponeurosis and Müller's muscle.

A detailed discussion of various reconstructive options in the periocular region is outside the scope of this chapter; however, a brief overview based on location of defect is provided below.

## *Upper Eyelid Defects*

Full-thickness upper eyelid defects involving less than one-third of the eyelid margin can be usually repaired by direct closure [9]. The defect size depends on the patient's age and the degree of horizontal eyelid laxity. A lateral canthotomy and a superior lateral cantholysis increase horizontal mobility of the residual eyelid and allow for direct closure of larger defects. During closure of the eyelid margin, three parallel sutures should be placed through the gray line, tarsus, and lash line. Excessive horizontal tension can cause postoperative ptosis, which tends to improve with time in elderly patients [9, 10].

Upper eyelid defects involving one-third to one-half of the eyelid margin can be repaired by a reverse Tenzel semicircular flap. This involves the rotation of a myocutaneous flap beginning at the lateral canthus, extending downward in a semicircular fashion [9, 11].

Upper eyelid defects involving more than half of the eyelid margin can be repaired by a Cutler-Beard procedure [12]. This involves the advancement of a composite full-thickness lower eyelid flap (excluding the tarsus) into the upper eyelid defect by passing it under the intact lower eyelid margin [13]. It is important to leave at least 5 mm of lower eyelid margin to preserve blood supply of the marginal arcade [9, 14]. This lid-sharing procedure requires a second stage to divide the pedicle, which is conducted 6–12 weeks after the first stage. Given that postoperative upper eyelid entropion and consequent corneal irritation is not uncommon, special attention should be paid during flap separation that the conjunctival surface is longer than the skin surface. A spacer, such as acellular dermal matrix (Alloderm®), ear cartilage, or donor sclera, can be grafted between the orbicularis muscle and conjunctiva to reinforce the missing tarsal support [15]. A reverse modified Hughes procedure can be an alternative to a Cutler-Beard procedure [16]. This involves the advancement of tarsoconjunctival flap from the lower eyelid and the coverage of the flap with a skin-muscle flap advancement from redundant upper eyelid. It has an advantage of avoiding the cutaneous scar of the donor lower eyelid, but for deep defects of the upper eyelid without adequate amount of remnant skin, a Cutler-Beard procedure would be a preferable choice.

## *Lower Eyelid Defects*

Full-thickness lower eyelid defects involving less than one-third of the eyelid margin can usually be repaired by direct closure. Primary repair of larger defects may cause excessive tension on the wound, leading to wound dehiscence. An additional medial mobilization of the residual eyelid can be obtained by a lateral canthotomy and inferior cantholysis, which is similar to what was describe with the upper eyelid [9, 17].

Lower eyelid defects involving one-third to one-half of the eyelid margin can be repaired by a Tenzel semicircular flap, typically combined with an inferior cantholysis [11]. If the lower eyelid retractors and inferior orbital septum are severed from their attachments, the flap may be used for defects up to 70% of the eyelid

margin. It is important that once the flap is rotated into the defect, the flap should be securely fixated to the periosteum inside the lateral orbital rim to prevent potential lid retraction or ectropion [9, 18].

The modified Hughes procedure is very useful for full-thickness lower eyelid defects involving more than half of the eyelid margin [9]. A tarsoconjunctival flap mobilized from the upper eyelid is advanced into the defect of the lower eyelid for posterior lamellar reconstruction. The tarsal incision should be approximately 4 mm from the upper eyelid margin to prevent donor-lid instability. The skin graft harvested by the upper blepharoplasty or vertical skin-muscle advancement can be used for anterior lamellar reconstruction [17, 19]. Since the flap must be left in place for 4–6 weeks prior to second-stage separation, it is not suitable for monocular patients and children in the amblyogenic age. Alternative procedures to avoid visual axis occlusion include a free tarsoconjunctival graft from the contralateral upper eyelid with skin-muscle flap, full-thickness pedicled flaps, and the Hewes tarsoconjunctival transposition flap, but the usefulness is not as good as the modified Hughes flap in our experience [20–23].

The Mustardé cheek rotation flap can be used to reconstruct a large anterior lamellar defect of the lower eyelid, typically also involving the cheek [24]. It mobilizes the lateral cheek and zygomatic skin, and the posterior lamella must be reconstructed separately with a tarsal substitute. The Mustardé flap is often associated with a high risk of postoperative ectropion of the lower eyelid [13].

## *Medial Canthal Defects*

Reconstruction of the medial canthal area is challenging due to the complexity of the anatomy and the importance of eyelid and lacrimal function. Surgeons should investigate involvement of the medial canthal ligament, lacrimal drainage system, and

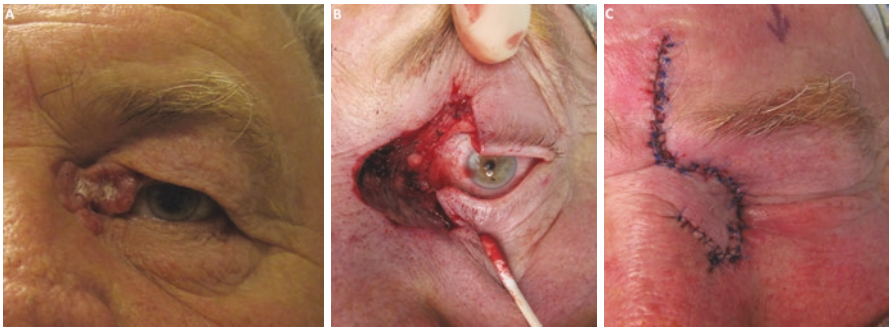


**Fig. 9.3** (**a**) Photograph of a 65-year-old man who presented with a 22 × 18 mm BCC involving the left medial canthus and the medial part of the upper eyelid close to the upper punctum. (**b**) He underwent a wide local excision with frozen section control of the margins. The upper punctum and both canaliculi were resected. (**c**) The upper eyelid had considerable laxity and was attached to the posterior lacrimal crest together with the lower eyelid. Reconstruction of the residual defect was achieved using a glabellar transposition flap

underlying bone and sinus before reconstruction. Medial canthal defects restricted to the anterior lamella can be repaired by spontaneous (laissez-faire) granulation or full-thickness skin graft, and the latter can achieve faster wound healing [13]. For larger soft-tissue defects, or those lacking a vascular bed, a glabellar transposition flap is very useful for this region (Fig. 9.3). The glabellar flap can also potentially obliterate exposed sinuses in smaller or partial sinus defects and can endure post-operative radiation [9, 25]. When the medial canthal ligament has been resected, the remaining upper and lower eyelids must be fixated to the deep tissues or periosteum in the region of the posterior lacrimal crest where the medial canthal ligament inserts. It is an essential step to achieve good apposition between the eyelid and globe and to avoid potential ectropion and lagophthalmos [13]. When the lacrimal drainage system, including the canaliculi, has been partially interrupted, silicone stents can be placed for its restoration. In cases of total loss of canaliculi or lacrimal sac, a conjunctivodacryocystorhinostomy may be required to address symptomatic epiphora, but this is delayed until at least 1 year after removal of tumor and should only be considered if patient has symptomatic epiphora [9, 13].

### *Lateral Canthal Defects*

Most lateral canthal defects are associated with the defects of the lateral portion of the upper or lower eyelids. Maintaining the appropriate position of the lateral canthus after reconstruction is important for cosmetic reasons as well as functional reasons to avoid the lower eyelid ectropion or lagophthalmos [26]. The reconstructed lower eyelid and lateral canthal ligament must be anchored to the inner aspect of the lateral orbital rim (Whitnall's tubercle) without laxity by primary suturing to periosteum, a drill hole fixation, or a periosteal flap [27, 28]. When larger lower eyelid defects extend to the lateral canthus, the posterior lamella can be reconstructed with a periosteal flap raised from the lateral orbital rim or a laterally positioned tarsoconjunctival flap from the upper eyelid [13]. For anterior lamellar reconstruction, a full-thickness skin graft or a semicircular advancement flap can be used [13].

## Locally Advanced Disease in the Periocular Region

### *Anatomic and Functional Considerations*

BCC of the eyelid can extend to adjacent structures by several mechanisms. It can directly infiltrate the deeper structures of the eyelid, from superficial to deep: the dermis, orbicularis oculi muscle, tarsus, and conjunctiva. Tumor can also infiltrate the levator muscle aponeurosis and Muller's muscle if higher in the upper eyelid or the equivalent lower eyelid retractors in the lower eyelid. The lacrimal system including the puncta, canaliculi, lacrimal sac, nasolacrimal duct, and adjacent maxillary bone

can be directly infiltrated by tumor originated from the medial canthus skin. This may be manifested clinically by new-onset of unilateral tearing or bloody tears. BCC of the medial canthus accounted for over 50% of the cases in a series of 64 patients with a locally advanced BCC invading the orbit [29]. BCC of the periocular area can also spread regionally by perineural or perivascular invasion. Common nerves that can be involved are the sensory nerves that innervate the periocular skin: cranial nerve V1 via the supraorbital, supratrochlear, and infratrochlear nerves and V2 via the infraorbital, zygomaticotemporal, and zygomaticofacial nerves. These can manifest clinically by local hypesthesia or pain. Deeper penetration into the orbit or cavernous sinus can manifest by various neurological deficits of the motor cranial nerves that innervate the muscles of the eye (manifested by limitation in eye movement or binocular diplopia) or of the eyelids (manifested as neurogenic blepharoptosis). Perineural invasion can be investigated using orbital MRI. Infiltration of the orbital soft tissues can cause globe dystopia, proptosis, corneal exposure and dryness (exacerbated by corneal hypesthesia and incomplete closure of the eyelids), and eventually optic nerve compression and vision loss. Other structures that may become involved by these mechanisms are the cheek, the brow, the temporal muscle and temporal fossa, the orbital bones, the nasal cavity, the paranasal sinuses, the skull base, and the central nervous system.

Locally advanced BCC in the periocular region maybe defined as a tumor that is either especially large, extends beyond the periocular structures (i.e., eyelids, canthi, brow) into adjacent tissues as mentioned above, or one that invades the orbital soft tissue to the point where eye salvage would be difficult and an orbital exenteration may even be necessary for surgical resection. It has usually been defined in the past as tumors that are T3b or more advanced, according to the American Joint Committee on Cancer (AJCC) *Seventh Edition Cancer Staging Manual* [30]. This included unresectable tumors (T4) and tumors that require enucleation, exenteration, or bone resection (T3b). These definitions were somewhat subjective and included tumors with very different extent under one category. Thus, the eighth edition of the *AJCC Cancer Staging Manual* (effective since 2018) included significant revision in the eyelid carcinoma staging system. In the eighth edition, T4 is defined as tumors that invade adjacent ocular, orbital, or facial structures. T4a is defined as tumors that invade ocular or intraorbital structures and T4b as tumors that invade (or erodes through) the bony walls of the orbit, extend to the paranasal sinuses, or invade the lacrimal sac, nasolacrimal duct, or brain [31]. Thus in the eighth edition of AJCC manual, locally advanced periocular carcinomas for the most part correspond to T4 tumors. Future validation studies are needed to evaluate the most recent T category criteria and may lead to further modification and enhancements.

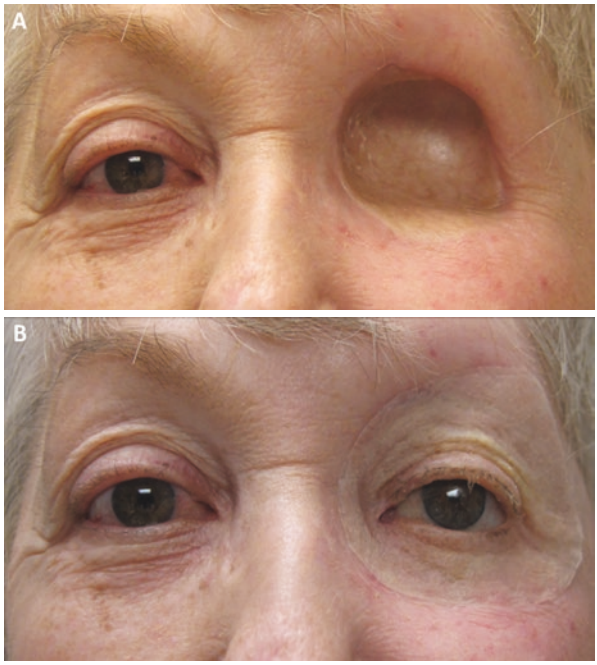


**Fig. 9.4** (**a**) Photograph of a 75-year-old woman who had on orbital exenteration and reconstruction using a radial forearm free flap. She has an unusually hollow orbital socket after a free flap. This hollow shape of the socket is advantageous if the patient desires to wear an orbital prosthesis. (**b**) Custom-made orbital prosthesis is shown in position and is usually glued to the surrounding skin

## *Orbital Exenteration*

Orbital exenteration is the surgical excision of the eye, orbital soft tissues, and ocular adnexa (lacrimal gland, lacrimal drainage apparatus, and eyelids). Orbital bones and adjacent structures can be also resected at the same time as needed. Historically, when deep orbital soft tissues are infiltrated with BCC, an orbital exenteration is considered as the surgical ablative procedure.

An orbital exenteration not only leads to complete loss of the eye and visual function but also is associated with significant orbitofacial deformity with significant social and psychological impact [32]. The bony orbital socket was traditionally partially covered by skin and allowed to re-epithelized over time, leaving a hollow socket that can be later fitted with an orbital prosthesis to enable a more pleasing aesthetic outcome. For larger defects involving loss of bony walls of the orbit, dura or brain exposure after loss of the roof or posterior orbital bony walls, or in cases where high dose radiation therapy is planned postoperatively, the orbital socket should be reconstructed using a vascularized regional flap or a free flap. These larger bulkier flaps lead to a less hollow sockets and make the fitting of an orbital prosthesis more challenging and less likely to succeed although some exceptionally hollow orbits can be accomplished with thinner flaps such as a radial forearm flap when the size and other characteristics of the defect makes the radial forearm an adequate flap to use (Fig. 9.4).

## *Radiation Therapy and Ocular Toxicity*

Radiation therapy (RT) has been used as an adjuvant therapy after orbital exenteration when final margins are still positive for carcinoma, when perineural invasion is found on the surgical specimen, in some instances for unresectable tumors as palliation, or historically in patients who may not be good surgical candidates. In cases of either local excision or exenteration of a locally advanced disease in which clear margins are achieved, adjuvant RT has not been shown to be advantageous in preventing local recurrence, and we do not use it routinely in such patients [33, 34]. Radiation as primary modality, whether as a standard fractionated RT, interstitial brachytherapy, or superficial contact therapy, has been shown to be effective for the treatment of BCC of the face, although it is not as effective as surgery [35, 36]. Previous studies have reported recurrence rates of 25% in patients who were treated with RT as primary modality. In one report, visible scars were more prevalent in surgical patients only in the first 12 months, but on longer follow-up, 20% more patients treated with RT had visible scars compared with surgical patients [35].

When considering radiation therapy in the orbit and periorbital region, the clinician must always weigh the serious potential side effects for the eye and eyelids against the potential benefit of radiation therapy. The common ocular toxicity associated with radiation therapy for periocular and orbital cutaneous cancers include loss of lashes on the eyelids, cicatricial eyelid ectropion, nasolacrimal duct stenosis, chronic conjunctivitis, reduced tear production, severe dryness, corneal epithelial damage, cataract formation, and rarely radiation retinopathy, neovascular glaucoma, radiation-induced optic neuropathy, and loss of vision. Various thresholds have been found for the development of these complications. Some advocate that globe position and direction of gaze during delivery of radiation can influence the risk for some of these structures [37].

## *Sonic Hedgehog Inhibitors for Locally Advanced BCC in the Periocular Region*

Mutations that abnormally activate the Sonic Hedgehog (SHH) pathway have been found in periocular BCC in patients with both sporadic BCC and basal cell nevus syndrome. Vismodegib (Erivedge™, Genentech) is approved for the treatment of metastatic BCC, for locally advanced BCC that has recurred after surgery and for patients who are not candidates for surgery or radiation therapy [38]. Similarly, sonidegib (Odomzo®, Novartis) is approved for the treatment of locally advanced BCC that has recurred after surgery or radiation and for BCC that is not amenable to surgery or radiation [39]. The published experience to date with SHH inhibition for periocular BCC has been limited to small case series of patients treated with vismodegib. In part, this may be owing to the fact that treatment is not FDA-approved as first line for locally advanced tumors. Reviewing the data from these case series

together suggests an impressive response rate of 100% for patients with BCNS, 86% for patients with locally advanced BCC in the periocular region, and 33% for patients with periocular BCC with metastasis [40–42].

We reported the outcome of vismodegib therapy for ten patients with a locally advanced periocular BCC, of whom all were not eligible for RT, and four had metastatic disease at presentation [42]. We observed complete response in two patients, partial response in four patients, and stable disease in four patients. Two other patients had progressive disease: one progressed after being 3 months off-therapy, following an initial partial response over prior 14 months of treatment, and the other demonstrated 16 months of stable disease with treatment and finally progressed and died of his metastatic disease. Overall, patients with nonmetastatic locally advanced BCC had response rate of 86%. Of note, we were able to spare the eyes of all patients in this study, meaning that treatment with vismodegib enabled us to avoid an orbital exenteration in five of ten patients (Fig. 9.5). In a recent report, Wong et al. treated 15 patients with locally advanced periocular BCC with vismodegib, for a mean treatment duration of 13 months and mean follow-up of 36 months. They reported that ten patients (67%) had a complete response, three patients (20%) had a partial response, and two patients (13%) had a progressive disease following an initial response [43]. Of note, this study defined complete response based on clinical findings and not by a repeated surgical biopsy, and in fact not all patients

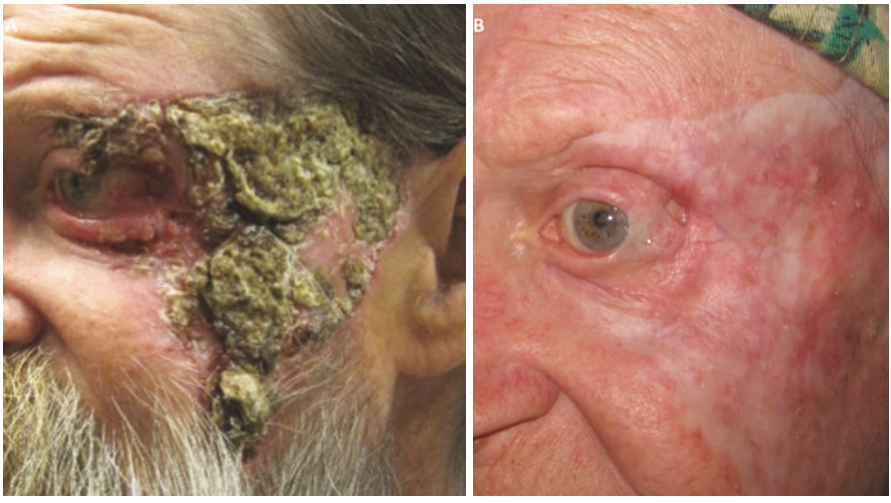

**Fig. 9.5** (**a**) This 55-year-old man presented with a locally advanced T4a BCC involving the left upper and lower eyelids, temporal and cheek region, with tumor present in the orbit, in contact with the globe, and the premaxillary space. He was treated with oral vismodegib for 18 months followed by surgery to correct the upper and lower eyelid retraction which had caused severe corneal exposure. Multiple map biopsies were done at the time of reconstructive surgery, and they were all negative for carcinoma. (**b**) Photograph of the same patient after additional 2 years of follow-up without therapy and without signs of local recurrence

underwent surgery. Combined use of SHH inhibitors with other treatments has also

been reported for periocular BCC. One study of six patients found that treatment with SHH inhibitors, combined with radiation and mTOR inhibitors, for very large BCCs enabled a less extensive surgical resection.

More recently, we have explored the possibility of using vismodegib as neoadjuvant treatment prior to eye-sparing surgery. Our data suggests that the rate of globe salvage is high and in majority of patients either surgery to remove residual tumors or reconstructive surgery to rehabilitate the eye is still necessary, but in all cases, eye removal can be avoided [44, 45].

We have also observed impressive responses to treatment with vismodegib in two patients with periocular basal cell nevus syndrome. Both patients were treated over a prolonged period of 19–38 months and demonstrated complete response of their periocular lesions [42].

At the time of writing this chapter, we were unable to find reports on the efficacy of sonidegib for locally advanced periocular BCC.

## Conclusions

Basal cell carcinoma is the most common malignancy of the eyelids and periocular region. The most common treatment for periocular BCC is surgery. Reconstruction in the periocular region is a critical component of surgical care. In the majority of cases, a specialized reconstructive surgery can restore function and aesthetics. Nonsurgical treatments historically have included radiation therapy and topical imiquimod.

For locally advanced disease in the periocular region, the judicious use of Sonic Hedgehog inhibitors has significantly improved treatment options for patients who would otherwise need an orbital exenteration or extensive and potentially disfiguring surgery. Future studies will focus on appropriate use of these drugs in the neoadjuvant setting. The indications and limitations need to be further studied.

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# Chapter 10
# Radiotherapy for Basal Cell Carcinoma


**Sweet Ping Ng, Jae Phan, Danna K. Fullen, William H. Morrison, and G. Brandon Gunn**

## Introduction

Basal cell carcinoma accounts for up to 80% of all non-melanoma skin cancers and is the most common cancer in the world [1]. The primary aim of treatment for basal cell carcinomas is local control, as regional and distant spread is very rare. Although surgery remains the preferred modality for definitive treatment at most centers, radiotherapy is frequently considered for those patients who are medically inoperable, unresectable tumors, or for those who decline surgery. Other relative indications for radiotherapy include cases where it would be difficult to achieve clear surgical margins and where surgery would result in unacceptable functional or cosmetic morbidity. For example, a small lesion of the eyelid or nose can be treated with radiotherapy if surgical resection would result in significant unacceptable cosmetic defect and/or reconstruction options are limited. Herein we describe the different radiation therapy techniques and the radiation modalities used at our center to

S. P. Ng
Peter MacCallum Cancer Centre, Department of Radiation Oncology, Melbourne, VIC, Australia

J. Phan
The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology-Research, Houston, TX, USA

D. K. Fullen
The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology-Therapy, Houston, TX, USA

W. H. Morrison · G. B. Gunn (✉)
The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX, USA
e-mail: GBGunn@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_10

treat basal cell carcinomas, decisions influenced by disease location and in attempt to mitigate the potential acute and late side effects of radiotherapy.

## Radiotherapy Options

### *Definitive Radiotherapy*

Surgery is generally preferred if the lesions are amendable to excision while the patient's function and cosmesis are preserved. Although occasional patients may prefer radiotherapy as definitive treatment, these patients may not be ideal candidates if the tumor is located in an area of poor vascularity or in a region which is prone to trauma. Examples are tumors located in the pretibial region and/or patients with advanced cancers invading the bone. Areas of low vascularity are at higher risk of skin necrosis and subsequent non-healing ulcer after radiotherapy; therefore, surgical treatment is preferred in these regions.

### *Adjuvant Radiotherapy*

In general, radiotherapy is recommended in the postoperative setting if there is high possibility of residual microscopic disease (e.g., positive or narrowly cleared surgical margins) and substantial risk of subsequent local recurrence. Some (relative) indications for postoperative radiotherapy include:

- Positive margin (risk of local recurrence is more than 25%), if re-resection of margin is not feasible
- Recurrent disease
- Infiltrative or morpheaform pathologic features
- Basosquamous histology
- Advanced tumors; invasion of skeletal muscle/cartilage/bone
- Perineural invasion

Patients with any of the above clinical or histological findings should be discussed by the multidisciplinary team and considered for further therapy after initial surgery. For tumors with perineural invasion, particularly for those with gross or clinical invasion of a named nerve, the nerve tract at risk is generally targeted for radiation therapy for some distance, especially for primaries of the head and neck region.

### *Radiotherapy to Regional Nodal Stations*

The risk of nodal and distant metastasis from basal cell carcinoma is less than 1% [2–4]. Therefore, local control is the primary focus of basal cell carcinoma treatment. In the absence of any adverse clinical and/or pathological features that indicate high risk of nodal disease (e.g., clinical nodal involvement or basosquamous histology), elective nodal irradiation is typically omitted in basal cell carcinoma treatment.

## Radiotherapy Modalities/Techniques

Factors influencing selection of optimal radiation therapy modality/technique for basal cell carcinomas include:

- Dose at skin surface (i.e., proximal aspect of lesion/target)
- Dose at depth (i.e., deepest aspect of lesion/target)
- Rate of dose drop-off at depth and dose to nontarget normal tissue structures deep to lesion/target
- Dose to the nontarget normal structures lateral to tumor (i.e., due to the lateral penumbra of radiation field)
- Size/complexity/geometry of lesion/target

### *Orthovoltage Irradiation*

Orthovoltage beams have the advantage of delivering 100% of the dose to the skin surface and having a sharp narrow penumbra, which helps to reduce dose to normal structures lateral to the lesion (Fig. 10.1a). Orthovoltage beams used to treat skin cancers are typically 75–150 keV and are suitable for lesions of approximately

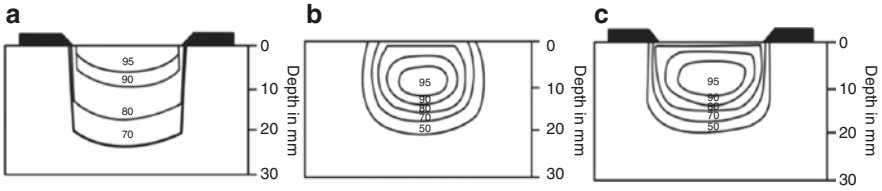


**Fig. 10.1** Radiation therapy isodose curves with corresponding estimated percentage of dose for orthovoltage beam (**a**), electron beam without skin collimation (**b**), and electron beam with skin collimation (**c**). (Note: Figures were generated in order to illustrate differences in dose profiles according to technique and do not represent physical measurements or clinical beam data)

5 mm or less in thickness. These beams are appropriate for irradiating superficial small lesions, particularly those near the eyes (e.g., medial canthus), as skin collimation/shieling can be easily fabricated with lead in order to further shape the beam; in addition, internal shielding can be utilized to eliminate dose to the underlying structures. Higher-energy orthovoltage beams, in the range of 150–300 keV, can be used to treat lesions up to 2–3 cm in depth. Orthovoltage technique has a more limited field size, typically 10 cm, depending on the available equipment. Orthovoltage X-rays have a radiobiologic effectiveness that is ~10% higher than megavoltage X-rays, so dose is usually prescribed at the surface and not at depth.

## *Electron Beam Therapy*

Electrons beams are suitable for superficial and deeper skin neoplasms. Electron beams have relatively rapid dose falloff at depth compared to high-energy photons and thereby ability to spare underlying normal tissue structures (e.g., underlying brain if treating a lesion on the scalp). Technical considerations when using electron beams to treat skin lesions include:

- Surface dose: To ensure adequate dose to the surface of the lesion/target and depending on the energy of electron beam required to treat the deepest aspect of the lesion/target, an appropriate thickness of tissue equivalent material, known as a bolus, is placed on the skin surface.
- Margin: An additional margin of at least 1 cm is placed around the area at risk (e.g., gross tumor and area of suspected microscopic disease) to account for constriction of prescription isodoses at depth (Fig. 10.1b, c).
- Bowing of lower isodose lines at depth needs to be considered if treating near critical structures (e.g., eyes) as these structures could potentially receive dose at depth (Fig. 10.1b).
- Skin collimation with customized lead shielding of sufficient thickness can be used to reduce dose to structures lateral to the target and to sharpen the lateral penumbra (Fig. 10.1c).
- Internal shielding (lead or tungsten) with thin wax or acrylic coating can be utilized to reduce dose to underlying structures (e.g., deeper oral cavity when treating the lip or anterior eye/cornea when treating periorbital skin); the wax/acrylic component will absorb backscattered electrons.
- Minimum field size with open fields should be at least 4 cm, depending on the energy of electron beam, to allow for electron equilibrium. With skin collimation, a slightly smaller field size generally can be used.
- Electrons are typically prescribed to the 90% isodose line.

When the treatment field is close to a dose-sensitive critical structure such as the eye, thermoluminiscent dosimeters (TLDs) should be used to ensure that the normal tissue structure is within tolerance and that the tumor is receiving the intended and planned dose.

### *Megavoltage Photons (Intensity-Modulated Radiotherapy (IMRT)/Volumetric Modulated Arc Therapy (VMAT))*

Megavoltage photons are typically used to treat locally advanced and more deep-seated tumors. This modality is also used in geometrically complex cases where nodal beds require treatment and/or extensive perineural tumor involvement requires nerve tract coverage (e.g., cranial nerve coverage toward base of skull). Since megavoltage photons have a relatively lower surface dose, a surface bolus of 0.5–1 cm is required to ensure that the lesion and surrounding at-risk skin surface is receiving adequate dose if IMRT/VAMT is used.

### *Proton Therapy*

Proton beam, given its inherent physical properties with deposition of energy toward its end range (i.e., Bragg peak) and advantage of dramatic dose fall off, is particularly useful for treating advanced tumors that are close to optic apparatus or extending toward the base of skull (Fig. 10.2). A spread-out Bragg peak is used for passively scattered proton beams. For skin cancers, the proton beam is further modified using an energy absorber or range shifter to ensure full surface dose.

### *Brachytherapy*

Brachytherapy is a treatment delivery technique involving the placement of radioactive sources on or into the target. Radioactive source can be loaded into a mold or applicator that can be placed directly onto the skin lesion to treat superficial tumors.

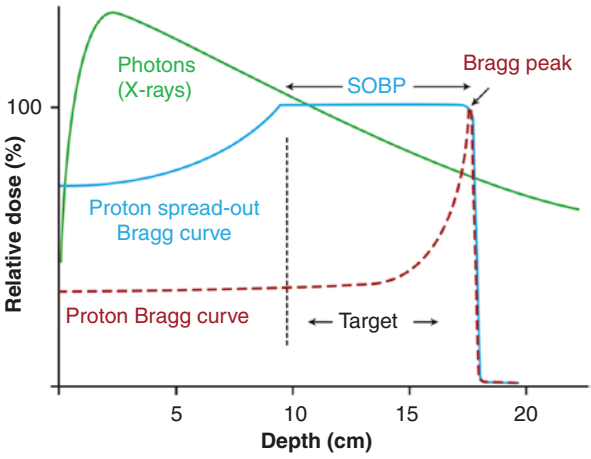


**Fig. 10.2** Depth dose curves depicting the fundamental differences of entrance doses and exit doses between proton and photon beams. SOBP – spread-out Bragg peak. (Note: For skin cancer treatment, the proton beam is further modified using an energy absorber or range shifter to ensure full surface dose)

Alternatively, catheters can be placed directly into the target tissue (e.g., nose or lip skin), and radioactive sources can be loaded to deliver radiation into the tumor. The advantage of this technique is that it allows delivery of therapeutic doses of radiation directly to the target in a very precise manner while further minimizing dose to the surrounding normal tissues due to the rapid dose falloff of this technique. Other than for the surface applications of this technique, the more complex logistics and invasive administration of treatment, this technique has been predominantly reserved as an alternative to the other radiation techniques for treatment of highly selected skin cancers at centers with sufficient experience.

## Side Effects

### *Acute Side Effects*

In general, radiotherapy to the local disease site is well tolerated. The acute effects of radiotherapy are limited to the local treatment fields. The most common local effect is radiation dermatitis, which may vary from mild erythema (Grade 1) to moist desquamation (Grade 3), depending on site, size of the treatment field, treatment modality, total dose, and fractionation schedule used. When tumors in close proximity to mucosa (e.g., nose and lip) are irradiated, mucositis may develop depending on the treatment modality and dose depth distribution of the radiation approach (typically if the mucosa-bearing receives more than 30 Gy). In hair-bearing regions, patients may experience alopecia during treatment within the radiation field. As a general rule, the acute effects start during treatment and peak in the weeks toward the end or after the radiation course is completed. However, for patients who receive a very accelerated radiation schedule or short treatment course, the acute effects may arise in the week or fortnight after completion of treatment. The acute effects may last several weeks posttreatment and are usually self-limiting. Fatigue may develop after large field irradiation and often does not subside for 3 months or more.

### *Late Side Effects*

Late effects of radiotherapy may be due to persistent interaction between irradiated cell populations with inflammatory and fibrogenic cytokines and growth factors. The risk of developing long-term late effects is dependent on the total radiation dose and dose/fraction, patient's age, smoking status, comorbidities, and previous surgery to the area. Patients may develop in-field hypo- or hyperpigmentation and telangiectasia. The risk of skin atrophy and fibrosis is often correlated with the pre-radiotherapy dermal health and factors such as the patient's age, comorbidities (e.g., diabetes mellitus, vascular disease), previous surgery, and location (e.g.,

pretibial region generally has poorer vascular supply than arms or neck). The risk of skin atrophy and contraction is approximately 5% at 5 years for areas that receive 60–65 Gy. For hair-bearing regions which receive greater than 30 Gy, there is a risk of permanent alopecia in the radiation field. Rarely, skin necrosis may occur, and this can range from a small lesion that can be managed conservatively to a larger ulceration that may require surgical repair/reconstruction. The risk of skin necrosis is dependent on patient's skin health (as above) and size of irradiated skin area and total dose. When radiation is delivered in the periorbital region with appropriate shielding of the globe, rare late toxicities may include cataracts, conjunctival scarring, and xerophthalmia.

**Table 10.1** Summary of the literature

| Reference | Nature of study | No of patients | Outcomes |
|---|---|---|---|
| Hall et al. [5] | Prospective, randomized (cryotherapy vs RT) | 93 | 2-year failure rate: 4% (RT) vs 39% (cryotherapy) |
| Abbatucci et al. [7] | Retrospective | 675 | 2-year failure rate: 4% |
| Avril et al. [6] | Prospective, randomized (surgery vs RT)<br>BCC of face <4 cm | 347 (173 received RT) | 4-year failure rate: 7.5% (RT) vs 0.7% (surgery) |
| Zagrodnik et al. [8] | Retrospective | 177 | 5-year failure rate: 15.8%<br>8.2% for nodular BCCs<br>26.1% for superficial BCCs<br>27.7% for sclerosing BCCs |
| Kwan et al. [9] | Retrospective | 61 | 4-year locoregional control: 86%<br>no deaths from BCCs |
| van Hezewijk et al. [10] | Retrospective, electron RT | 332 | 3-year locoregional failure: 97.6% (54Gy), 96.9% (44Gy)<br>no deaths from BCCs |
| Cognetta et al. [11] | Retrospective, superficial RT | 712 | 5-year failure rate: 4.2% |
| Krema et al. [12] | Retrospective; orthovoltage RT | 90 | 10-year local control: 94% |
| Rishi et al. [13] | Retrospective; with high-risk features (>1 cm, >2 recurrences or extracutaneous extension) | 108 | 3-year locoregional control: 87%<br>3-year overall survival: 87% |

## Expected Outcomes After Radiotherapy

There is limited category 1 evidence for treatment of basal cell carcinoma. Two randomized studies [5, 6] and several retrospective series [7–13] have reported good to excellent local control rates with radiotherapy. Reported recurrence rates after treatment with radiotherapy are in the range of 3–15% at 5 years. Most recurrences can be salvaged, and death due to basal cell carcinoma after treatment with radiotherapy is rare [9, 10]. Tumor control outcomes following radiation therapy are summarized in Table 10.1.

## Case Studies

### *Electron Beam Therapy*

Eighty-year-old man, of good performance status, presented with an ulcerated lesion of the right dorsum of his nose, on a background of previous multiple non-melanoma skin cancers. His only risk factor for non-melanoma cancers was a long history of sun exposure. Clinical examination revealed a 1 cm ulcerated lesion with rolled edges on the right nasal dorsum with surrounding skin changes consistent with previous prolonged sun exposure. Biopsy of the lesion confirmed nodular basal cell carcinoma. He decided to pursue definitive radiotherapy instead of Mohs surgery due to the extent of resection required.

He was simulated for radiation therapy to be delivered using electron beam to ensure adequate coverage of the nasal region while minimizing dose to the underlying normal structures and adjacent optic apparatus. A 2 cm margin around the lesion/nose was demarcated, and a tissue equivalent material was inserted into his nostrils to reduce air gaps that can affect the dose distribution of electrons (Fig. 10.3a). A customized lead shielding was fabricated for skin collimation (Fig. 10.3b). Finally, a customized wax bolus of 1 cm thickness was constructed to ensure adequate skin surface dose for the selected electron energy (Fig. 10.3c). The patient was immobilized using a custom thermoplastic mask (Fig. 10.3d).

He was treated to a total dose of 55 Gy in 20 fractions using 9 MeV electron beam (Fig. 10.4). He tolerated treatment very well; he developed acute Grade 3 dermatitis at the end of treatment with resolution of dermatitis at first follow-up. With 2 years of follow-up, there has been no evidence of local disease recurrence.

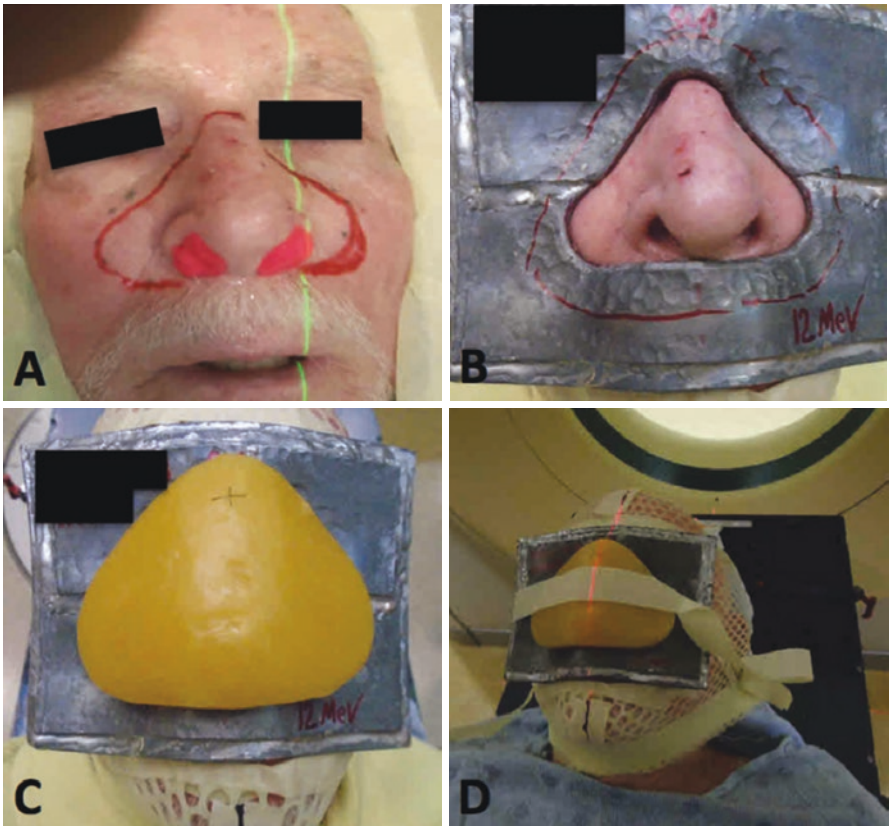


**Fig. 10.3** Representative images of the planning process for the patient treated with electron beam. (**a**) Two cm margin demarcated with tissue-equivalent material inserted into both nostrils, (**b**) Customized lead shielding used as skin collimation and to ensure eye and upper lip shielding, (**c**) Customized 1 cm thick wax bolus, (**d**) Final radiotherapy treatment set up and patient position for treatment

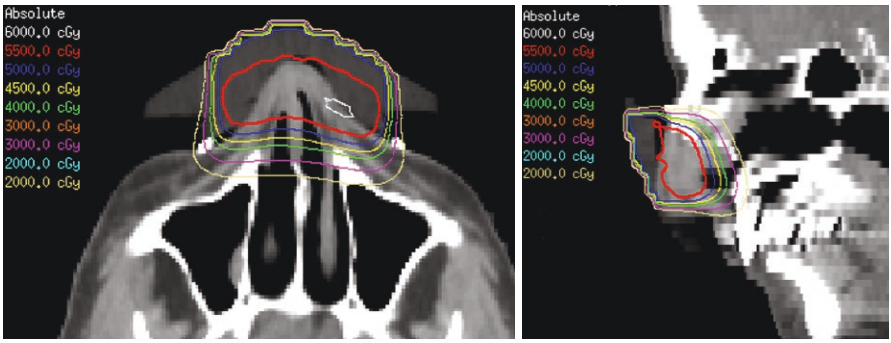


**Fig. 10.4** Representative axial (left) and sagittal (right) images of the treatment plan with corresponding isodose distribution is shown, with full surface dose and relative sparing of underlying nasal cavity and sinuses

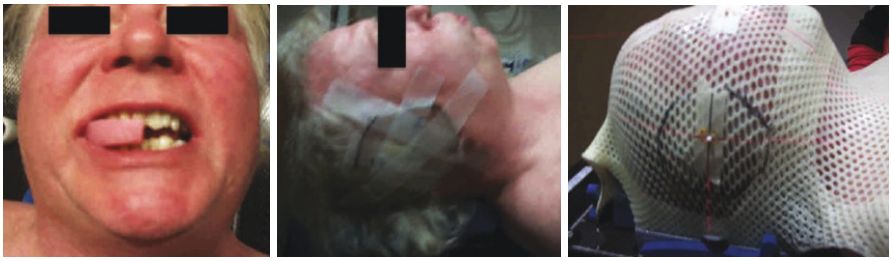

**Fig. 10.5** Images depicting the placement of the tongue-deviating intraoral stent (left panel), demarcation and placement of a surface bolus material over the flap and operative bed area (middle panel), and patient immobilization with custom thermoplastic head, neck, and shoulder mask (right panel)

## *Megavoltage Photon Therapy (VMAT)*

A 55-year-old man presented with a history of multiply recurrent basal cell carcinoma of the right ear, which was previously treated with repeated Mohs surgery and vismodegib. He had a renal transplant 10 years prior and remained on immunosuppressants. He had his fourth Mohs surgery on his right ear performed at an outside facility prior to his presentation to our center. On clinical examination, the right ear had an approximate 2.5 cm defect along the superior helix which encroached onto the antihelix. There was an ulcerated lesion on the posterior part of his ear and biopsy of the lesion confirmed basal cell carcinoma of infiltrative pattern. He underwent completion auriculectomy with myocutaneous free-flap reconstruction. Final pathology revealed basal cell carcinoma excised with clear margins of resection.

Given his history of immunosuppression and multiply recurrent basal cell carcinoma, the multidisciplinary recommendation was for postoperative radiotherapy to improve local regional control.

Two weeks after surgery, he was brought to the radiotherapy simulation suite. A custom-made tongue lateralizing stent was used to deviate the oral tongue away from the intended radiation target region. The flap and surgical scars were marked with a radio-opaque wire to facilitate target volume delineation. A 5 mm thick bolus was placed over the marked target area (with an additional 1 cm lateral margin) to ensure adequate surface dose. He was immobilized with a custom thermoplastic mask (Fig. 10.5). CT-based simulation was performed, and these images were imported to the treatment planning system for VMAT treatment planning.

The tumor bed was treated to a total dose of 60 Gy and the surrounding operative bed to 57 Gy, all in a single integrated plan given in 30 fractions over 6 weeks. Given the irregular geometry of the target and thickness/bulk of the flap, VMAT technique was used to generate the needed conformality of dose around the com-

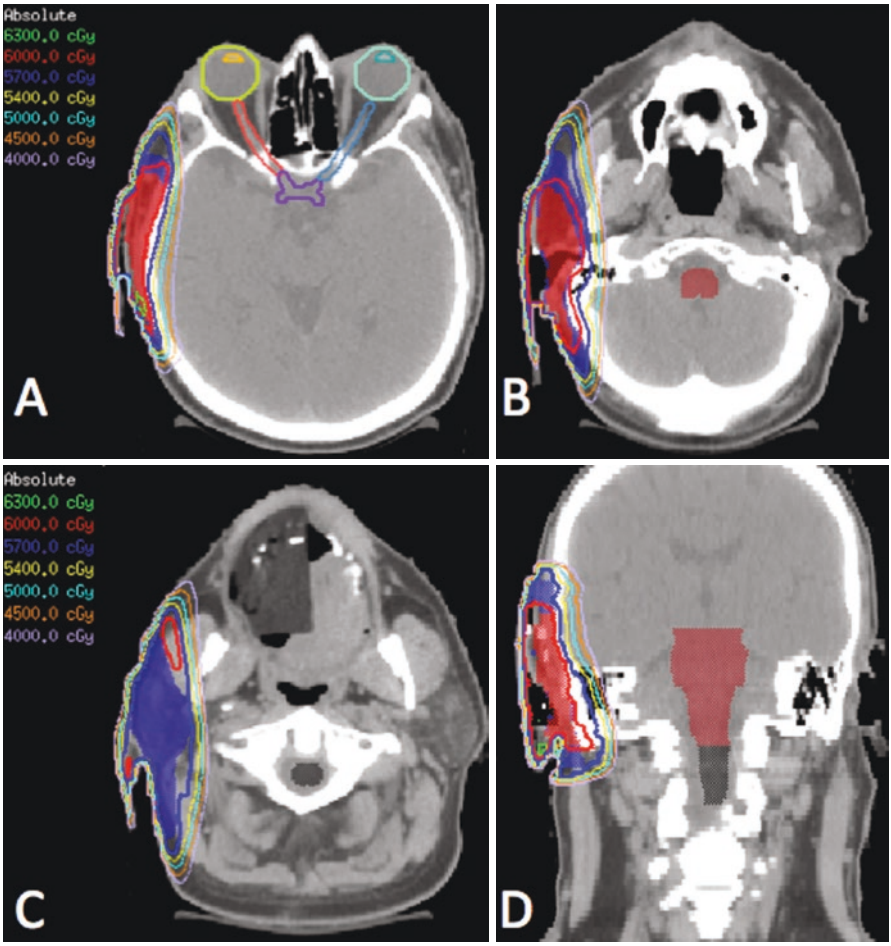


**Fig. 10.6** Representative axial (**a**–**c**) and sagittal (**d**) images of the patient's VMAT (photon) treatment plan

plex target shape at the deeper areas, while still sparing the underlying brain at the more shallow aspects of the target areas (Fig. 10.6).

He tolerated the treatment very well; he developed Grade 3 dermatitis by the end of treatment. He did not develop significant oral tongue or buccal mucosa mucositis. At his 3-year follow-up, he had no clinical evidence of disease recurrence within his right ear operative bed. He has ongoing dermatologic follow-up.

## Conclusion

The primary aim of treatment for localized basal cell carcinoma is local control. This can be achieved via various modalities of treatment including radiotherapy. Overall, treatment with radiotherapy alone can achieve local control rates of 85–97% at 5 years. Selection of therapy is individualized, considering patient age, tumor location, and cosmetic and functional outcomes. In addition to the use of postoperative radiotherapy to improve local control in those with high-risk clinical or pathology features, radiotherapy can be a good definitive treatment option, particularly for the elderly, those with multiple comorbidities, and/or those medically inoperable or with unresectable disease. Tumor location and extent of target volumes determine the optional radiation therapy technique.

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# Chapter 11
# Photodynamic Therapy for the Treatment of Basal Cell Carcinoma

**Natalie Kash and Sirunya Silapunt**

## Introduction

The National Comprehensive Cancer Network (NCCN) 2018 Clinical Practice Guidelines in Oncology for basal cell carcinoma (BCC) identifies risks factors for recurrence of BCCs and classifies tumors as high, medium, or low risk based on tumor characteristics such as location, histologic subtype, size, and prior treatment (see section "Introduction" in Chap. 4) [1]. Based on the NCCN recommendations, superficial therapies such as topical therapies, cryotherapy (CT), and photodynamic therapy (PDT) should be considered in low-risk, superficial BCCs in patients where surgical therapy (ST) and radiotherapy (RT) are contraindicated or impractical [1]. In this chapter, PDT will be discussed as a nonsurgical treatment option for BCC. Additional nonsurgical treatment options including topical therapies, CT, electrodesiccation and curettage (ED&C), laser therapy (LT), RT, intralesional therapy, and systemic therapy such as targeted therapy and immunotherapy will be discussed in other chapters (see Chaps. 4, 6, 12, 10, 5, 13, and 14).

## Background

In PDT, a topical photosensitizing agent is applied to the lesion, and the area is then irradiated with visible light leading to localized tissue destruction. The photosensitizing compound ideally has a higher affinity for tumor cells than normal cells and accumulates within target cells. The photosensitizing agent may be initially taken

N. Kash · S. Silapunt (✉)
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA
e-mail: Sirunya.Silapunt@uth.tmc.edu



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_11

up by all cells but ideally stays longer in rapidly proliferating cells such as tumor cells [2, 3]. This is not well understood but is thought to be related to increased vascular supply to and decreased drainage from tumor cells [4]. In addition, lower pH in the interstitial fluid of tumors contributes to increased lipophilic characteristics and uptake of photosensitizing agents into tumor cells [5, 6]. Additionally, there is a "photobleaching" effect where photosensitizing agents, especially porphyrins, are modified and destroyed with light exposure which inactivates the compound in normal cells but does not affect the degree of tissue destruction in tumor cells given the higher concentration of the compound in these cells [3, 7–9].

Tissue penetration depth is based on the wavelength of light used. For example, light with a wavelength of 630 nm, 700–800 nm, and >850 nm reaches a tissue depth of about 5 mm, achieves depth of up to 10–20 mm, and does not produce enough energy to create an adequate photochemical response, respectively [10–13]. Given that blue light has a wavelength of 450–495 nm and red light has a wavelength of 620–750 nm, there have been efforts to develop regimens of PDT utilizing photosensitizers with absorption spectrum wavelengths and light sources emitting wavelengths of light in the spectrum of red and near-infrared to allow adequate tissue penetration [14].

There are a number of variations utilizing different photosensitizing agents, corresponding wavelengths of light, and options of light sources. Light of a wavelength within the absorption spectrum of the compound is used to activate the compound. The timing of light irradiation after the application of the photosensitizer depends on the time needed to have an adequate concentration of photosensitizing compound within tumor cells which is dependent on both tumor type and the photosensitizer used [15]. The most commonly used and well-studied photosensitizing agents are photofrin (porfimer sodium), methyl aminolevulinate (MAL), and aminolevulinic acid (ALA). The NCCN recommends the use of PDT with porfimer sodium or ALA as a photosensitizing agent, as MAL is no longer available in the United States [1]. The FDA has approved the use of ALA-PDT and MAL-PDT for the treatment of non-hyperkeratotic actinic keratosis (AKs) of the face and scalp, but the use of ALA-PDT and MAL-PDT for BCC is not FDA-approved and considered off-label [16]. Additionally, there are a number of other photosensitizing compounds, which are briefly reviewed, along with porfimer sodium, ALA, and MAL, below.

Porphyrins were the first photosensitizing agents described in the use of PDT. Porphyrins were noted to localize to tumor cells, and a purified compound, hematoporphyrin derivative (HPD), was developed and initially thought to have better tumor-detecting abilities [17–23]. However, HPD was later shown to have higher affinity for normal tissue than tumor cells [22, 24–28]. Subsequently, a new porphyrin, porfimer sodium, was developed and is currently used in clinical PDT [25, 29, 30]. The absorption of porphyrins is highest between 360 and 450 nm but also has four smaller peaks between 500 and 635 nm [4, 14, 31]. However, tissue penetration is maximized in the 630–635 nm range, which is the weakest absorption peak [32, 33].

A popular photosensitizing agent, ALA, is a hydrophilic porphyrin precursor which leads to the endogenous production of protoporphyrin IX (PpIX) after

application [34]. A 20% ALA oil-in-water emulsion is typically used and occluded with a dressing to enhance penetration and prevent photobleaching by visible light [4]. Increased ALA permeability through abnormal keratin of tumors is thought to contribute to tumor selectivity; however, this may also explain poor penetration and efficacy in the treatment of nodular tumors which have intact keratin [34]. Typically, 3–6 hours after ALA application, the area is irradiated with light with a wavelength between 630 and 635 nm to target PpIX [4]. Broad-band illumination is also used as activated products are also formed at wavelengths outside the activation spectrum of PpIX [34]. A number of formulations have been developed to improve the efficacy of ALA including the addition of compounds that affect heme synthesis such as desferrioxamine, dimethyl sulfoxide (DMSO), and ethylenediaminetetraacetic acid (EDTA) [34–38]. The addition of topical calcitriol prior to ALA-PDT has also been shown in mouse models to increase the level of PpIX production and the degree of tumor destruction [39]. Additionally, the depth of skin penetration of ALA is limited by its hydrophilic nature, and different chemical formulations of ALA such as lipophilic ALA ester derivative and a methylated ester form (MAL) (available as a 160 mg/g or 16.8% cream) have been developed to increase tissue penetration depth [40, 41].

There are a number of other photosensitizing agents and combinations of multiple agents which can be used for PDT such as tetra-sodium-meso-tetraphenylporphine-sulfonate activated at 630 nm associated with neurotoxicity, chloroaluminum phthalocyanine tetrasulfonate (ALPcTS) and silicon-based Pc4 activated at 650–700 nm allowing deeper penetration with minimal associated cutaneous photosensitivity, lutetium texaphyrin (Lu-Tex) with maximum absorption at 732 nm, benzoporphyrin derivative-monoacid ring A (BPD-MA) with maximum activation at 690 nm, N-Aspartyl-chlorin e6 (NPe6) with maximum absorption at 664 nm, tin etioporphyrin ($SnET_2$) with maximum absorption at 660 nm, and a number of other agents [9, 32, 42–63].

In regard to the various light sources used in PDT, both coherent light (lasers) and incoherent light (lamps) have been used. Lasers allow light of a particular wavelength to be delivered, while lamps deliver light with a broad range of wavelengths [14]. Lasers allow irradiation of many body sites and the precise delivery of wavelengths corresponding to the absorption spectrum of the photosensitizer [4]. A number of different lasers may be used as light sources. One of the most popular has been the argon-dye laser (ADL) which can be tuned to emit light to match absorption peaks from 350 to 700 nm [18, 64]. One of the limitations of ADLs is the very small cross section of its output beam resulting in the need for a beam expander, which reduces the fluence rate, for the treatment of large lesions [14]. Also useful for PDT are solid-state lasers, such as the neodymium:YAG (Nd:YAG) laser which can emit light with a wavelength of 690–1100 nm which is useful to match the absorption spectrums of newer photosensitizing agents such as BPD-MA, phthalocyanines, and Lu-Tex [65]. Portable diode lasers, such as gallium-aluminum-arsenide lasers, can emit light with a wavelength of 770–850 nm which is also in the absorption spectrum of many new photosensitizing agents [13]. Advantages of diode lasers include their portability and ease of use [14].

Sources of incoherent light, including lamps, have been designed specifically for PDT. These include tungsten filament quartz halogen lamps, short-arc xenon lamps, metal-halide lamps, and phosphor-coated sodium lamps which emit light with wavelengths ranging 350–850 nm, 300–1200 nm, 590–720 nm, and 590–670 nm, respectively [14, 33, 66–69]. These lamps use narrow-band, longpass, and shortpass filters to select the desired wavelength within 10 nm, reduce associated high-power ultraviolet radiation, and reduce associated infrared emission, respectively [14]. Additionally, there are fluorescent lamps which emit light with wavelength mostly in the range of 412–422 nm which are able to target the maximum absorption spectrum of many porphyrin-based photosensitizers (Soret band) of 360–450 nm [14]. However as discussed earlier, the depth of penetration is reduced at this wavelength, and thus, the use of these fluorescent lamps is generally limited to the treatment of very superficial lesions [14]. Advantages of lamps compared to lasers include lower associated cost, less associated upkeep and maintenance requirements, portability, ease of use, and the ability to quickly treat a large area [14]. Limitations of these incoherent light source lamps include lower irradiance at the periphery of lesions compared to the center and thus potentially insufficient treatment of peripheral tumor edges [70]. However, see comparative studies section regarding studies comparing the efficacy of PDT with different light sources.

Newer light sources include light emitting diodes (LED) and femtosecond solid-state lasers for two-photon PDT. The use of LED allows the emission of light with wavelengths ranging from 350 to 1100 nm. Other advantages include that LED is cost-effective and portable and its ability to arrange the LED lights in different geometric arrangements allows treatment of difficult to treat anatomic areas with a large degree of curvature such as the face [14]. Femtosecond solid-state lasers have also been recently studied as a light source in PDT. Two-photon excitation allows the photosensitizer to absorb the sum of the energy from two photons of equal energy. This allows light with a higher wavelength and depth of penetration (such as in the 800–900 nm range) to be used via two photons to excite photosensitizers with a maximum absorption at a wavelength of half of the wavelength of the light delivered (400–450 nm range, such as porphyrin-derived photosensitizers) [14, 71, 72]. Disadvantages of femtosecond lasers include longer treatment time and the requirement of a high degree of maintenance and operational skill [14].

Light sources for PDT generally require light to be emitted at a wavelength between 630 and 800 nm to allow adequate tissue penetration. Light dosing for PDT varies based on tumor characteristics including size, location, and histologic subtype [15, 65].

## Mechanism of Action

Photodynamic therapy leads to a number of biochemical and molecular reactions that cause tissue destruction through direct cell damage, vascular changes, inflammation, and activation of a host immune response [2, 4, 43, 63, 65, 73–75]. The

photosensitizer absorbs a light photon causing it to go from a stable ground state to an unstable excited singlet state [4]. The photosensitizer can either convert to a triplet excited state or emit light as fluorescence and decay back to the ground state [65, 76, 77]. Tumor destruction is optimized with compounds that have a long triplet excited state half-life as the triplet sensitizer causes photo-oxidative reactions in which there is the production of singlet oxygen through the transfer of energy from the sensitizer to ground state oxygen [2, 9, 76]. The production of singlet oxygen is key to cell damage as the singlet oxygen interacts with many different biomolecules efficiently [2, 9, 65, 77]. These changes cause lipid peroxidation and affect protein cross-linking which in turn affects depolarization and the activity of membrane enzymes [13, 43, 63, 78]. Additionally, there is increased membrane permeability, increased photosensitizer uptake, and disruption of amino acid, nucleoside, and sugar transport [15, 79]. Within hours there is bleb formation, cell-cycle dysregulation, and cell lysis [43, 80]. There is also induction of apoptosis and inactivation of mitochondrial enzymes important for cellular respiration [21, 58, 81–84].

Oxygen radicals also lead to increased endothelial cell permeability, platelet activation, and the release of pro-aggregatory agents resulting in arteriolar constriction, venular thrombus formation, and stasis of blood flow [85–87]. These changes affect the vasculature of both tumor and normal tissue and lead to localized tissue destruction [85, 88]. Vascular damage also leads to inflammation which ultimately leads to recruitment of neutrophils and macrophages to the area [89–91]. Neutrophil degranulation then leads to tissue damage and a further immune response [63]. The host then develops tumor-specific immune cells, and host immunity then plays a role in selective tumor destruction [92, 93].

## Efficacy

A prospective study by Christensen et al. evaluated the 10-year efficacy of ALA-PDT for the treatment of BCC [94]. They found treatment of a recurrent rather than primary BCC with PDT to be statistically significantly associated with a higher risk of treatment failure ($p = 0.0047$) [94]. A study by Fantini et al. evaluated factors associated with a higher risk of treatment failure in the use of PDT for the treatment of BCC [95]. They performed a multicenter, prospective non-comparative trial of 194 BCCs treated with MAL-PDT with red light with a median follow-up time of 20 months [95]. They found a complete response to PDT in 62% of all BCCs with a complete response rate (CRR) of 82% (95/116) for superficial BCCs and 33% (26/78) for nodular BCCs [95]. The investigators performed univariate and multivariate analyses of a number of clinical and pathologic factors and found that nodular histologic subtype, infiltrative histologic subtype, location on the limbs, presence of ulceration, and increased tumor thickness were statistically significantly associated with a lower CRR to therapy [95]. Location on the trunk, superficial histologic subtype, absence of ulceration, and thickness $\leq$0.5 mm were associated with a higher CRR to therapy [95]. Tumors located on the trunk were associated

with lower failure rates compared to tumors located on both the head and neck and limbs, and tumors on the limbs were associated with higher failure rates compared to tumors located on both the trunk and head and neck [95]. Age, gender, and tumor diameter were not found to significantly predict the risk of treatment failure [95]. Thus, the authors recommend careful case selection with primary, superficial, non-ulcerated BCCs located on the trunk being the most appropriate for consideration of treatment with PDT.

Studies have noted that PDT may be an appropriate treatment option with an acceptable recurrence rate (RR) and good cosmetic outcome (CO) in cases where there is concern for poor CO, disfigurement, or recurrence with more traditional treatment methods. A European prospective, non-comparative study by Horn et al. treated superficial and nodular BCCs classified as "difficult to treat" either based on location on the mid-face or ears, size >15 mm on the face, size >20 mm on the extremities, size >30 mm on the neck or trunk, treatment failure of two prior treatments in the last 1 year, or location on severely sun-damaged skin with MAL-PDT (1 or 2 cycles, each cycle comprised of 2 treatments 1 week apart) with response assessed both clinically and histologically 3 months after the last treatment [96]. They reported a RR of 18% (12/66) at 24 months, and the CO was graded as excellent or good in 94% at 24 months [96]. Vinciullo et al. performed a multicenter, prospective, non-comparative study evaluating MAL-PDT (red light source, 570–670 nm, 75 J/cm$^2$, 3-hour incubation) in 148 "difficult to treat" superficial or nodular BCCs defined as size ≥15 mm on the extremities above the knees, ≥10 mm on the extremities below the knees, ≥20 mm on the trunk, ≥15 mm on the face, located on the H-zone or ear, or in patients with comorbidities such as with bleeding disorders, on anticoagulants, or with a cardiac history considered high risk for surgical complications [97]. They found estimated sustained lesion CRRs of 90%, 84%, and 78% at 3 months, 12 months, and 24 months, respectively, and excellent or good COs in 79% of patients at 12 months and 84% of patients at 24 months [97]. These two sets of authors, thus, concluded that MAL-PDT might be an appropriate treatment consideration where there is concern for poor CO, disfigurement, or recurrence with more traditional treatment options.

Two small prospective, non-comparative studies reported specifically on the efficacy of PDT for treatment of BCCs located on the eyelid. Kotimaki reported a series of six patients with BCCs on the lower eyelid treated with MAL-PDT (prior tumor debulking with curettage, 2 sessions 1 week apart, 3-hour incubation, 634 nm LED light, 37 J/cm$^2$) and followed the patients for 20–36 months with no observed recurrence and good patient satisfaction [98]. A study of BCCs located on the eyelid margin treated with MAL-PDT (prior tumor debulking with curettage, 2 sessions 1 week apart, 3-hour incubation, 632 nm diode lamp, 37 J/cm$^2$) reported a CRR of 75% at 21 months [99].

A systematic review and meta-analysis of treatment success after treatment of primary biopsy-proven superficial BCCs by Roozeboom et al. in 2012 included randomized and nonrandomized trials from 1946 to October 2010 with

a minimum follow-up period of 12 weeks to look at the probability of complete response at 12 weeks and tumor-free survival at 1 year [100]. The 12-week CRR was 79.0% [95% confidence interval (CI) 71–87%] for PDT and 86.2% [95% CI 82–90%] for imiquimod based on pooled estimates of percentages of superficial BCCs with complete response at 12 weeks posttreatment from 28 studies [100]. They reported a 1-year tumor-free survival rate of 84% [95% CI 78–90%] for PDT and 87.3% [95% CI 84–91%] for imiquimod in the treatment of primary, superficial BCCs from pooled estimates from 23 studies [100]. There was no statistically significant difference in either the 12-week complete response or 1-year tumor-free survival rate between PDT and imiquimod shown by this study [100]. However, the authors noted that there were differences in case selection, treatment regimens, and study design between the studies included. They also noted that there were no randomized controlled studies directly comparing PDT to imiquimod in the literature at that time and called for such studies in the future. There were not enough studies to compare PDT to other superficial BCC treatment modalities including LT, topical 5-FU, topical ingenol mebutate, CT, or surgical excision (SE) [100]. However, since that time a number of comparative trials have been performed comparing PDT to other treatment modalities (see section "Comparative Studies").

There have been limited prospective nonrandomized studies suggesting a possible benefit in treatment efficacy with more than one cycle of PDT. Haller et al. performed a prospective study of 26 BCCs treated with two sessions of ALA-PDT (1 week apart) and reported a RR of 4% (1/26) with a median follow-up of 27 months which was noted to be lower than RRs of previously published studies reporting the RR after single session PDT [101]. The prospective study by Christensen et al., evaluating the 10-year efficacy of ALA-PDT for the treatment of BCC, found the overall 10-year CRR to be 75% but 60% in those treated with one PDT session and 87% in those treated with two PDT sessions [94]. A sensitivity analysis by Roozeboom et al. in their systematic review indicated that PDT efficacy may increase with the number of cycles used [100]. The 12-week CRR increased from 75.6% to 79%, and the 1-year tumor-free survival increased from 76.2% to 84.0% when pooled estimates included data from the use of repetitive PDT treatments from Haller et al. [100, 101]. The authors thus suggested that by fractionating ALA-PDT or providing two cycles of MAL-PDT, the efficacy of PDT may be improved. However, randomized prospective trials are needed to directly compare PDT with multiple cycles to PDT with a single cycle.

Different light sources may be used for PDT including lasers. Souza et al. performed a prospective study of ALA-PDT with a 630 nm diode laser (single session, 6-hour incubation, 20% ALA, occlusive dressing, 100 or 300 J/cm$^2$) for the treatment of 15 BCCs and reported a 5-year tumor-free rate of 63.6% (7/11) [102]. There are limited comparative studies evaluating different light sources in PDT (see section "Comparative Studies").

More recently, there have been reports of a number of treatment modalities in combination with PDT to increase the efficacy of PDT in the treatment of various

cutaneous lesions by increasing the depth of tissue penetration by reducing hyperkeratosis overlying the lesion, including occlusion with a keratolytic agent the night before treatment, tape-stripping, microneedling, microdermabrasion, laser treatment, and curettage [103–108]. Shokrollahi et al. studied the efficacy of UltraPulse® carbon dioxide ($CO_2$) laser treatment in combination with MAL-PDT (1–3 cycles until no evidence of residual tumor) for the treatment of 177 biopsy-proven BCCs with a mean follow-up time of 32.2 months [109]. They reported a RR of 2.82% (5/177) with 4/5 recurrences treated successfully with a repeat laser-PDT treatment and 1/5 requiring treatment with SE [109]. Complications included mild hypopigmentation and discomfort as expected with PDT, and the authors concluded that combined $CO_2$ laser and PDT may be useful as a treatment modality for the treatment of superficial and nodular BCCs with higher tissue penetration and efficacy than PDT in nonsurgical candidates [109]. There have been a limited number of randomized comparative studies comparing combined LT and PDT to PDT alone with varying results, and further and larger randomized comparative studies are needed to compare combined LT and PDT with other treatment modalities such as PDT alone and SE in the treatment of superficial and nodular BCCs (see section "Comparative Studies") [110–112].

Similarly, in recent years methods of intralesional PDT have been described as part of efforts to increase the depth of tissue penetration of the photosensitizing agent in order to increase the efficacy of PDT in the treatment of nodular BCCs. Rodríguez-Prieto et al. described injecting the base of the tumor with a 1% solution of ALA (an estimated dose of 1 mL/cm$^2$) followed by 2-hour postinjection exposure to a 630 nm diode laser with a power of 1 W with a fluence of 240 J/cm$^2$ in a series of 20 cases of nodular BCCs [113]. They more recently reported the over 5-year follow-up data on these patients [114]. They reported a median follow-up of 6 years with recurrence in 1/20, no recurrence in 15/20, and death from a different cause in 4/20. They reported a long-term success rate of 93.75% [95% CI 69.7–99.8%] [114]. A retrospective study of 102 patients with different histologic subtypes of BCC published in 2018 compared 51 patients treated with intralesional PDT with injection of 1% ALA solution and later irradiation with 630 nm laser (intralesional irradiation in 25 and external irradiation in 26) to 51 patients treated with SE and found no statistically significant difference in success rates (assessed histologically) between intralesional PDT and SE [115]. They additionally found no statistically significant difference in success rates between intralesional irradiation versus external irradiation in the intralesional PDT group [115]. However, prospective randomized controlled trials are still needed to compare intralesional PDT to other treatment modalities in the treatment of BCC.

Additionally, PDT has been described in combination with other treatment modalities including SE. Lu et al. performed a prospective study of non-melanoma skin cancers including 32 BCCs treated with SE followed by ALA-PDT (635 nm wavelength laser, 120 J/cm$^2$, 3 sessions) and reported a 6-month RR of 0% [116]. They concluded that ALA-PDT may be a useful addition to SE for the treatment of BCCs to decrease RRs but called for larger studies with longer follow-up and comparative studies [116].

## Safety

Adverse reactions with PDT are generally limited to the treated area and include localized erythema, edema, pain, pruritus, stinging, burning and prickling sensations, photosensitivity, blistering, hypopigmentation, and hyperpigmentation [4, 117]. The most common adverse event with PDT is pain during the procedure [118]. Allergic contact dermatitis has also been rarely reported following PDT. Cordey and Ibbotson reported allergic contact dermatitis with positive patch testing to PDT prodrugs in 10/1532 patients (0.65%) [119]. Pain with PDT can be severe leading to incomplete treatments and avoidance of repeat treatments [120]. Photodynamic therapy with MAL has been shown to be associated with decreased pain levels compared to ALA-PDT, and PDT with coherent light from pulsed dye laser (PDL) has been shown to be associated with less pain and increased willingness to undergo subsequent PDT treatments compared to PDT with non-coherent light (see section "Comparative Studies") [121–123]. A number of interventions to try to decrease pain associated with PDT have been studied. Cooling and pauses during treatment have been shown to be effective in reducing pain [124]. Inhaled nitrous oxide/oxygen administered during PDT treatment decreased PDT-associated pain by 55.2% and therapy interruptions by 82% in a prospective, single-center study by Fink et al. using intraindividual comparison [120]. Morphine 0.3% gel was shown not to lead to a significant reduction in pain when compared to placebo gel [125]. Absolute contraindications to PDT include a known allergy to one of the active ingredients of the photosensitizing agent or a history of a photosensitive dermatosis (such as porphyria or systemic lupus erythematosus).

## Comparative Studies

### *PDT Versus Placebo*

Treatment with MAL-PDT has been shown to be more effective in the treatment of nodular BCCs than treatment with placebo-PDT. An Australian study performed two multicenter, prospective, randomized, double-blind trials comparing treatment with MAL-PDT (3-hour incubation, 570–670 nm red light, 75 J/cm$^2$, repeat session after 7 days) with placebo-PDT in the treatment of primary nodular BCCs with a depth ≤5 mm [126]. They found a higher CRR at 6 months of 73% (55/75) in the MAL-PDT group compared to a CRR of 27% (20/75) in the placebo-PDT group [126].

### *PDT Versus Other Treatment Modalities*

Photodynamic therapy has been demonstrated in multicenter, prospective randomized trials to have higher RRs and better COs compared to SE [127, 128]. A study by Szeimies et al. compared MAL-PDT to SE (with 3 mm margins) in superficial

BCCs that were 8–20 mm in diameter [127]. They performed the MAL-PDT in two sessions which were 1 week apart and repeated treatment if persistent tumor was noted at 3-month follow-up [127]. They applied the MAL to the lesions and 5–10 mm of normal surrounding skin, followed by a 3-hour incubation, and used a large-field LED red light source to deliver 37 J/cm$^2$ [127]. The study demonstrated a statistically significant higher 1-year RR of 9.3% (11/118) in the PDT group compared to a 0% (0/117) RR in the SE group [127]. A randomized prospective trial by Rhodes et al. of nodular BCCs compared MAL-PDT versus SE (with ≥5 mm margins) [128]. This study performed 1–2 cycles of MAL-PDT, and each cycle had two sessions 1 week apart [128]. They used a 3-hour incubation period, non-coherent red light (570–670 nm), and fluence of 75 J/cm$^2$ [128]. They also found a higher RR of 14% (7/49) in the MAL-PDT group compared to a RR of 4% (2/52) in the SE group; however, the difference was not statistically significant [128]. The 5-year sustained lesion CRR was found to be statistically inferior with MAL-PDT vs SE (76% vs 96%, $p = 0.1$) [128]. Both studies found better COs with PDT compared to SE [127, 128]. The Szeimies et al. study found that 94.1% versus 59.8% of patients in the MAL-PDT and SE groups, respectively, had COs assessed by the investigators as excellent or good at 1-year follow-up [127]. Rhodes et al. also found a higher percentage of patients with excellent or good COs in the MAL-PDT group (87%) versus the SE group (54%) [128].

Similarly, ALA-PDT compared to SE has been shown to have higher failure rates in the treatment of nodular BCC [129, 130]. Two studies, by Mosterd et al. and Berroeta et al., evaluated the efficacy of curettage followed by ALA-PDT versus SE for the treatment of nodular BCC [129, 130]. They used curettage prior to treatment with PDT in the PDT group in order to debulk the tumor and increase the depth of tissue penetration with hope that this would increase efficacy; however, both studies still found lower efficacy in the ALA-PDT groups compared to SE [129, 130]. Mosterd et al. performed a randomized trial of ALA-PDT versus SE (with 3 mm margins) for the treatment of primary, nodular BCCs that were <20 mm [129]. They performed curettage to all tumor rising above the level of the skin 3 weeks prior to PDT, applied ALA to the lesion and 5 mm of surrounding normal skin, used a 4-hour incubation period, irradiated the area using an incoherent metal-halogen light source (585–720 nm, 75 J/cm$^2$), and then repeated the illumination after 60 minutes (total light dose of 150 J/cm$^2$) [129]. They found a statistically significantly higher 3-year cumulative failure rate calculated using Kaplan-Meier survival analysis of 30.3% in the ALA-PDT group compared to 2.3% in the SE group [129]. The 5-year follow-up data by the same group was reported by Roozeboom et al. and similarly showed a higher 5-year cumulative probability of recurrence in the fractionated ALA-PDT with prior debulking group of 30.7% [95% CI 21.5–42.6%] compared to 2.3% [95% CI 0.6–8.8%] in the SE group [131]. They did find the 5-year cumulative probability of recurrence-free survival after fractionated ALA-PDT with prior debulking to be dependent on the nodular BCC tumor thickness [131]. Tumors ≤0.7 mm deep had a 5-year cumulative probability of recurrence-free survival of 94.4% versus 65.0% in tumors >0.7 mm ($p = 0.018$) [131]. Berroeta et al. included well-defined, primary nodular BCCs that were ≤20 mm and not located on a high-risk site [130]. They

performed superficial curettage followed by the application of ALA with a 6-hour incubation period [130]. They then illuminated the area with a 630 nm laser with a total dose of 125 J/cm$^2$ [130]. If there was clinical evidence of residual tumor at 3-month follow-up, then they repeated treatment with PDT [130]. The 1-year failure rate was significantly higher in the ALA-PDT group (5/18) compared to the SE group (0/15) [130]. There was significantly higher associated pain during the procedure and immediately post-procedure in the ALA-PDT group compared to the SE group [130]. There was no statistically significant difference in CO between the ALA-PDT and SE groups [130].

A meta-analysis by Zhou et al. of PDT versus SE for the treatment of nodular BCC found no statistically significant difference in the CRR at 3 months, 1, 2, 3, 4, or 5 years but did find an increased cumulative probability of recurrence with PDT compared to SE [132]. A systematic review and meta-analysis by Wang et al. included randomized controlled trials comparing PDT to non-PDT treatment in the treatment of BCC [133]. They found that PDT compared to SE for the treatment of BCC had a lower CRR with a risk ratio of 0.93 [95% CI 0.89–0.98], higher 1-year RR with risk ratio of 12.42 [95% CI 2.34–66.02], higher 5-year RR with risk ratio of 6.79 [95% CI 2.43–18.96], and better COs [133].

These findings support the recommendation of ST as first-line for the treatment of BCCs with nonsurgical treatment modalities such as PDT being reserved for cases of superficial BCC in which surgery is contraindicated or not appropriate. In cases of superficial, low-risk BCC where CO is of high priority, PDT may be an appropriate treatment consideration given demonstration of its superior CO compared to SE. Photodynamic therapy is not recommended in the treatment of nodular BCC given the high RRs reported in the literature, even when it is preceded by curettage.

Notably, PDT has been shown to have comparable RRs with better COs compared to CT in the treatment of superficial BCCs. Randomized prospective trials comparing PDT to CT by Wang et al. and Basset-Seguin et al. demonstrated statistically comparable RRs and better COs with ALA-PDT and MAL-PDT compared to CT, respectively (see Chap. 6 for details) [134, 135]. The meta-analysis by Wang et al. reported that there was no statistically significant difference in the complete clearance rate, 1-year RR, or 5-year RR between PDT and CT, but PDT did have a statistically significantly improved CO compared to both CT and SE [133]. Thus, PDT may be a better treatment option compared to CT in cases where CO is of particular importance in choosing a nonsurgical treatment option for the treatment of a low-risk, superficial BCC [136].

The meta-analysis by Wang et al. noted no statistically significant difference in the complete clearance rate or 1-year RR of PDT compared to topical imiquimod or topical 5-FU; however, this meta-analysis only included data from the 1-year follow-up data of Arits et al. and did not include the 3-year and 5-year follow-up data by the same group reported by Roozeboom et al. and Jansen et al. [133, 137–139]. The report by Jansen et al. on the 5-year results from the multicenter randomized trial comparing MAL-PDT, topical 5% imiquimod cream, and 5% 5-FU cream showed 5% imiquimod cream to be superior to and 5% 5-FU

to be non-inferior to MAL-PDT in the treatment of superficial BCCs based on calculated hazard ratios for treatment failure at 5 years after treatment (see section "Comparative Studies" in Chap. 4) [139]. A subgroup analysis of their 1-year data found imiquimod to be superior to or have a higher probability of treatment success compared to MAL-PDT in most subgroups of superficial BCCs, with the exception of superficial BCCs located on the lower extremities in patients greater than 60 years of age where MAL-PDT was found to have higher treatment success rates than imiquimod cream (see section "Comparative Studies" in Chap. 4) [140].

### *Comparison of Different PDT Treatment Regimens*

Treatment with multiple fractions of ALA-PDT has been shown to be superior to single fraction ALA-PDT. A randomized controlled trial by de Haas et al. compared double illumination ALA-PDT (2 fractions 4 and 6 hours after application, first fraction with 20 J/cm$^2$, second fraction with 80 J/cm$^2$) to single illumination ALA-PDT (1 fraction, 4 hours after application, 75 J/cm$^2$) for the treatment of superficial BCCs [141]. They found a statistically significant difference between the two groups with a higher 12-month CRR in the twofold illumination group (97%) compared to the single illumination group (89%) with $p = 0.002$ [141]. In a follow-up study by the same group, the 5-year CRR was reported to be 88% in the twofold illumination group and 75% in the single illumination group ($p = 0.0002$) [142]. Prospective randomized trials comparing single PDT cycles to multiple PDT cycles are still needed.

Treatments with MAL-PDT and ALA-PDT have been shown to be comparable in terms of efficacy. A prospective study by Kuijpers et al. looked at PDT using MAL versus ALA, measured patient pain scores, and histologically evaluated for evidence of residual tumor at 8-week posttreatment [143]. They found no statistically significant difference in the short-term rate of residual tumor or pain scores between PDT with MAL versus ALA [143].

However, Kasche et al. reported lower levels of pain associated with MAL-PDT compared to ALA-PDT with a lower percentage of patients requiring discontinuation of treatment due to pain in the MAL group (14%) versus the ALA group (54%) in patients treated for scalp AKs [121]. A double-blind randomized intraindividual study compared pain experienced with ALA-PDT (applied to normal skin on one forearm) with pain with MAL-PDT (applied to normal skin on the other forearm) in 20 healthy patients and found that ALA-PDT was associated with statistically significant increased pain compared to MAL-PDT during treatment ($p = 0.001$) and immediately after treatment ($p = 0.1$) with no statistically significant difference in pain after 24 hours [122].

Photodynamic therapy with MAL versus ALA has also been compared in patients being treated with PDT for BCCs. A study by Kessels et al. compared fractionated ALA-PDT (2 fractions 4 and 6 hours after application, first fraction with 20 J/cm$^2$, second fraction with 80 J/cm$^2$, 630 nm LED light source) to MAL-PDT (3-hour

incubation, 37 J/cm$^2$, 630 nm LED light source, repeated 1 week later) for the treatment of biopsy-proven superficial BCCs (not located on the H-zone of the face, hair-bearing scalp, or a location with a high degree of concavity or convexity such as the ear or fingers) [144]. They found a higher cumulative probability of treatment success at 12 months in the ALA-PDT group compared to the MAL-PDT group; however, this difference was not statistically significant [144]. They did find that the ALA-PDT group had significantly higher mean pain scores (3.36 ± 2.57 in the ALA group versus 2.48 ± 2.57 in the MAL group with $p = 0.039$) and higher incidence of other adverse events including erythema and wound, erosion, and vesicle formation compared to the MAL-PDT group [144].

A recent European multicenter randomized controlled study by Morton et al. compared PDT with BF-200 nanoemulsion ALA gel (138 patients) to PDT with MAL cream (143 patients) for the treatment of biopsy-proven nonaggressive BCCs with thickness ≤2 mm located on the face, scalp, neck, trunk, or extremities [145]. Both groups received one cycle of PDT with two sessions, 1 week apart, and were illuminated with red light (635 nm, 37 J/cm$^2$) [145]. If there was evidence of residual tumor at 12 weeks, then a second PDT cycle was performed [145]. This study reported no statistically significant difference in the 12-week CRR in the ALA group (93.4%) compared to the MAL group (91.8%) [145]. Additionally, there was no statistically significant difference in the 12-month RRs between the ALA group (8.4%) and the MAL group (8.5%) [145]. However, the 12-month RR for nodular BCCs was 6.7% in the ALA group compared to 14.3% in the MAL group, although the difference was not statistically significant in this study [145]. There was no difference in adverse events between the two groups [145]. The authors concluded that nanoemulsion ALA-PDT was non-inferior to MAL-PDT in the treatment of nonaggressive BCCs [145].

There is variability in results from studies comparing different light sources in PDT or differences in irradiation intensity or dosing in PDT, and many of these studies are evaluating PDT for the treatment of AKs. Studies comparing pain levels with different light sources in PDT for AKs have shown variable results. Two studies on PDT for the treatment of AKs by Babilas et al. and Hamby et al. found no statistically significant difference in pain levels when comparing a filtered halogen red lamp (120 mW/cm$^2$, 100 J/cm$^2$) versus a LED light source (120 mW/cm$^2$, 40 J/cm$^2$) and a filtered halogen red lamp (570–730 nm, 50 J/cm$^2$) versus LED red light (630 nm, 37 J/cm$^2$), respectively [146, 147]. However, studies by Giehl et al. and von Felbert et al. did show significantly lower mean pain scores with a visible light source with water-filtered infrared compared to an incoherent lamp and to a LED light source, respectively [148, 149]. A study by Clark et al. of 483 skin lesions including Bowen's disease (129), AKs (23), and superficial BCCs (87) compared ALA-PDT with four different light sources, including xenon, metal-halide, halogen, and laser, and found the percentages of treatments with severe pain requiring topical anesthesia were 2%, 16%, 16%, and 21%, respectively [150].

A few small randomized controlled trials have compared PDT with different light sources in the treatment of BCC. A small prospective intraindividual pilot study of 6 superficial BCCs compared MAL-PDT with a coherent light source (595 nm) PDL

to MAL-PDT with the more commonly used incoherent light source (630 nm red light LED) [151]. They included superficial BCCs >3 cm and applied MAL to the entire lesions [151]. They then irradiated half the lesion with PDL (3-hour incubation, 595 nm, 7 mm spot size, 6 ms pulse duration, 3 passes, 2 sessions 1 week apart) and the other half with red light LED (3-hour incubation, 630 nm, 37 J/cm$^2$, 2 sessions 1 week apart) and followed patients for 6 months [151]. They reported that 5/6 patients achieved an incomplete response in the half treated with MAL-PDL-PDT while achieving a complete response in the half treated with MAL-PDT, indicating that MAL-PDT with red light LED as a light source is superior to MAL-PDT with 595 nm PDL as a light source [151]. However, the sample size of 6 in this study was a great limitation. A randomized controlled intraindividual prospective study by Carija et al. compared ALA-PDL-PDT (585 nm, 7 mm spot size, 10 J/cm$^2$, 10 ms pulse duration, 3 passes) to ALA-PDT (630 nm LED light source, 30 mW/cm$^2$, 150 J/cm$^2$ total dose) in the treatment of 62 superficial and nodular BCCs and assessed the CRR at 12 months, pain immediately after treatment, and CO at 12 months [152]. They found a lower CRR in the ALA-PDL-PDT group compared to the ALA-PDT group; however there was no statistically significant difference in the 12-month CRR with a 59% CRR in the ALA-PDL-PDT group [95% CI 41–75%] and a 75% CRR in the ALA-PDT group [95% CI 55–89%] [152]. There was no statistically significant difference in the COs at 12 months, and there was a slightly higher mean pain score in the ALA-PDL-PDT group of 2.6 compared to 1.7 in the ALA-PDT group ($p = 0.049$) [152]. They noted that their study may have been limited by small sample size [152].

Newer studies have described the combination of PDT with other treatment modalities (see section "Efficacy"); however, few prospective randomized controlled trials have been performed to compare these combination treatments to a single treatment. One of these few randomized controlled studies performed is a study by Osiecka et al. of 34 patients with biopsy-proven recurrent, facial BCCs who were randomized either to ALA-PDT in combination with topical imiquimod cream (applied 72 hours after irradiation, two times per week before bedtime for 5 weeks) or ALA-PDT plus placebo cream and followed for 14 months [153]. The authors found a higher CRR of 75% (18/24) in the ALA-PDT plus imiquimod group compared to a CRR of 60% (6/10) in the ALA-PDT plus placebo group (see section "Combination Therapies" in Chap. 4) [153].

Additionally, PDT combined with laser ablation has been compared to PDT alone. Smucler and Vlk performed a study comparing MAL-PDT alone, erbium-doped yttrium aluminum garnet (Er:YAG) laser ablation alone, and combined Er:YAG laser ablation for tumor size reduction to <2 mm followed by MAL-PDT for the treatment of recurrent nodular BCCs in patients with three or more BCCs with each of the three treatment options performed in all patients [111]. They followed patients for 12 months with evaluations at 3, 6, and 12 months following treatment [111]. The authors treated 286 patients with 194 presenting for follow-up [111]. The authors reported a statistically significantly higher CRR of 98.97% for combination Er:YAG laser ablation and MAL-PDT compared to both MAL-PDT alone (94.85%) and Er:YAG laser treatment alone (91.75%) [111]. They also reported better COs

with combined treatment compared to both MAL-PDT alone and Er:YAG laser ablation alone [111]. The authors concluded that combined Er:YAG laser ablation and MAL-PDT may be a more effective treatment than either treatment modality alone [111].

Similarly, a randomized trial in Korea by Choi et al. compared Er:YAG ablative fractional laser-primed MAL-PDT (single session) to MAL-PDT alone (2 sessions, 7 days apart) for the treatment of 42 primary biopsy-proven nodular BCCs [112]. The patients were assessed at 1 week, 3 months, and 12 months following treatment [112]. The authors found a statistically significantly higher 3-month CRR in the Er:YAG plus MAL-PDT treatment group of 84.2% compared to 50% in the MAL-PDT alone group ($p = 0.026$) [112]. The 1-year RR was statistically significantly lower in the Er:YAG plus MAL-PDT group (6.3%) compared to 55.6% in the MAL-PDT alone group ($p = 0.006$) [112]. The authors found no statistically significant difference in CO or safety between the two groups [112]. These two studies showed that combined Er:YAG and MAL-PDT has higher efficacy than MAL-PDT alone; however, larger multicenter studies with longer follow-up are needed as well as comparative studies comparing combined Er:YAG laser ablation and MAL-PDT with other treatment modalities including ST and superficial therapies such as topical imiquimod for the treatment of different histologic subtypes of BCC [111, 112].

Later, a report by Lippert et al. compared laser ablation followed by fractional laser treatment and MAL-PDT (treatment group) to laser ablation followed by MAL-PDT alone without fractional laser treatment (control group) for the treatment of nodular BCCs [154]. They included 56 patients with 56 biopsy-proven nodular BCCs with a diameter of 20–30 mm (excluding tumors located on the central face, periocular area, and ears) who had contraindications to ST such as difficult to treat tumors including those previously treated with multiple STs [154]. Ultrasound-guided laser ablation (gallium arsenide diode laser; 980 nm, 3–9 W) at least to the level of the tumor was performed in both halves of all tumors [154]. Seven days later, each of the 56 tumors was divided in half [154]. Half of each tumor received treatment with ablative fractional $CO_2$ laser (10,600 nm, 15% density, 15 W) followed by PDT (treatment group) and the other half with PDT alone (control group) [154]. Both halves of the tumor were then treated with MAL-PDT (3-hour incubation, occlusive dressing, 570–670 nm red light illumination with peak wavelength at 632 ± 3 nm, 37 J/cm$^2$, 70 mW/cm$^2$) [154]. After 14 days the same procedure was repeated with fractional $CO_2$ laser followed by MAL-PDT in the treatment group and MAL-PDT alone in the control group [154]. After treatment completion, 5 mm punch biopsies were taken from both sides to histologically evaluate for residual tumor [154]. The treated areas were evaluated clinically and dermoscopically at 6-month, 12-month, and 18-month posttreatment follow-up [154]. A biopsy was taken if there was any clinical suspicion for residual tumor or recurrence [154]. The authors compared PpIX fluorescence between halves of the tumors in the treatment group to halves in the control group and found higher fluorescence in the treatment group half compared to the control group half in 94.6% of cases (53/56) and indeterminate results in the remaining 5.4% (2/56) [154]. The 18-month CRRs were 92.9% (52/56) in the treatment group and 80.4% (42/56) in the control group [154].

There were no major adverse effects in either group [154]. Some patients reported increased burning and pain in the half of the lesion in the treatment group compared to the half in the control group [154]. The authors concluded that pretreatment with fractional laser increased the efficacy of ablative laser followed by MAL-PDT but noted that efficacy was still lower than efficacy reported for ST [154]. The authors suggested that laser ablation followed by pretreatment fractional laser and MAL-PDT may be an appropriate treatment option for nodular BCCs in patients were ST is contraindicated but called for larger multicenter studies and studies in different histologic subtypes of BCCs [154].

Further, Haak et al. performed a randomized clinical trial comparing ablative fractional $CO_2$ laser (5% density, 80 mJ, 1000 μm ablation depth) followed by PDT ($n$ = 16) to PDT alone ($n$ = 16) for the treatment of 32 facial nodular BCCs determined to be high-risk by the presence of either diameter >15 mm, location in a high-risk zone, or location on skin with severe sun damage [110]. In both treatment groups, MAL-PDT was performed with a 3-hour incubation time under occlusion with illumination with a LED source (633 nm, 37 J/cm$^2$) [110]. The sites were clinically examined for evidence of recurrence at 3, 6, 9, and 12 months following treatment, and biopsy was taken at 12-month posttreatment follow-up to allow for histologic determination of tumor clearance [110]. The authors found a higher short-term (3-month) clinical cure rate (CR) in the PDT plus laser group of 100% (16/16) compared to a 3-month clinical CR of 88% (14/16) in the PDT alone group; however the difference was not statistically significant ($p$ = 0.484) [110]. At 6-, 9-, and 12-month follow-up, the clinical RRs were lower and later in the PDT plus laser group (6%, 19%, and 19%, respectively) compared to the PDT alone group (25%, 38%, and 44%, respectively); however, again this difference was not statistically significant ($p$ = 0.114) [110]. There was no statistically significant difference in the 12-month histologic tumor clearance rates between the PDT plus laser group (63%) compared to the PDT alone group (56%) [110]. The authors did not demonstrate a statistically significant difference in efficacy between PDT with ablative fractional $CO_2$ laser compared to PDT alone for the treatment of high-risk facial nodular BCCs, and thus did not recommend PDT plus laser over PDT alone for treatment of nodular BCCs at this time [110]. They called for further studies to determine optimal treatment parameters of PDT with $CO_2$ LT for nodular BCCs and larger comparative studies to further investigate the efficacy of this treatment modality compared to other treatment modalities including PDT alone for the treatment of BCCs [110].

## Discussion

A number of new modalities including both new photosensitizers, intralesional delivery of photosensitizers, new light sources, and the use of ablative laser prior to PDT have been described in the literature and may potentially increase PDT efficacy (see sections "Background" and "Efficacy") but many have yet to be studied

in terms of their efficacy for PDT in the treatment of BCC or lack prospective randomized trials comparing these combined methods to a single treatment modality. For example, the use of femtosecond laser ablation prior to ALA-PDT was shown to increase the depth of PDT effects in healthy rat skin, but the method has not been studied in humans for the treatment of BCCs [155]. Thus a number of new technologies and techniques may emerge in the treatment of BCC with PDT in coming years, as their efficacy and safety in the treatment of BCC are studied. Laser ablation in combination with PDT has been shown to have good efficacy in the treatment of superficial and in some reports nodular BCCs (see sections "Efficacy" and "Comparative Studies"). Laser ablation prior to the performance of PDT, intralesional delivery of photosensitizers, the use of photosensitizers with higher wavelength absorption spectrums, and light sources with higher wavelengths such as lasers with two-photon excitation may be promising in the future to increase the efficacy of PDT by increasing the depth of tissue penetration.

## Conclusions

Photodynamic therapy has been shown to have acceptable CRs in the treatment of superficial BCCs; however, the CRs have been shown to be lower than SE. Thus, ST is still recommended as first-line in the treatment of low-risk BCCs. However, in cases of superficial BCC where surgery is contraindicated or not appropriate to the patient situation (such as concern for CO, ability to tolerate higher RR, and patients with multiple small low-risk superficial BCCs), PDT is an appropriate treatment modality. Of note, PDT is not recommended for nodular BCCs given lower CCRs shown in this group. Photodynamic therapy has been shown to have superior COs compared to SE and CT, and thus, in cases where CO is of high importance, PDT may be a more appropriate choice than CT as a nonsurgical treatment modality for superficial BCCs. The NCCN recommends that superficial treatments such as PDT be reserved for the treatment of low-risk, superficial BCCs where ST and RT are contraindicated or impractical [1].

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# Chapter 12
# Laser Therapy for the Treatment of Basal Cell Carcinoma


**Natalie Kash and Sirunya Silapunt**

## Introduction

The National Comprehensive Cancer Network (NCCN) 2018 Clinical Practice Guidelines in Oncology for basal cell carcinoma (BCC) classifies tumors as high, medium, and low risk based on tumor characteristics and risk factors (see Introduction section of Chap. 4) [1]. Based on the NCCN recommendations, superficial therapies such as topical therapies, cryotherapy (CT), and photodynamic therapy (PDT) should be considered in low-risk, superficial BCCs in patients where surgical therapy (ST) and radiotherapy (RT) are contraindicated or impractical [1]. The NCCN 2018 Clinical Practice Guidelines in Oncology for BCC does not mention laser therapy (LT) in their treatment recommendations [1]. In this chapter, LT will be discussed as a nonsurgical treatment option for BCC.

## Background

Laser therapy, as a primary treatment modality rather than as a light source in PDT, is a relatively new treatment modality for the treatment of BCCs that has not been as well studied as other therapeutic options. The NCCN does not currently list LT as one of the superficial therapies, such as CT, PDT, topical imiquimod cream, and topical 5-fluorouracil (5-FU) cream, that are appropriate in cases of low-risk, superficial BCCs where ST or RT are contraindicated or otherwise inappropriate [1].

N. Kash · S. Silapunt (✉)
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA
e-mail: Sirunya.Silapunt@uth.tmc.edu



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_12

Continuous carbon dioxide ($CO_2$) lasers were first developed and emit light in the infrared spectrum with a wavelength of 10,600 nm [2]. More recently, high-energy pulsed $CO_2$ lasers have been developed, are used commonly for aesthetic skin resurfacing, and have been studied in the treatment of superficial skin cancers such as superficial BCCs [3].

Pulsed dye laser (PDL) initially emitted light with a wavelength of 577 nm, but later PDLs with a wavelength of 585 nm and 595 nm were developed to allow greater depth of vascular damage to 1.2 mm [4]. Pulsed dye laser was first FDA-approved for the treatment of cutaneous vascular disorders and was later FDA-approved for various benign nonvascular skin conditions [4]. More recently PDL has been described in the treatment of premalignant and malignant skin disorders such as actinic keratosis (AK), actinic cheilitis, squamous cell carcinoma (SCC) in situ, and superficial BCC, but these indications are off-label and require further study [4].

Overall, there have been limited studies investigating the efficacy of different types of LT in the treatment of BCCs (see Efficacy and Comparative Studies section), but further studies comparing LT to other treatment modalities are still needed to further characterize the appropriate use of LT in the treatment of BCC.

## Mechanism of Action

Anderson and Parrish described the theory of selective photothermolysis in which the wavelength of light emitted by a laser targets a specific chromophore such as melanin, water, or oxygenated hemoglobin [5]. The chromophore absorbs more energy from the laser than other tissue components which is converted to heat in the target [5]. As long as the pulse duration is shorter than the target's thermal relaxation time, the heat remains localized to the target chromophore without spread of heat and resultant damage to surrounding tissue, and this selective heat-induced destruction is termed selective photothermolysis [5].

Solid-state lasers use a laser medium in a solid state, and examples include neodymium-doped yttrium aluminum garnet (Nd:YAG), erbium-doped yttrium aluminum garnet (Er:YAG), and alexandrite lasers [6, 7]. Other types of laser media include semiconductor diodes, organic dyes, and gases [6]. The range of wavelengths of light emitted is generally narrower with solid-state and diode lasers and wider with dye lasers. Dye lasers, such as PDL, emit light with a shorter wavelength (500–700 nm), while gas lasers, such as $CO_2$ laser, emit light with a longer wavelength (>10,000 nm) [6].

Ablative lasers include the 10,600 nm $CO_2$ laser and 2940 nm Er:YAG laser, emit light in the infrared spectrum, and cause direct thermal injury, tumor and tissue water vaporization, and tumor destruction [8, 9]. When adequate fluence is achieved, there is water vaporization and ablation [8, 9]. However, when adequate fluence is not achieved, there is coagulation rather than vaporization leading to hemostasis and collagen synthesis [8, 9]. Both continuous and pulsed $CO_2$ lasers have been shown

to lead to tumor ablation. When used for skin resurfacing, pulsed $CO_2$ laser has been shown to have ablation depths of 20–30 μm with one pass, the papillary dermis with two passes, and deeper in the papillary dermis with three passes [10]. When used for the treatment of superficial BCCs, histologic exam has revealed epidermal ablation, collagen fiber coagulation necrosis ranging from 0.10 to 0.28 mm in depth, and rete ridge pattern disruption after three passes following pulsed $CO_2$ laser [3]. The Er:YAG laser has a more shallow depth of tissue ablation with a single pass and higher water affinity and thus potentially more vaporization, less coagulation, and less associated hemostasis and collagen stimulation compared to $CO_2$ laser [8, 11].

Pulsed dye lasers emit light with a wavelength of 585 nm or 595 nm which is in the yellow light spectrum and targets and is absorbed by the chromophore oxyhemoglobin (which has absorption peaks at 418 nm, 542 nm, and 577 nm) leading to selective photothermolysis and selective destruction of vascular tissue [12]. Given its selectivity for hemoglobin and thus vasculature, PDL has been used for a number of vascular conditions but has only more recently been used in the treatment of skin cancers such as in BCCs [4]. In BCCs, PDL is thought in part to target the increased vasculature of tumors [4, 13]. Basal cell carcinomas have been shown to have increased angiogenesis and dilated blood vessels, and PDL is thought to target and destroy the increased microvasculature of these tumors [13–15]. However, some authors point out that PDL at the same settings for the treatment of other dermatologic conditions does not lead to destruction of any nonvascular tissue suggesting there are other mechanisms, such as triggering an immune response, that may play a role [16]. This has yet to be studied specifically in PDL for the treatment of BCC, but PDL has been shown to trigger an immune response and activate complement in normal skin and hemangiomas [16–18]. Additionally, normal skin treated with PDL was shown to have increased extravascular neutrophils, monocytes, and mast cells in the dermis 3 hours and 1 week posttreatment and increased lymphocytes and fibroblasts 4 weeks posttreatment [18].

Pulsed dye laser with a wavelength of 595 nm has been shown to have a greater depth of coagulation than PDL with a wavelength of 585 nm in studies of vascular lesions and normal skin, and this is supported by prospective studies in BCCs with higher efficacy reported in studies using PDL with a wavelength of 595 nm compared to those using PDL with wavelength of 585 nm (although there are other differences in treatment parameters; see Efficacy section) [19, 20]. Overall the effects of PDL are limited to the upper dermis, and lasers also thought to target tumor vasculature with longer wavelengths, such as the 755 nm alexandrite laser and 1064 nm Nd:YAG laser, are able to penetrate and treat tumors deeper in the dermis [21, 22].

## Efficacy

The first report in the literature to describe LT for the treatment of BCCs was a case report by Goldman and Wilson [23]. They reported a case of a nodular BCC on the forearm which appeared to respond to treatment with a pulsed ruby laser (100 J/cm$^2$,

0.900 $cm^2$ target area, four overlapping passes); however, this was an early single report, and the authors called for further investigation into LT for the treatment of BCCs [23].

## $CO_2$ Laser

An early study by Adams and Price reported on continuous $CO_2$ laser for the treatment of 24 BCCs with 12-month follow-up [24]. They reported a 12-month recurrence rate (RR) of 50% with good or better cosmetic outcome (CO) in 90.9% (10/11) of lesions evaluated with mild hypopigmentation, erythema, and depression reported in a number of patients [24]. They noted that the RR following treatment with continuous $CO_2$ laser may have been lower with more aggressive laser settings than those used in their study [24].

Later, a study by Wheeland et al. reported $CO_2$ laser ablation (4–5 W, 160–510 $W/cm^2$, 1–2 mm spot size) in combination with curettage for the treatment of 370 superficial BCCs in 52 patients [25]. They reported that following $CO_2$ laser treatment, tumors appeared whitish-yellow and friable compared to normal tissue allowing improved tumor visualization for curettage [25]. The authors repeated cycles of $CO_2$ laser treatment followed by curettage until no residual tumor was visualized (1–3 cycles) [25]. Patients were followed for 6–65 months with a mean follow-up time of 19.93 months, and they reported no cases of tumor recurrence and hypertrophic scar formation in 5% of patients [25]. The authors reported overall that the advantages of this treatment method compared to other treatment modalities in their experience included creation of a bloodless field and resultant improved tumor visualization, decreased non-specific tissue damage, improved wound healing, and decreased associated pain [25].

A prospective study by Horlock et al. of 51 BCCs with diameter 4–35 mm (excluding periorbital, large infiltrative, large morphoeic, or difficult recurrent tumors) performed excision following $CO_2$ laser ablation (10 W in combination with a microprocessor-controlled optomechanical flash scanner) in order to allow histologic determination of tumor clearance rates (CRs) [26]. A punch biopsy was taken from the tumor, and the tumors were then ablated using a combination of curettage and $CO_2$ laser [26]. Initially the tumors were ablated based on the technique described by Wheeland et al. with tumor ablation performed until no residual tumor was visualized; however, the authors noted that blood from the punch biopsy interfered with complete tumor visualization and reported high failure rates with this method [25, 26]. The authors then modified their technique and performed an additional two passes after no tumor was visualized with ablation to the level of the deep dermis or subcutis in most cases with this method [26]. The authors reported an overall complete tumor CR of 67% (34/51) [26]. However, there was a difference in the CRs with early techniques used (20%) and the later techniques used with greater depth of ablation (80%) [26]. There was a statistically significant correlation ($p = 0.006$) between laser ablation depth and deep margin clearance with

deep margin CRs of 40%, 60%, 93%, and 92% with tumor ablation to the level of the upper dermis, middle dermis, lower dermis, and subcutaneous tissue, respectively [26]. Additionally, they found a statistically significantly higher tumor CR in superficial BCCs of 85.7% (18/21) compared to 50% (14/28) in nodular BCCs [26]. They found a CR of 100% (17/17) in superficial BCCs treated with laser ablation to the level of the middle dermis or deeper [26]. They found a CR of 50% for nodular BCCs, but when stratified by size and depth of ablation, they found a tumor CR of 100% (8/8) for nodular tumors with a diameter of <10 mm with laser ablation to the level of the lower dermis or subcutaneous tissue [26]. The authors concluded that $CO_2$ laser ablation with depth of ablation to at least the mid dermis or lower dermis may be an efficacious treatment option for the treatment of superficial BCCs and small nodular BCCs with diameter < 10 mm, respectively [26].

More recently, pulsed $CO_2$ laser has been studied for the treatment of superficial BCCs. A small prospective study by Humphreys et al. investigated pulsed $CO_2$ laser for the treatment of superficial BCC and SCC in situ. They included 17 biopsy-proven superficial BCCs in patients amenable to surgical excision (SE), excluding tumors <0.5 cm in diameter or large tumors where SE would be disfiguring, treated with either two or three passes of pulsed $CO_2$ laser (500 mJ, 2–4 W, 3 mm margins) [27]. The depth of superficial BCC on initial biopsy varied from 0.16–0.64 mm [27]. Deep and lateral margins were evaluated with closer histologic exam (5 μm intervals) following excision of the site compared to histologic evaluation in other studies of different treatment modalities which the authors concluded may have increased the sensitivity of persistent tumor detection and decreased CRs reported in this study compared to other studies with larger intervals between histologic sectioning [27]. They found a statistically significantly higher complete BCC ablation rate of 100% (9/9) in patients treated with three passes of $CO_2$ laser compared to a complete BCC ablation rate of 62.5% (5/8) in patients treated with only two passes ($p = 0.005$) [27]. In all patients in the study, $CO_2$ laser treatment was well-tolerated without complications [27]. The authors concluded that treatment with three passes of pulsed $CO_2$ laser may be an effective treatment method for the treatment of superficial BCCs but that further studies including larger prospective studies and comparative studies were needed to compare the efficacy and COs of pulsed $CO_2$ laser to other treatment modalities [27].

Later, a case series by Nouri et al. reported three cases of patients with basal cell nevus syndrome with multiple BCCs each treated with ultrapulse $CO_2$ laser (500 mJ, 5 W, 3 mm spot size, 3–4 passes) [28]. At 1–6 months posttreatment follow-up, treatment sites were randomly selected to undergo Mohs micrographic surgery (MMS) in order to allow histologic evaluation of tumor clearance [28]. In all sites treated with MMS at posttreatment follow-up, complete histologic clearance following treatment with $CO_2$ laser was demonstrated with no residual tumor identified [28]. The authors reported no serious adverse effects and minimal associated scarring [28]. They concluded that ultrapulse $CO_2$ laser may be an effective option for the treatment of low-risk BCCs but called for larger prospective studies and comparative studies in order to better characterize the safety and efficacy and compare this treatment to other treatment modalities for the treatment of BCC, respectively [28].

A retrospective chart review by Iyer et al. included 23 patients with 61 primary biopsy-proven superficial and nodular BCCs (diameter 0.5–4.0 cm) treated with pulsed $CO_2$ laser (either 9 mm spot size with 300 mJ pulse energy or 3 mm spot size with 500 mJ pulse energy depending on tumor characteristics for the first pass, 3 mm spot size for subsequent passes, 2–8 passes until no residual tumor visualized, 4–6 mm margins) and followed for 15–85 months [29]. The authors reported a clinical RR of 3.2% (2/61) with hypertrophic scarring in 1.6% (1/61) and hypopigmentation in 1.6% (1/61) [29]. They concluded that pulsed $CO_2$ laser may be a safe and effective treatment option for primary superficial and nodular BCCs [29].

A prospective study by Kavoussi et al. included 74 patients with 113 biopsy-proven BCCs with a diameter ≤3 cm (67 nodular, 35 pigmented, 7 superficial, 4 morphoeic, excluding tumors extending deeper than the mid dermis) treated with tumor debulking with curettage followed by $CO_2$ laser treatment (8–12 W, 2–4 passes, 2–5 mm margins, 600–800 ms pulse duration, parameters adjusted based on tumor characteristics) with 15–40-month follow-up [30]. After one treatment session, the authors reported a 93.7% (106/113) cure rate with a RR of 6.2% (7/113) [30]. However, the authors reported a 100% complete cure rate after a second treatment session was performed in 100% (7/7) of initially recurrent tumors [30]. They reported good to excellent, moderate to good, and poor COs in 85.8% (97/113), 12.4% (14/113), and 1.6% (2/113) of treated lesions, respectively [30]. They noted higher RRs of BCCs located in the nasal area (57.1%) and in tumors >2 cm (40%) [30]. The authors concluded that tumor debulking with curettage followed by treatment with $CO_2$ laser may be a safe and effective treatment option for low-risk BCCs but recommended larger studies with longer follow-up to further investigate [30].

Reflectance confocal microscopy (RCM) and intraoperative pathologic or cytologic examination have also been described as ways to confirm tumor clearance at a cellular level during and following $CO_2$ laser ablation and thus increase the efficacy (see Laser Therapy with Intraoperative Cellular Evaluation section) [31, 32].

## Pulsed Dye Laser

Early studies investigated single-treatment PDL for the treatment of BCCs but found unacceptably low CRs with only a single pulse and single treatment of PDL. A study by Allison et al. in 2003 of seven patients with superficial BCCs treated with a single treatment of 585 nm PDL reported an 8-week posttreatment CR of only 14% (1/7) [33]. The authors concluded that PDL was not an effective treatment modality for the treatment of superficial BCCs [33].

Later, a prospective study by Ballard et al. reported seven patients with nine biopsy-proven primary BCCs (<1 cm in diameter, excluding tumors with morpheaform/sclerosing or basosquamous histologic subtypes) treated with a single treatment of 585 nm PDL (single pulse, 0.45 ms pulse duration, 7 mm spot size, 9.0 J/cm$^2$, 4 mm margins, no dynamic cooling) [34]. At 4 weeks posttreatment, they performed a deep shave to histologically evaluate for residual tumor [34]. The

4-week histologic CR was 55.6% (4/9) with residual tumor present in 44.9% (4/9) of sites, and the authors concluded that single-treatment, single-pulse 585 nm PDL did not have high enough CRs to be an appropriate treatment option for BCCs [34]. They called for further studies investigating appropriate PDL treatment settings and number of treatments for acceptable efficacy and tolerability for the treatment of BCCs [34].

However, numerous studies using different laser parameters including PDL with a wavelength of 595 nm, higher fluence, and multiple consecutive treatments or stacked pulses of PDL report higher CRs for PDL than the early studies above in the treatment of BCCs. Campolmi et al. performed a prospective study of 20 patients with nonpigmented superficial BCCs treated with flashlamp-pumped PDL (5 treatments, every 20 days, 595 nm, 5 mm margin, 5–10 passes until observed purpura) [13]. Patients either had contraindications to ST or had tumors located on a cosmetically sensitive area (nasal tip in six patients, nasal wings in four patients, and décolleté area in four patients) [13]. Laser parameters were either set to 7.5 J/cm$^2$ with 1.5 ms pulse duration and 7 mm spot size or to 6.5 J/cm$^2$ with 0.5 ms pulse duration and 10 mm spot size [13]. Patients were followed clinically for evidence of persistent or recurrent tumor for 12–24 months after the last treatment [13]. The authors reported a clinical complete response rate (CRR) of 80% (16/20) with a RR of 15% (3/20) and no clinical resolution in 5% (1/20) [13]. The treatment was well-tolerated in all patients [13]. There was purpura in all patients (indicating adequate treatment) which faded within 2 weeks, pain/discomfort during treatment, itching during healing, and hyperpigmentation following treatment in a few patients which faded in all patients without any scarring [13]. The authors concluded that in patients with contraindications to ST or with tumors in cosmetically sensitive areas, PDL may be an effective and well-tolerated option for the treatment of superficial, nonpigmented BCCs [13].

Further, a study by Shah et al. studied 595 nm PDL treatment (4 consecutive treatments with 2-week intervals, 4 mm margin, 1 pass, 15 J/cm$^2$, 3 ms pulse duration, 7 mm spot size, 10% overlap, no cooling) in 12 patients with 21 biopsy-proven superficial or nodular BCCs located on the trunk and extremities [35]. They matched these tumors based on diameter, histologic subtype, and location with control BCCs treated with biopsy only followed by SE [35]. At 2 weeks or later posttreatment, SE was performed to allow determination of the histologic CR [35]. They demonstrated a statistically significantly higher complete histologic CR with PDL of 65% (13/20) compared to 10% (2/20) of controls with an odds ratio of 16.7 ($p$ = 0.0004) [35]. They did find a correlation between smaller diameter and higher histologic CR with average diameter of responders of 1.1 cm and average diameter of non-responders of 2.2 cm ($p$ = 0.005) [35]. The authors stratified the tumors by diameter into ≤1.4 cm and >1.5 cm and found a statistically significantly higher histologic CR in the ≤1.4 cm group of 91.7% compared to a histologic CR of 25% for BCCs >1.5 cm (odds ratio = 67.0, p = 0.0004) [35]. They did find a higher histologic complete CR in superficial BCCs of 77% (7/9) compared to other histologic subtypes, but the difference was not statistically significant [35]. The authors also calculated the ratio of pretreatment max clinical diameter of BCCs with incomplete response to posttreatment

max diameter and found that the residual tumor diameter was <1–29% of the pre-treatment diameter (a 71–99% reduction in tumor diameter) in all eight incomplete responders with a statistically significant greater reduction in tumor burden compared to the control tumors which had posttreatment tumor diameter of 13–68% of the pre-treatment diameter ($p = 0.05$) [35]. There was healing without scarring in all patients, and the histologic evaluation of the excision specimens supported this with no evidence of scarring, necrosis, or post-inflammatory hyperpigmentation which is in contrast to the destructive changes observed with ablative lasers such as $CO_2$ lasers [27, 35]. The authors concluded that PDL may be an effective treatment option with good CO in superficial and nodular BCCs <1.5 cm in diameter and may be a useful method to debulk tumors and decrease tumor burden prior to ST even in larger tumors [35]. However, the authors called for studies with long-term follow-up.

In another prospective study by Konnikov et al., they followed 14 patients with 20 primary biopsy-proven BCCs located on the trunk and extremities (8–35 mm in diameter, excluding tumors with a morpheaform subtype) treated with 595 nm PDL (4 consecutive treatments, 3–4-week treatment intervals, 4 mm margins, 15 J/cm$^2$, 3 ms pulse duration, 7 mm spot size, 1 pass, no pulse stacking, with cryogen spraying cooling) for 12–21 months posttreatment [36]. They performed biopsy or SE to allow for the evaluation of histologic evidence of recurrence in 13/20 lesions (in 7/20 lesions the patients refused biopsy and SE as there was no clinical evidence of recurrence) [36]. They reported no clinical or histologic evidence of recurrence with 12–21-month follow-up in 90% (18/20) of BCCs [36]. One tumor did not respond to treatment with clinical and histologic evidence of residual tumor noted, and one was noted to have recurred clinically and histologically at 17-month follow-up [36]. They reported a histologic CR of 85% (11/13) of the tumors that were evaluated histologically [36]. The treatment was overall well-tolerated with pigmentary change noted at 12–21 months in the majority of cases (15 with hypopigmentation, 1 with post-inflammatory hyperpigmentation, and 1 with hypertrophic scar formation) [36]. The CO was graded by patients as excellent in 18/20, good in 1/20, and not graded in 1/20 [36]. The authors concluded that consecutive treatments with 595 nm PDL with the above settings may be an effective and well-tolerated treatment option for primary non-morpheaform BCCs located on the trunk and extremities [36].

A case series of 29 patients with 39 biopsy-proven BCCs (located on the face and trunk; superficial, nodular, micronodular, infiltrative, ulcerative, sclerotic, pigmented, and mixed histologic subtypes) treated with 1–4 sessions of PDL (595 nm, 14 J/cm$^2$, 3 ms pulse duration, 7 mm spot size, no dynamic cooling) at 2–4-week intervals followed patients for 3–25 months with a mean follow-up time of 11 months [37]. They reported a 3-month CRR of 75% (24/32), a RR of 16% (5/32), and an incomplete response rate after four treatments of 9% (3/32) [37]. The authors noted that tumors with nodular, infiltrative, and mixed histologic subtypes were more likely to recur or have an incomplete response to treatment [37]. The authors noted that their response rate may be lower compared to other studies due to the inclusion of BCCs of all histologic subtypes and sizes, a large percentage of tumors located on the face, and a longer period of follow-up [37].

A small prospective study by Alonso-Castro et al. histologically evaluated the efficacy of PDL with stacked pulses (3 sessions, 4-week intervals, 595 nm, 15 J/cm$^2$, 2 ms pulse duration, 7 mm spot size, 4 mm margins, 2 stacked pulses with 1-second delay) for the treatment of seven high-risk facial BCCs (recurrent, infiltrative, and/or nodular and > 6 mm in diameter in the H-zone) by performing MMS at least 1 month after LT completion [38]. The authors found a complete clinical response at 1-month posttreatment follow-up in 5/7 patients [38]. However, subsequent MMS performed in 6/7 patients revealed complete histologic clearance in 4/6 and residual tumor in 2/6 [38]. Additionally, the one patient who did not undergo MMS was found to have tumor recurrence at 14-month follow-up [38]. Overall 4/7 high-risk facial BCCs treated with three sessions of PDL with stacked pulses had no clinical or histologic evidence of recurrence [38]. The authors concluded that multiple treatments with PDL with stacked pulses may allow greater depth of treatment and may be a potentially effective treatment option for high-risk facial BCCs but recommended MMS in these cases to allow determination of histologic clearance until more conclusive data is found from larger studies with optimized laser parameters [38].

## Other Lasers

A number of lasers with higher wavelengths (and thus greater depth of penetration) than PDL including the 755 nm alexandrite, 1064 nm Nd:YAG, and the ablative 2940 nm Er:YAG lasers have more recently been studied in the treatment of BCCs.

Ibrahimi et al. reported a case of a patient with basal cell nevus syndrome with 18 BCCs treated with a single treatment of long-pulsed 755 nm alexandrite laser with clinical evaluation at 2-month and 7-month follow-up and histologic evaluation at 7-month follow-up [39]. The authors reported complete clinical clearance without histologic evidence of residual tumor in 83% of lesions treated (15/18) at 7-month follow-up [39].

A prospective study by El-Tonsy et al. followed 37 patients with BCCs located on the head and neck (0.5–3.5 cm in diameter; superficial, nodular, pigmented, and morphea-like histologic subtypes) treated with Nd:YAG (1064 nm, 8 mm spot size, up to 1-minute pulse duration) at 6-week treatment intervals [40]. The number of sessions was determined based on the lesion diameter with up to 2, 3, and 4 sessions for lesions ≤1 cm, 1–2 cm, or >2 cm in diameter, respectively [40]. Additionally, if there was clinical or histologic evidence of recurrence, an additional session was performed [40]. Patients were followed for 3–5 years with clinical evaluation for recurrence, and biopsy was performed 3 months posttreatment to allow histologic evaluation [40]. The authors reported a RR of 2.7% (1/37) for multiple sessions of Nd:YAG in the treatment of facial BCCs [40]. However, the study may have had a falsely elevated histologic cure rate as biopsy rather than excision was performed to determine histologic clearance.

Further, a prospective study by Moskalik et al. followed 3346 facial BCCs treated with neodymium (Nd) (1060 nm, 1–4.5 ms pulse duration, 700 or 100 J, and 0.5 or 1.5 cm spot diameter) and Nd:YAG (1060 or 1320 nm, 1 ms pulse duration, 10–40 Hz, 0.6 J maximum pulse energy, 1 mm spot size) laser with follow-up time ranging from 3 months to >5 years [41]. They reported a RR of 1.8% and 2.5% for LT of BCCs with Nd laser and Nd:YAG laser, respectively, with reportedly acceptable COs [41]. The authors concluded that Nd and Nd:YAG LT may be an acceptable treatment option for facial BCCs not extending more than 2–3 mm below the skin surface [41].

A later retrospective study by Moskalik et al. included 2743 primary BCCs and 172 recurrent limited BCCs located on the face treated with 1060 nm wavelength Nd laser [42]. The mean follow-up time was 13.4 months, and they found the RR for facial BCCs treated with Nd laser to be 2.2% [42].

Treatment with Nd:YAG laser has also been studied for the treatment of BCCs on the trunk and extremities. A prospective study by Ortiz et al. of 10 patients treated with 1064 nm long-pulsed, high-fluence Nd:YAG laser (10 ms pulse duration, 1064 nm, 5 mm spot size, 80 or 120 J/cm$^2$, no epidermal cooling) for the treatment of 13 biopsy-proven BCCs on the trunk and extremities (<1.5 cm in diameter with superficial, nodular, or micronodular histologic subtype) was performed [21]. The tumor and surrounding 4 mm margin was treated with three passes and an additional three stacked pulses with a repetition rate of 1 Hz to the center of the tumor [21]. The treatment endpoints included graying or darkening of the tumor without a change in appearance of the normal surrounding skin [21]. At least 1 month following treatment, SE was performed to allow histologic determination of clearance [21]. The authors reported a histologic CR of 92% (12/13) overall, histologic CR of 100% (10/10) in patients in whom the higher 120 J/cm$^2$ fluence was used, no scarring, and no significant adverse effects [21]. They did note mild erythema immediately following 1 month after treatment and moderate edema immediately after treatment [21]. They concluded that 1064 nm long-pulsed Nd:YAG laser may be a safe and effective treatment option for BCCs on the trunk and extremities, although larger and comparative studies are still needed [21].

More recently, the same group published a prospective study of 31 patients with 31 biopsy-proven BCCs (excluding patients on anticoagulation or immunosuppression and including tumors located on the trunk and extremities with diameter <2.1 cm) treated with a single treatment of long-pulsed Nd:YAG laser (1064 nm, 5–6 mm spot size, 125–140 J/cm$^2$, 7–10 ms pulse duration, 13–68 pulses, no epidermal cooling) [43]. At 3 days posttreatment, the area was surgically excised with 5 mm margins to allow determination of histologic clearance [43]. The authors found a complete tumor CR of 90% (28/31), and the treatment was relatively well-tolerated [43]. The authors reported adverse effects including immediate burning, erythema, edema, and residual mild erythema and crust at 1-month follow-up in some patients [43].

Different lasers may also be used in combination, and the use of different lasers in combination for the treatment of BCCs has only more recently been studied. Jalian et al. performed a prospective non-randomized study of 13 biopsy-proven BCCs

(<2 cm in diameter; superficial, nodular, or micronodular histologic subtypes) in 10 patients treated with four treatments at 2–4-week intervals of PDL (585 nm, 7 mm spot size, 8 J/cm$^2$, 2 ms pulse duration) with a 250 ms delay followed by Nd:YAG (1064 nm, 40 J/cm$^2$, 15 ms pulse duration, 10% overlap) with 4 mm margins of normal-appearing skin [44]. Excision was then performed 2–4 weeks after the last treatment to allow histologic determination of tumor clearance [44]. The authors found a 58% tumor CR (7/12) overall but a higher tumor CR of 75% (6/8) when excluding tumors ≥1 cm in diameter [44]. They also noted that all patients with incomplete tumor responses to treatment were on anticoagulation and hypothesized that given that coagulation has been shown to be important in the mechanism of action of vascular lasers, patients on anticoagulants may have lower response rates [44]. Many subsequent studies have excluded patients on anticoagulants besides aspirin and nonsteroidal anti-inflammatory drugs [44]. The authors also noted that the lower efficacy in their study may be in part secondary to laser parameters used with lower fluence, shorter pulse duration, and shorter wavelength used compared to prior studies of PDL for the treatment of BCC with higher reported efficacy rates [44]. The authors concluded that further studies were needed to optimize laser parameters in patients off of anticoagulation for both PDL and Nd:YAG alone and in combination for the treatment of BCC [44].

## Laser Therapy with Intraoperative Cellular Evaluation

Intraoperative pathologic or cytologic examination and RCM during LT for the treatment of BCCs have been described as ways to confirm tumor clearance at a cellular level and thereby increase efficacy.

For example, RCM has been shown to be useful in allowing the detection of BCCs with a sensitivity of 92–100% and specificity of 88–97% [45, 46]. Laser ablation combined with the utilization of RCM has been described as a means of improving tumor visualization and thus potentially improving efficacy. Given that RCM allows tumor visualization at the cellular level, it has been proposed as a mechanism by which to visually confirm tumor clearance given the lack of opportunity to histologically evaluate for tumor clearance with LT for the treatment of BCCs. Sierra et al. in an ex vivo study of BCC and normal skin discarded during MMS demonstrated that RCM is able to detect residual BCC following treatment with Er:YAG laser ablation and that a fluence of 25 J/cm$^2$ was required for tumor ablation [47]. A case report by the same group by Chen et al. reported two patients with two biopsy-proven superficial or early nodular BCCs treated with Er:YAG laser ablation (≤25 J/cm$^2$, 4 mm spot size, 250 ms pulse duration) in combination with RCM laser therapy (LT)/intraoperative cellular evaluation, in order to allow pre-treatment determination of borders and posttreatment confirmation of tumor clearance [48]. They varied laser parameters based on the three-dimensional topography of the tumor and found tumor clearance in all cases based on RCM and confirmed histologically with MMS [48].

Further, Hibler et al. performed a prospective study of seven patients with eight shave biopsy-proven superficial or nodular BCCs located on low-risk sites in which RCM identified BCC-specific features in 8/8 cases, and RCM was used to determine the tumor borders [31]. The tumors were then treated with $CO_2$ laser ablation (10,600 nm, 0.75 ms pulse duration, 7.5 J/cm$^2$, 2–9 mm square pattern, 30% density) [31]. Between each pass, RCM was utilized to determine if there was residual tumor present, and in cases where tumor persisted an additional pass was performed until the tumor was cleared by RCM with up to three passes [31]. The histologic clearance was then determined first by MMS and later by traditional breadloafing histologic processing of the specimen [31]. The authors found complete tumor clearance in 6/8 tumors and residual tumor present in 2/8 tumors, and the assessments of the presence or absence of residual tumor were congruent between RCM and histologic evaluation in all cases [31]. Thus, the authors concluded that RCM may be useful in combination with $CO_2$ laser ablation in the treatment of BCC to allow confirmation of tumor clearance at a cellular level but called for larger studies in the future [31].

Similarly, cytologic examination during LT has been described. Campolmi et al. performed a prospective study of 140 patients with biopsy-proven superficial and nodular BCCs with diameters <1.5 cm treated with $CO_2$ laser ablation (2–3 ms pulse duration, 10 Hz frequency, 1–3 mm spot size) with intraoperative cytologic examination [15]. The authors described performing scrape biopsies by scraping the lesion, fixing the material on a slide, staining the material with the Papanicolaou method, and then examining microscopically for cytologic features of BCC cells such as irregular grouping of cells, loss of polarity, hyperchromic nuclei, and polymorphic nuclei [15]. This was performed prior to starting the procedure, at the level of the papillary dermis, and when the operator clinically saw no evidence of residual tumor [15]. If there was tumor present with cytologic examination, then treatment was repeated until there was no cytologic evidence of tumor [15]. The authors reported a 3-year complete CR of 100% with no recurrences reported [15]. The authors concluded that intraoperative cytologic examination with $CO_2$ laser ablation allowed cytologic confirmation of tumor clearance with excellent efficacy and may be an effective and safe treatment option for the treatment of superficial and nodular BCCs <1.5 cm in diameter [15].

Additionally, a prospective study by Ebrahimi et al. followed 20 patients with 21 biopsy-proven primary periorbital BCCs involving the eyelash line (including superficial, nodular, and pigmented subtypes; excluding morpheaform histologic subtype) treated with superpulsed $CO_2$ laser with intraoperative pathologic evaluation for 36 months [32]. The clinically identifiable tumor was curetted [32]. The defect was then treated with superpulsed $CO_2$ laser with eye protection (12 W, 600–800 ms pulse duration, 4 passes) [32]. Following LT, the base and margin of the defect were curetted to allow histologic examination [32]. If there was persistent tumor, the $CO_2$ laser treatment was repeated as well as curettage to allow histologic evaluation [32]. This was repeated until there was no evidence of residual tumor histologically. The authors reported a RR of 4.8% (1/21), cure

rate of 95.2% (20/21), eyelash damage in 10% of patients (2/20), and no cases of ectropion [32]. They concluded that superpulsed $CO_2$ laser with intraoperative histologic assessment may be a safe and effective treatment of BCCs located in the periorbital area [32].

## Combination Therapy

Laser treatment has also been combined with a number of different treatment modalities including PDT and topical therapies including 5-FU to increase the depth of tissue penetration and as a light source in PDT (see PDT Efficacy section in Chap. 11 and Topical 5-FU Efficacy section in Chap. 4) [49–57]. A study in porcine skin has shown a potential increase of the depth of penetration of topical ingenol mebutate with pre-treatment with 2940 nm Er:YAG laser and called for further studies to investigate combined LT with topical ingenol mebutate to increase the penetration and potentially the efficacy in the treatment of non-melanoma skin cancers such as BCCs (see Topical Ingenol Mebutate Efficacy section in Chap. 4) [58]. However, further studies including large prospective studies and randomized controlled studies are needed to determine the efficacy and safety of LT combined with other treatment modalities for the treatment of BCC.

## Safety

Generally LT may lead to purpura, erythema, pain/discomfort, pruritus, pigmentary alteration (either hyperpigmentation or hypopigmentation), and scarring (including atrophic scar, hypertrophic scar, and keloid formation) at the treatment site. Continuous $CO_2$ laser ablation has been shown to lead to hypopigmentation, erythema, pain, and the formation of atrophic and hypertrophic scars [24, 25]. Pulsed $CO_2$ laser has similar localized treatment site effects as continuous $CO_2$ laser. However, of note pulsed $CO_2$ laser has been associated with lower rates of scarring including hypertrophic scar formation compared to continuous $CO_2$ laser [27, 59–63].

Pulsed dye laser most commonly leads to purpura (typically fading within 2 weeks), pain/discomfort during treatment, crust formation, pigmentary alteration (including hyperpigmentation and hypopigmentation) following treatment, and less commonly scar formation including hypertrophic scar formation [13, 36, 64].

Adverse effects reported with Nd:YAG laser treatment for the treatment of BCCs include immediate effects such as burning sensation, edema, superficial erosions, crusting, and infection; temporary effects lasting <3 months including hypopigmentation, hyperpigmentation, and alopecia; and permanent effects such as scar formation including the development of depressed scars [21, 40, 43].

Adverse effects with LT are largely dependent on the laser parameters used and can be minimized by optimizing settings, but this must be balanced with achieving optimal efficacy for the treatment of BCCs. Generally, continuous wave lasers have less selectivity causing more nonselective tissue damage with a higher risk of burning and scarring compared to pulsed and Q-switched lasers [65].

## Comparative Studies

### *$CO_2$ Laser*

A randomized trial by Zane et al. compared pulsed $CO_2$ laser ablation to SE and CT for the treatment of superficial BCCs located on the trunk or extremities [66]. The authors included 240 patients randomized to the three groups and assessed complete remission rate, CO, and patient satisfaction at 3-month follow-up [66]. They found a 3-month CRR for superficial BCCs treated with pulsed $CO_2$ laser of 78.8% which was statistically significantly lower than in the SE group and not statistically significantly different than the CRR in the CT group [66]. However, the authors did find high levels of patient satisfaction (65.0%) in the pulsed $CO_2$ laser group, but there was no statistically significant difference in the level of patient satisfaction between the pulsed $CO_2$ laser and CT groups [66]. The CO of the pulsed $CO_2$ laser treatment group was worse than with SE at 3-month follow-up, but there was no statistically significant difference in the CO between the pulsed $CO_2$ laser and CT treatment groups [66]. The wound healing time was statistically significantly shorter in the pulsed $CO_2$ laser group compared to the SE and CT groups [66]. The authors noted that the study was limited by the relatively short follow-up time [66].

### *Pulse Dye Laser*

A randomized controlled study by Karsai et al. investigated the safety and efficacy of PDL for the treatment of superficial BCCs located at low-risk sites [64]. They included 39 patients with 100 biopsy-proven superficial BCCs with diameter ≤30 mm located on the trunk and extremities (excluding patients on anticoagulants and with tumors located on the hands, feet, or genitalia) and randomized tumors to receive either four treatments of PDL at 3-week intervals (595 nm, 8 J/cm$^2$, 0.5 ms pulse duration, 10 mm spot size, minimal overlap, with air cooling system) or sham treatment [64]. Sites were evaluated clinically and histologically with a 4 mm punch biopsy of the most clinically suspicious area at 6-month follow-up [64]. They found a statistically significantly higher CRR of 78.6% (44/56) in the PDL laser group compared to 4.5% (2/44) in the sham treatment group ($p < 0.0001$) [64]. The main adverse effects noted in the laser group were hyperpigmentation

(37%), hypopigmentation (93%), and crust formation [64]. The authors concluded that PDL may be a safe and effective treatment option for superficial BCCs located on low-risk sites [64].

Given increased efficacy reported with multiple treatments of PDL, Tran et al. sought to investigate the efficacy of stacked pulses of PDL in a single treatment to avoid the need for multiple treatments [67]. They performed a pilot randomized controlled study of 23 biopsy-proven BCCs (21 with superficial, nodular, or multicentric histologic subtypes) and SCC in situs [2] located on the trunk and extremities (0.4–3 cm in diameter) randomized to a no treatment control, PDL laser without stacked pulses (595 nm, 15 J/cm$^2$, 3 ms pulse duration, 7 mm spot size, 10% overlap of pulses, 2 passes, 4 mm margins, no dynamic cooling), and PDL laser with stacked pulses (595 nm, 7.5 J/cm$^2$, 3 ms pulse duration, 10 mm spot size, 10% overlap of pulses, double-stacked pulses, 4 mm margins, no dynamic cooling) groups [67]. Surgical excision was then performed to allow histologic determination of tumor clearance [67]. The authors found a trend toward a significant difference with Fisher's exact test with Bonferroni correction ($p = 0.028$) with a higher histologic CR in the stacked pulse treatment group of 71% (5/7) compared to 28% (2/7) in the control group and 25% (2/8) in the PDL without stacked pulses group [67]. The authors concluded that a single treatment with PDL with stacked pulses may effectively lead to tumor clearance in the treatment of BCCs and SCC in situ but noted that their study was limited by a small sample size and larger studies were needed in the future [67].

### *Other Lasers and Combination Therapy*

The Smucler and Vlk study compared MAL-PDT alone, Er:YAG laser ablation alone, and combined Er:YAG laser ablation followed by MAL-PDT for the treatment of recurrent nodular BCCs in 286 patients with three or more BCCs all of whom were treated with all three treatments [68]. The authors found a statistically significantly higher complete CR of 98.97% for Er:YAG in combination with MAL-PDT compared to both Er:YAG laser treatment (91.75%) and MAL-PDT alone (94.85%) [68]. Additionally, they found better COs with combined Er:YAG laser ablation and MAL-PDT than with either treatment modality alone [68]. The authors concluded that combined Er:YAG laser ablation and MAL-PDT may be a more effective treatment than either treatment modality alone for the treatment of nodular BCCs (see PDT Comparative Studies section in Chap. 11) [68]. However, larger studies with longer follow-up are needed to compare Er:YAG combined with MAL-PDT to other treatment modalities including Er:YAG laser ablation alone, MAL-PDT alone, ST, and other nonsurgical options such as topical therapies for the treatment of superficial and nodular BCCs.

There have been prospective studies reporting the efficacy of different types of LT in combination with topical therapies including topical 5-FU and ingenol mebutate; however, randomized comparative studies on LT in combination with topical

therapies compared to topical therapy alone, LT alone, and other treatment modalities for the treatment of BCCs are lacking [55–58]. Thus, future studies are needed to compare different types of LT in combination with other treatment modalities such as topical therapy to single-treatment modalities including LT alone, topical therapy alone, and ST for the treatment of BCCs.

## Discussion

Laser treatments have great variability in the type of laser used, wavelength of light emitted, and specific laser settings used which may in part explain the variability in the efficacy and COs reported by different studies in addition to variation in study parameters such as patient and tumor selection, outcomes measures, and follow-up time.

In general, advantages of LT include speed of treatment, decreased non-specific tumor destruction, improved wound healing, good CO, and decreased associated pain. However, like other nonsurgical treatment options, LT is limited by the lack of the ability to histologically confirm tumor clearance and like other superficial therapies is additionally limited by the depth of penetration and generally recommended as a potential treatment option only for the treatment of superficial BCCs. Laser therapy also requires in-office visits and may be associated with greater cost to patients compared to other superficial therapies. Another potential concern regarding the use of LT for the treatment of BCCs is potential masking of classic clinical or dermoscopic features of BCC and thus potential delay in the detection of residual or recurrent tumor as supported by a case-control study by Kim et al. showing a statistically significant decreased rate of classic dermoscopic patterns in pigmented BCCs previously misdiagnosed and treated with laser ablation compared to control pigmented BCCs not previously treated with laser ablation [69].

Additionally, long-term data on specific types of lasers and comparative studies comparing LT to other treatment modalities for the treatment of BCCs is limited, and larger long-term prospective studies and comparative trials are still needed to further investigate the safety and efficacy of LT for the treatment of BCCs.

## Conclusions

Overall, certain types of LT with appropriate settings may be efficacious, well-tolerated, and an appropriate nonsurgical treatment option for the treatment of superficial BCCs in cases where ST is contraindicated or not appropriate. However, care should be taken that the appropriate type of laser with appropriate settings is used by the clinician. Of note, the long-term data on specific types of lasers is limited, and there are few comparative trials comparing specific types of LT to other treatment modalities for the treatment of BCC. In fact, the NCCN guidelines do

not currently include LT as one of the superficial treatment modalities listed as an appropriate treatment option for the treatment of primary, low-risk, superficial BCCs located in low-risk sites where ST is contraindicated or inappropriate [1]. Future larger and more long-term prospective studies investigating different types of LT as well as comparative studies to compare different types of LT to other treatment modalities such as SE, CT, ED&C, PDT, and topical therapies are still needed in order to better characterize the efficacy, tolerability, and CO of different types of LT for the treatment of superficial low-risk BCCs.

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# Chapter 13
# Hedgehog Signaling Pathway Inhibitors for Basal Cell Carcinoma


**Leon Chen, Sirunya Silapunt, and Michael R. Migden**

## Introduction

As the most common cancer in humans, basal cell carcinomas (BCCs) affect approximately 2.8 million people [1]. Depending on the location, size, tumor subtype, and other factors, treatment may include topical therapy with imiquimod or 5-fluorouracil, cryotherapy, radiation, photodynamic therapy, electrodesiccation and curettage, surgical excision, and Mohs micrographic surgery, the latter of which has the lowest 5-year recurrence rate: between 0.7% and 2.4% [2–5]. BCC is mainly a localized neoplasm, although less commonly, it can become locally advanced or even metastatic (0.0028–0.55%) [6, 7]. Locally advanced BCC (laBCC) and metastatic BCC (mBCC) are both considered advanced BCC. Due to the lack of available therapies, the potential for disfigurement, and surgery-associated morbidity, the unmet medical need for the treatment of advanced BCC warrants an effective therapeutic option.

Mutations in protein patched homolog-1 (PTCH-1) and smoothened (SMO) in the Hedgehog signaling pathway have been implicated in the pathogenesis of BCC [8]. It has been estimated that 95% of patients with sporadic BCCs have mutations identified in this particular pathway [9]. Currently, there are two US Food and Drug

L. Chen
The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

S. Silapunt
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

M. R. Migden (✉)
The University of Texas MD Anderson Cancer Center, Departments of Dermatology and Head and Neck Surgery, Mohs Surgery Center, Houston, TX, USA
e-mail: mrmigden@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_13

**Table 13.1** Comparison between sonidegib and vismodegib

| | Sonidegib | Vismodegib |
|---|---|---|
| Brand name | Odomzo | Erivedge |
| Year approval in the USA | 2015 | 2012 |
| Countries with approval for laBCC | USA, EU, Switzerland, and Australia | USA, EU, Switzerland, Australia, and other countries |
| Countries with approval for mBCC | Switzerland and Australia | USA, EU, Switzerland, Australia, and other countries |
| Dosing recommendation | 200 mg daily | 150 mg daily |
| Pill picture |  |   |
| Name of pivotal trial | BOLT | ERIVANCE |
| Drug interaction with CYP3A hepatic enzyme | Yes | No |
| Most common adverse events | Muscle spasm, alopecia, and dysgeusia | Muscle spasm, alopecia, and dysgeusia |

*laBCC* locally advanced basal cell carcinoma, *mBCC* metastatic basal cell carcinoma, *EU* European Union

Administration (FDA)-approved medications: vismodegib and sonidegib. As of late 2017, vismodegib is approved in the USA, European Union, Switzerland, Australia, and other countries for laBCC and mBCC. Sonidegib has been approved in the USA, European Union, Switzerland, and Australia for the treatment of laBCC. Additionally, sonidegib is also approved in Switzerland and Australia for mBCC. Vismodegib and sonidegib are summarized in Table 13.1.

In this chapter, we discuss treatment using Hedgehog pathway inhibitors (HPIs), with particular focus on vismodegib and sonidegib.

## Background

The Hedgehog pathway was first discovered during the investigation of *Drosophila melanogaster* embryogenesis [10]. Interestingly, the Hedgehog pathway is primarily activated during embryogenesis to ensure proper embryonic cell differentiation; however, this pathway remains quiescent in most adult tissues. In the absence of the Hedgehog ligand signaling, a cell surface transmembrane protein, PTCH-1, keeps the activity of a seven-membrane spanning receptor SMO suppressed [11, 12]. When the Hedgehog signaling ligand is present and bound to PTCH-1, SMO is disinhibited, which enables transcription factor Gli to enter the cell nucleus, promoting cell division and tumorigenesis (Fig. 13.1) [13].

Cyclopamine is a naturally occurring alkaloid in the corn lily (*Veratrum californicum*) in the western USA that behaves as an SMO antagonist [14]. After an 11-year investigation initiated in 1957 by the US Department of Agriculture, cyclopamine was identified to be the cause of the midline single-eyed appearance of

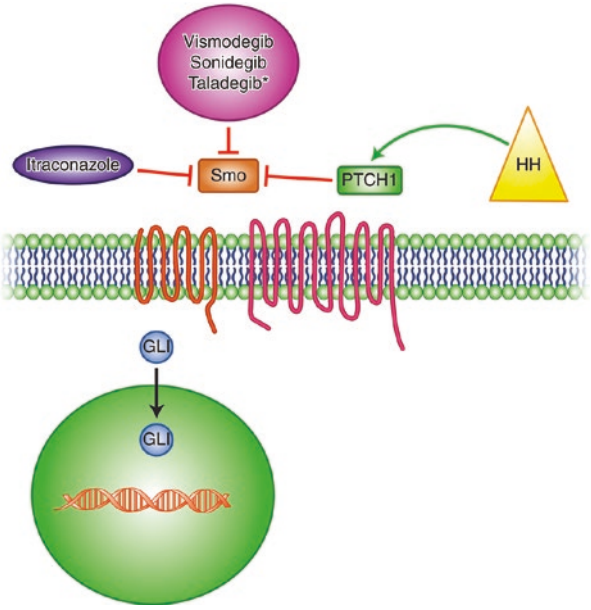


**Fig. 13.1** In the absence of the Hedgehog signal (HH), the PTCH1 cell surface transmembrane protein keeps the activity of SMO suppressed. However, when the HH is present and bound to PTCH1, SMO is no longer inhibited and allows the transcription factor Gli to enter the cell nucleus, stimulating cell division and tumorigenesis. Vismodegib, sonidegib, and taladegib inhibit SMO. Itraconazole inhibits the Hedgehog signaling pathway by preventing the ciliary accumulation of SMO. (∗not US FDA approved)

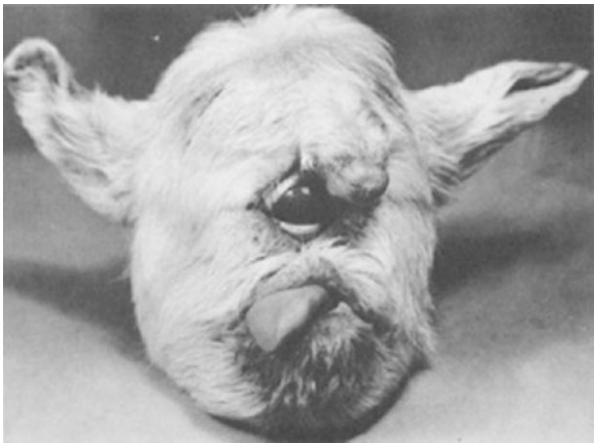

**Fig. 13.2** Midline single-eyed appearance of lamb born by corn lily-consuming ewe in an Idaho sheep ranch in the 1950s. (Reproduced with permission [61])

many lambs born by corn lily-consuming ewes on an Idaho sheep ranch (Fig. 13.2). These fetal birth defects induced by cyclopamine include holoprosencephaly (fused cerebral hemispheres) and cyclopia (single orbit); thus, the prefix "cyclo-" was given to name this teratogenic compound [15]. Later, cyclopamine was confirmed to antagonize the function of the Hedgehog signaling pathway and shown to induce remission of medulloblastoma in mice [16, 17]. The clinical use of cyclopamine has been limited by its poor aqueous solubility and chemical stability [18].

## Vismodegib

### *Drug Development*

GDC-0449, later named vismodegib, is a first-in-class SMO inhibitor with the chemical structure of 2-chloro-N-(4-chloro-3-(pyridine-2-yl) phenyl)-4-(methylsulfonyl)benzamide [19]. Vismodegib has more favorable pharmaceutical properties than cyclopamine. In a phase I study, patients with refractory solid tumors were tested with three different daily doses of vismodegib (150 mg, 270 mg, and 540 mg). The maximum concentration of vismodegib was reached within 2 days after a single dose administration for all three dosages. With once-daily dosing, all three vismodegib dosages reached steady-state concentrations in 7–14 days [20]. The volume of distribution of vismodegib ranged from 16.4 L to 26.6 L. Vismodegib is 99% protein bound to human plasma, and its level appeared to correlate with levels of alpha-1-acid glycoprotein [21, 22]. The recommended phase II trial dose was 150 mg daily, based on achievement of maximal plasma concentration pharmacodynamics response with this dose [20].

### *Clinical Trials*

Given the positive response observed in the phase I trial of vismodegib, a phase II international, multicenter trial (ERIVANCE) was initiated to assess the objective response rate (ORR) of vismodegib at a dosage of 150 mg daily in patients with either laBCC or mBCC [23]. For laBCC, the ORR was defined as a reduction of 30% or more in the externally visible (including any residual scarring) or radiographic dimension or complete resolution of ulceration if present initially. Complete response (CR) was defined as the absence of any residual BCC on assessment of a biopsy specimen. Progressive disease (PD), on the other hand, was defined as an increase of 20% or more in externally visible tumor size or radiographic dimension, formation of new lesion, or the presence of new ulceration. Response Criteria in Solid Tumor (RECIST) was used to assess mBCC [23].

In the primary analysis, the ERIVANCE trial had a total of 104 patients enrolled, and analysis was performed on 96 patients, including 63 with laBCC and 33 with mBCC. In 63 patients with laBCC, the ORR was 43% per central review, and CR was seen in 13 patients. The ORR was 30% per central review in 33 patients with mBCC. The median duration of response (DOR) and progression-free survival (PFS) were 7.6 months and 9.5 months, respectively [23]. At 12-month follow-up, the ORR increased from 42.9% to 47.6% in the laBCC subgroup and from 30.3% to 33.3% in the mBCC subgroup per central review [24]. The final update of the ERIVANCE trial had data cutoff 39 months after completion of study accrual, and 8 patients were still receiving vismodegib out of 69 patients in survival follow-up. ORR was 60.3% in the laBCC group and 48.5% in the mBCC group per investigator

review as central review only collected data up to 12-month follow-up. The ORR assessed by the investigator review is often found to be higher than that of central review. The median DOR was 26.2 months in the laBCC group and 14.8 months in the mBCC group. This long-term final update of the ERIVANCE trial further confirmed the efficacy and durability of vismodegib [25]. The efficacy data are summarized in Table 13.2. The adverse event profile for vismodegib including safety and tolerability are discussed in the section below.

## *Safety and Tolerability*

In the ERIVANCE trial, adverse events were reported in every study patient, although most (57%) reported events were either grade 1 or grade 2. The most common reported adverse events were muscle spasm (68%), followed by alopecia (63%), dysgeusia (51%), weight loss (46%), and fatigue (36%). Seven patients had a fatal grade 5 adverse event; however, all of these cases were thought to be unrelated to the study drug. At the time of cutoff for the 12-month update, 75 out of 104 enrolled patients discontinued treatment due to adverse events, disease progression, or patient decision. Among all the adverse events that led to study discontinuation, muscle spasm, weight loss, and dysgeusia were the most frequent reasons [23]. Overall, the safety profile for vismodegib at the 12-month update was similar to that in the primary analysis, without the occurrence of additional grade 5 fatal events [24]. The final update with data cutoff 39 months after completion of accrual showed that the incidence of treatment-emergent adverse events was higher in patients who were on vismodegib treatment longer than 12 months; however, the risk of another adverse event was reduced beyond the first year of treatment. Seventeen deaths were reported, with only one death documented as an adverse event. None of the deaths was thought to be related to vismodegib [25].

## *Administration and Precautions*

Vismodegib, with the brand name Erivedge, comes in 150-mg capsules that have a pink opaque body and a gray opaque cap. The recommended dose is 150 mg once daily by mouth until disease progression or until patients can no longer tolerate its associated toxicity. Patients may take the capsule with or without food. No clinically relevant interactions are expected between vismodegib and other substrates or inducer/inhibitor of cytochrome 450 enzymes [26].

The importance of the Hedgehog signaling pathway in fetal development and the teratogenicity of HPIs have been well described. Females with childbearing potential should have a negative pregnancy test within 7 days prior to vismodegib administration. In addition, females with childbearing potential should use effective contraception during the treatment and for 24 months after the last dose. Vismodegib

**Table 13.2** Response rate comparison between sonidegib in BOLT versus vismodegib in ERIVANCE

| | BOLT (sonidegib 200 mg only) | | | | | | ERIVANCE (vismodegib 150 mg daily) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Primary analysis | | 12-month update | | 30-month update | | Primary analysis | | 12-month update | | Long-term analysis[a] | |
| | laBCC | mBCC | laBCC | mBCC | laBCC | mBCC | laBCC | mBCC | laBCC | mBCC | laBCC | mBCC |
| | (*n* = 66) | (*n* = 13) | (*n* = 66) | (*n* = 13) | (*n* = 66) | (*n* = 13) | (*n* = 63) | (*n* = 33) | (*n* = 63) | (*n* = 33) | (*n* = 63) | (*n* = 33) |
| ORR, % (*n*) | 47.0 (31) | 15.4 (2) | 57.6 (38) | 7.7 (1) | 56.1 (37) | 7.7 (1) | 42.9 (27) | 30.3 (10) | 47.6 (30) | 33.3 (11) | 60.3 (38) | 48.5 (16) |
| CR, % | 3.0 | 0 | 4.5 | 0 | 4.5 | 0 | 20.6 | 0 | 22.2 | 0 | 31.7 | 0 |
| PR, % | 43.9 | 15.4 | 53.0 | 7.7 | 51.5 | 7.7 | 22.2 | 30.3 | 25.4 | 33.3 | 28.6 | 100 |
| SD, % | 43.9 | 76.9 | 33.3 | 84.6 | 34.8 | 84.6 | 38.1 | 63.6 | 34.9 | 60.6 | 23.8 | 87.5 |
| PD, % | 1.5 | 0 | 1.5 | 0 | 1.5 | 0 | 12.7 | 3.0 | 12.7 | 3.0 | 9.5 | 12.5 |
| Median DOR, mo | NR | NR | NR | NR | 26.1 | NR | 7.6 | 7.6 | 9.5 | 7.6 | 26.2 | 14.8 |
| Median PFS, mo | NR | 13.1 | NE | 13.1 | NE | 13.1 | 9.5 | 9.5 | 9.5 | 9.5 | 12.9 | 9.3 |

All data reported are based on central review except for data from ERIVANCE long-term analysis where only investigator-assessed response is available. The ORR assessed by the investigator review is often found to be higher than that of central review

*ORR* objective response rate, *CR* compete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *DOR* duration of response, *PFS* progression-free survival, *NR* not reached, *NE* not estimable

[a]Data from investigator-assessed response; 39 months after completion of accrual

is also present in semen. Although a potential link to embryo-fetal harm has not been established, male patients should wear condoms and avoid donating semen during and for 3 months after the last dose of vismodegib [26].

## Sonidegib

### *Drug Development*

LDE225—N-(6-((2S, 6R)-2, 6-dimethylmorpho-lino) pyridine-3-yl)-2-methyl-50-(trifluoromethoxy) biphenyl–3- carboxamide—was found to be a potent and selective SMO antagonist [27]. Its high tissue penetration, ability to cross the blood-brain barrier, and exceedingly high oral bioavailability made LDE225 an attractive compound for potential pharmaceutical development. In the phase I study, the maximum tolerated dose in patients with advanced solid tumor was determined to be 800 mg daily and 250 mg twice daily. Although, in theory, the twice-daily dosing regimen can reach steady state at a faster rate than once-daily dosing, no clinical advantage was observed, and therefore the once-daily dosing was recommended for subsequent clinical trials [28]. The main dose-limiting toxicity was elevated serum creatine kinase without evidence of cardiac muscle injury. Muscle spasm was the most commonly reported adverse event in the phase I trial, although no clear association was found between elevated creatine and muscle spasm [28]. The long half-life (29.6 days) of sonidegib may be due to its high binding capacity to serum protein [29]. Sonidegib has a maximum serum concentration of 1030 ng/ml, with a time to achieve this concentration of 2–4 hours. It takes approximately 4 months for sonidegib to reach steady state after initial dosing. CYP3A is the main enzyme responsible for sonidegib metabolism; therefore, drug interaction with this hepatic enzyme can potentially increase the risk of adverse effects, such as muscle spasm. Absorbed sonidegib is eliminated predominantly through hydrolytic and oxidative metabolism and excreted in the feces (70%) and urine (30%). The unabsorbed form is excreted in the feces [30].

### *Clinical Trials*

The Basal cell carcinoma Outcomes with LDE225 Treatment (BOLT) trial was a multicenter, phase II, randomized, double-blind clinical trial studying the use of two different doses of sonidegib for the treatment of laBCC and mBCC [9]. Patients 18 years of age and older were randomized into two treatment arms of 200 mg (dose with lowest efficacy) and 800 mg (maximum tolerated daily dose) sonidegib once daily in a 1:2 ratio, respectively [9]. Both the investigators and the central review committee assessed mBCC tumors based on RECIST version 1.1. Based on regulatory agency regulation, the modified RECIST criteria was developed to assess

laBCC, which was more stringent than RECIST version 1.0 used in previous similar studies [31]. In addition, central review was performed in all time points in the BOLT trial.

The primary endpoint of the BOLT trial was the proportion of patients with laBCC or mBCC who achieved an ORR that included both CR and partial response (PR). CR was defined by complete response in all categories of clinical assessment, radiographic assessment, and multiple surveying biopsies all being negative. PR was achieved when a 50% or greater decrease was observed in the sum of products of perpendicular diameter (World Health Organization [WHO] criteria) based on photographs of lesions and when a minimum 30% reduction was observed in the sum of diameter of all target lesions by magnetic resonance imaging (RECIST). For the primary efficacy analysis that contained data collected up to 6 months after randomization of the last patient, the ORR for laBCC by central review was 43% and 38% in the 200-mg arm and the 800-mg arm, respectively. For mBCC, the ORR by central review was 15% and 17% in the 200-mg group and the 800-mg group, respectively. Although the efficacy for both the 200-mg and 800-mg treatment arms was similar, patients in the 200-mg treatment arm were found to have a lower rate of reported adverse events, longer treatment duration, and a lower treatment discontinuation rate. Thus, the 200-mg dosing was considered to have a more favorable benefit-to-risk profile than the 800-mg dosing [9]. The data from the 12-month update showed a higher ORR in both laBCC 200-mg and 800-mg treatment arms, up to 15% (58% vs 43%) and 6% (44% vs 38%) per central review, respectively. Based on central review, 92% of patients (48/42) treated with sonidegib 200 mg and 90% of patients (91/101) treated with sonidegib 800 mg had laBCC tumor shrinkage by photograph per WHO criteria. Fifty-three percent of responding patients treated with 200 mg of sonidegib and 54% of responding patients treated with 800 mg of sonidegib had long-lasting tumor response for more than 6 months, with a median DOR of approximately 20 months for both groups. Of 94 patients with laBCC, 15 patients (16%) experienced disease progression, and three patients (3.2%), all of whom had significant cardiac risk factors, died from cardiac events deemed to be unrelated to sonidegib. In the mBCC subgroups, the ORRs by central review from the 12-month analysis in the 200-mg and 800-mg arms were 8% and 17%, respectively. Approximately 85% of patients treated with 200 mg and 82% of patients treated with 800 mg demonstrated tumor shrinkage; however, the Kaplan-Meier median DOR was not reached for either arm by central review [32]. At the 30-month update, in comparison to the 12-month data, ORRs per central review for laBCC patients for both the 200-mg group (56% vs 58%, respectively) and the 800-mg group (45% vs 44%, respectively) were very similar. Clinical benefit, defined as the percentage of patients who had a reduction in the maximal change in tumor size from baseline, remained unchanged between the 12- and 30-month updates per central review. Clinical benefit was demonstrated in 92% of patients (48/52) in the 200-mg group and 90% of patients (91/101) in the 800-mg group. At 30 months, the DOR of laBCC patients increased for both the 200-mg and 800-mg groups to 26.1 months versus 20.2 months in the 12-month analysis and 23.7 months

versus 19.8 months in the 12-month analysis, respectively. Based on central review, the median durations of PFS were 22.1 months in the 200-mg group and 22.0 months in the 800-mg group. A total of 16 patients (5 in the 200-mg arm and 11 in the 800-mg arm) with laBCC had died by the 30-month update. For patients with mBCC, the ORRs for both 200-mg and 800-mg arms remained unchanged for the 30-month data in comparison to the 12-month data per central review and were approximately 8% and 17%, respectively. Clinical benefit also remained the same at 30 months for both the 200-mg (92%) and 800-mg arms (84%) compared to data from the 12-month analysis. The median DOR for the 200-mg arm was 24.0 months; however, median DOR was not reached for the 800-mg arm due to many patients continuing to respond to treatment at the time of data cutoff. Based on central review, the median PFS was 13.1 months in the 200-mg group and 11.1 months in the 800-mg group. By the 30-month analysis data cutoff, 11 patients in the mBCC group had died [33]. The efficacy data are summarized in Table 13.2.

In addition to systemic sonidegib, its topical formulation was evaluated in a double-blind, randomized, vehicle-controlled study. Eight basal cell nevus syndrome patients with a total of 27 BCCs were treated twice daily with 0.75% sonidegib topical cream or with the vehicle, for a total duration of 4 weeks. In the treatment group, three BCCs demonstrated CR, nine BCCs demonstrated PR, and only one BCC demonstrated no clinical response, as opposed to only one BCC demonstrating PR in the vehicle control group [34]. Although its topical application was well tolerated, trials with larger sample sizes failed to reproduce the same efficacy, perhaps due to limited drug penetration over the skin barrier.

## Safety and Tolerability

Similar to that reported for vismodegib, the most common adverse events seen in the BOLT trials include muscle spasm, alopecia, dysgeusia, nausea, elevated blood creatinine kinase, and fatigue. These adverse events were more frequently reported in the 800-mg treatment arm than the 200-mg arm. In the primary efficacy analysis, elevated creatine kinase concentration was the most frequently reported grade 3–4 adverse event. As of the primary efficacy analysis data cutoff, 3 of 79 patients in the 200-mg arm and 13 of 150 patients in the 800-mg arm had discontinued the treatment due to muscle spasm. Rhabdomyolysis was the most frequently reported serious adverse event and was seen in 14% of patients in the 200-mg arm and 30% of patients in the 800-mg arm. These rhabdomyolysis cases failed to meet the criteria set forth by the independent safety review committee of muscle toxicity, which were a 10-fold increase in creatine kinase concentration from baseline and a 1.5-fold increase in serum creatinine concentration from baseline. The safety profile of sonidegib in the 12-month and 30-month follow-up data remained consistent with what was previously reported in the primary efficacy analysis. By the 30-month data cutoff, eight patients had died while receiving treatment, including four with laBCC

(one patient in the 200-mg group and three in the 800-mg group) and four with mBCC (all in the 800-mg group). None of the deaths was thought to be related to sonidegib [33].

## Administration and Precautions

Sonidegib, with the brand name Odomzo, has a recommended dose of 200 mg taken orally once daily until disease progression or unacceptable toxicity. Sonidegib comes as 200-mg opaque pink-colored capsules. Because sonidegib is metabolized by hepatic enzyme CYP3A, drug interaction with CYP3A inhibitors can potentially increase the risk of further muscle toxicity; therefore, concomitant administration of sonidegib and strong CYP3A inhibitors should be avoided. Also, moderate or strong CYP3A inducers might increase metabolism of sonidegib and therefore decrease the efficacy of this medication [35].

Similar to vismodegib that inhibits the Hedgehog signaling pathway, sonidegib can cause embryo-fetal death or severe birth defects when given to pregnant women. Females of childbearing potential should use effective contraception during treatment and for at least 20 months after the final dose. Because of the potential risk of exposure through semen, male patients, while on treatment with sonidegib and for at least 8 months after the final dose, should wear condoms during sexual intercourse with someone who is either pregnant or has childbearing potential.

## Post-trial Concerns and Present Challenges

Acquired resistance, as first demonstrated in nude mice implanted with medulloblastoma, is a major concern for HPI [27]. Hedgehog pathway reactivation was confirmed by molecular tumor biopsied in patients who developed acquired resistance to vismodegib [36]. This reactivation is mainly caused by SMO mutations and less so by a gain-of-function mutation in Gli2 as well as a loss-of-function mutation in suppressor of fused, which negatively regulates the Hedgehog pathway. In a case report of a 68-year-old woman who experienced complete regression of her laBCC after 16 weeks of vismodegib before developing recurrent tumors around the primary site after 20 weeks, distinct novel heterozygous missense SMO mutations were identified that were not previously noted in pretreatment tumor tissue [37].

In a retrospective review of patients treated with vismodegib, 21% of the patients (6/28) demonstrated tumor regrowth while on treatment [38]. Similarly, treatment resistance with vismodegib was also noted in patients with basal cell nevus syndrome [39]. In an investigator-initiated open-label trial of sonidegib for the treatment of nine advanced BCC patients who were resistant to vismodegib, five patients experienced PD with sonidegib, and three patients experienced stable disease before stopping sonidegib, due to either an adverse event ($n = 1$) or the pursuit of surgical

intervention ($n$ = 2) [40]. However, this study was limited by the relatively short duration of treatment, as only one of nine patients received treatment with the second HPI agent beyond 14 weeks, and some were treated for only 3 weeks. Therefore, the short duration of sonidegib exposure may not have been adequate to confer a detectable clinical response. Besides, the only patient who received treatment beyond 14 weeks (58 weeks) had an identifiable mutation on D473H and later developed disease progression. Data performed with [3]H-cyclopamine competition binding assays showing affinity (pKi) of vismodegib (GDC0449) and sonidegib (NVP-LDE225) for SMO both demonstrated a significant drop from 8.32 to 5.95 (>100 fold) and 7.68 to 6.91, respectively, in the setting of SMO D473A mutations compared to wild type [41]. On the other hand, if the mutation occurs at residue E518A, the affinity for vismodegib (GDC0449) decreases from 8.32 to 6.68 and increases slightly for sonidegib (NVP-LDE225). In other words, if a patient develops resistance to vismodegib due to a mutation at E518, they may still respond to treatment with sonidegib, based on the findings above [42]. Another SMO antagonist, LY29040680, has been shown to be unaffected by a mutation at residue D473, with an affinity of 7.62 versus 7.51 in the wild type, although LY29040680 and vismodegib share 14 contact residues [41]. Based on the recently solved crystal structure of the SMO transmembrane protein, the computational docking of vismodegib onto the SMO structure revealed that the mutations SMO-W281, SMO-V321, SMO-I408, and SMO-C469 are located in close proximity to the drug-binding pocket [36, 43]. These mutations disrupt the binding of vismodegib by interfering with the hydrophobic pocket and changing the conformations of the residues, thus eliciting steric effects on the binding pockets [36]. Patients with acquired resistance to one specific HPI due to mutations in SMO may still respond to a different HPI depending on the binding location, specific mutation/residue affected, and whether a conformational change is triggered to block drug binding in a direct or indirect manner. The above findings, in addition to patient sequencing data, may help predict a patient's treatment response to a new HPI after developing acquired resistance to another.

Another shortcoming of HPIs is the possible development of squamous cell carcinoma (SCC) due to an unclear mechanism. One study reported a 62-year-old patient with BCC on the back with metastasis to a left axillary lymph node who had an initial CR in both her primary BCC lesion and lymph node metastasis after 9 months of vismodegib therapy. Thirteen months later, she developed an SCC in the left axillary node that shared the same PTCH-1 and TP53 mutations as well as 90% of the genomic identity of the original BCC [44]. Furthermore, this particular SCC also carried NOTCH1/2 and KMT2C mutations, which are commonly seen in cutaneous SCC. This finding suggests that the newly developed SCC may have derived from a preexisting BCC through selective squamatization no longer suppressed by vismodegib. A single institution case-control study investigating the risk of developing non-BCC malignancy after HPI exposure found a hazard ratio of 8.12 for the development of cutaneous SCC in the vismodegib-exposure group [45]. Interestingly, patients in the vismodegib group typically were screened more frequently than the control group because they were either enrolled in clinical trials

that required multiple study visits or they were being monitored closely for vismodegib-associated side effects. A previous study suggested that cancer screening alone was associated with an increase in the incidence of non-melanoma skin cancers [46]. In a retrospective study comparing the risk of cutaneous SCC development in patients treated with vismodegib as part of phase I and phase II clinical studies versus patients who received standard therapy for primary BCC, no association between vismodegib and an increased risk of subsequent SCC development was observed. Rather, elevated cutaneous SCC risk in patients treated with vismodegib is most likely a result of more frequent screening in the setting of patients having cumulative ultraviolet exposure [47].

## Management of HPI-Associated Adverse Events

Proper management of HPI-associated adverse effects such as muscle spasm, dysgeusia, and alopecia may prolong treatment duration so that the maximum benefit of the HPI can be achieved. To reduce the risk and severity of muscle spasm during HPI therapy, patients should be advised to keep hydrated and limit physical activity [48]. Amlodipine, a calcium channel blocker, was shown to be effective in reducing vismodegib-induced muscle cramps when given for a 2-week period at 10 mg [49]. Quinine at a dose of 200 mg also demonstrated some benefit to reduce symptoms of muscle spasm [48]. The use of levocarnitine in alleviating HPI-associated muscle spasm has been investigated, with results pending [50]. When adverse effects of HPI treatment become intolerable, treatment breaks can be helpful. Exploratory analysis from the STEVIE trial showed an increase in treatment median duration corresponding with an increase in the number of treatment breaks, with no effect on the overall efficacy of vismodegib [51]. Muscle spasms generally resolve 4–8 weeks after HPI discontinuation. Alopecia may take 6–12 months to resolve, and treatment options include 2%–5% minoxidil topical that can be used in addition to concealment measures such as wearing a wig [48, 52]. However, a longer duration of vismodegib treatment and an increased degree of treatment-related alopecia can lead to permanent impairment in hair growth even after treatment completion [53]. For dysgeusia, finding the types of food that are more pleasant for the patient as well as dietician referral can be helpful, as it is only temporary and typically resolves 2–6 months after stopping vismodegib. When the patient is able to maintain treatment, HPI therapy can result in dramatic improvement (Fig. 13.3).

## Neoadjuvant Use of HPIs

Neoadjuvant use of vismodegib was investigated in an open-label, three-cohort, nonrandomized phase II study to evaluate the rate and durability of complete histologic clearance of operable nodular BCC in patients who were given vismodegib

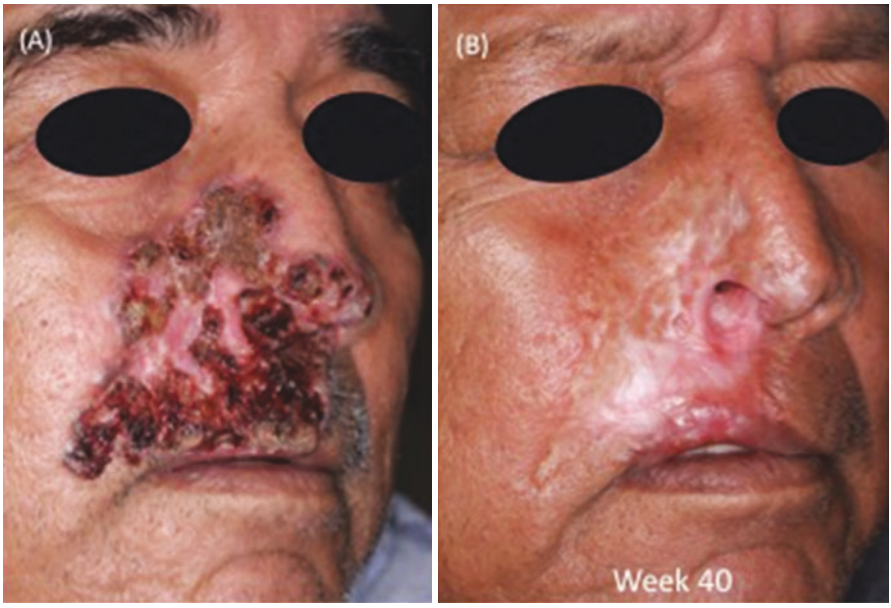


**Fig. 13.3** (**a**) A 62-year-old Hispanic male patient with locally advanced basal cell carcinoma involving the medial cheek, distal nose, and the upper lip prior to initiation of HPI therapy with vismodegib at 150 mg daily. (**b**) Apparent tumor resolution with residual scarring at week 40 of the vismodegib treatment. (Reproduced with permission [62])

prior to Mohs micrographic surgery. All three cohorts from this phase II trial did not meet the primary efficacy endpoints despite other smaller studies that reported tumor size reduction with concurrent vismodegib therapy [54–57].

## Other HPIs

Itraconazole is an FDA-approved oral antifungal drug that also inhibits the Hedgehog signaling pathway by preventing the ciliary accumulation of SMO [58]. In an open-label, exploratory phase II trial of oral itraconazole for the treatment of BCC, two cohorts consisted of patients who received oral itraconazole 200 mg twice daily for 1 month (Cohort A) and patients who received 100 mg twice daily for an average of 2.3 months (Cohort B). The primary endpoint was measuring the change in level of Ki67 tumor proliferation biomarker and that of Hedgehog pathway activity in Cohort A only. Of a total of 29 enrolled patients, 19 were treated with itraconazole. Itraconazole was found to reduce cell proliferation by 45% in vismodegib-naïve patients, reduce Hedgehog pathway activity (measured as GLI1 mRNA level) by 65%, and reduce tumor area (longest perpendicular diameters) by 24%. Of eight patients with multiple BCCs, four patients achieved PR, while the

other four had stable disease. Tumors from an untreated control group had no significant tumor reduction or change in proliferation activity. Two patients discontinued the study due to adverse events: grade 2 fatigue and grade 4 congestive heart failure [59].

Taladegib (LY2940680) is another SMO inhibitor that was previously shown to inhibit the activity of vismodegib-resistant SMO mutant at D473H as it binds to the extracellular end of the transmembrane helix bundle of SMO. This medication has potential to overcome SMO mutation seen in patients treated with vismodegib or sonidegib [60].

## Conclusion

HPIs have shown promise as a treatment option for patients with laBCC and mBCC who are poor candidates for surgical intervention or radiotherapy. Futures studies are likely to shed light on ways to overcome acquired resistance to HPIs. Dosing regimen adjustment with potential treatment holidays may prolong treatment duration in patients who experience HPI-related toxicity. The idea of combining HPIs with other agents is currently being investigated in a wide variety of human tumors. The approval of vismodegib and sonidegib has offered a targeted therapeutic option for those advanced BCC patients with unmet medical needs.

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# Chapter 14
# Immunotherapy for Basal Cell Carcinoma


**Leon Chen, Sirunya Silapunt, and Michael R. Migden**

## Introduction

Non-melanoma skin cancer (NMSC) is the most common cancer diagnosis in the United States. Approximately 3.3 million people are diagnosed with a total of 5.4 million NSMCs annually [1]. Basal cell carcinoma (BCC) is the most common type of NMSC; however, cancer registries do not collect information on BCC, and thus the data regarding its prevalence and true incidence are not obtainable. Previous population-based studies estimated the age-standardized annual incidence of BCC in both Caucasian men and women to be 146–422 cases per 100,000 people [2, 3]. BCC is largely a localized neoplasm with an estimated metastatic rate of 0.0028–0.55% [4, 5]. Depending on the histologic subtype, location, size, patient's immune status, and other factors, BCC can be treated with various modalities, including Mohs micrographic surgery, which provides the highest cure rate possible [6, 7]. When BCC becomes locally advanced or metastatic, surgical resection may result in disfigurement and significant morbidity; therefore, an alternative therapeutic approach is needed.

L. Chen
The University of Texas MD Anderson Cancer Center, Department of Dermatology, Houston, TX, USA

University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

S. Silapunt
University of Texas McGovern Medical School at Houston, Department of Dermatology, Houston, TX, USA

M. R. Migden (✉)
The University of Texas MD Anderson Cancer Center, Departments of Dermatology and Head and Neck Surgery, Mohs Surgery Center, Houston, TX, USA
e-mail: mrmigden@mdanderson.org



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_14

In 1957, Burnet postulated the idea of immunosurveillance, in which the immune system could identify and destroy nascent tumor [8]. The role of immunosuppression on NMSC pathogenesis is well documented. A study demonstrated the presence of mononuclear cells encompassing tumor nests of NMSC, which may facilitate regulation of tumor proliferation [9]. As a result of immunosuppressive therapies, the incidence of BCC increases roughly tenfold after organ transplantation [10]. In addition, ultraviolet radiation, which is a known risk factor for BCC, is proven to cause dose-dependent suppression of cellular immunity and interfere with proper immunosurveillance [11, 12]. Human tumors can bypass immunosurveillance by activating immune system regulatory checkpoint molecules; accordingly, checkpoint inhibitors such as programmed cell death-1 (PD-1) inhibitor have emerged as an effective agent against many types of cancer. Furthermore, NMSCs, including BCCs, express tumor-associated antigens that elicit tumor-specific response, making them excellent candidates for immunotherapy. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a T-cell receptor protein that prevents T-cell activation when bound to B7, a co-stimulatory protein receptor. Owing to the recent success of immunotherapy on metastatic melanoma and other cancer types, this treatment modality has been offered to patients with advanced BCC, which includes both locally advanced BCC and metastatic BCC. Currently, several ongoing trials are investigating the efficacy of various immunotherapy agents against advanced BCC. In this chapter, we will discuss two main classes of immunotherapeutic agents—PD-1 inhibitor and CTLA-4 inhibitor—for the treatment of advanced BCC.

## PD-1 Inhibitor

### *Background and Mechanism of Action*

The PD-1 gene was first isolated in 1992 with the subtractive hybridization technique. The researchers found that the expression of the PD-1 mRNA in mice was confined to the thymus, and its level became elevated after anti-CD3 antibody was purposely injected into the mice to induce thymocyte death [13]. In 1999, the B7 homolog that is now commonly referred to as programmed death ligand-1 (PD-L1) was identified as an inhibitor of human T-cell response in vitro [14]. Later, it became evident that the PD-1/PD-L1 interaction plays a critical role in the suppression of T-cell responses in the tumor microenvironment [15]. PD-1 is a checkpoint molecule that is highly expressed on T cells in the tumor microenvironment. When PD-1 is stimulated, the cascade leads to the activation of apoptosis in antigen-recognizing T cells as well as the suppression of apoptosis in regulatory T cells. PD-L1, a ligand for PD-1 receptor, is expressed on the surface of tumor cells. This interaction between PD-1 and PD-L1 then induces T-cell suppression (Fig. 14.1) [16]. Compared to standard chemotherapy where a specific molecule is being targeted, immunotherapy activates an antitumor immune response that targets a wide range of cancer types, including their tumor-specific mutant antigens, thus providing a more durable response [17].

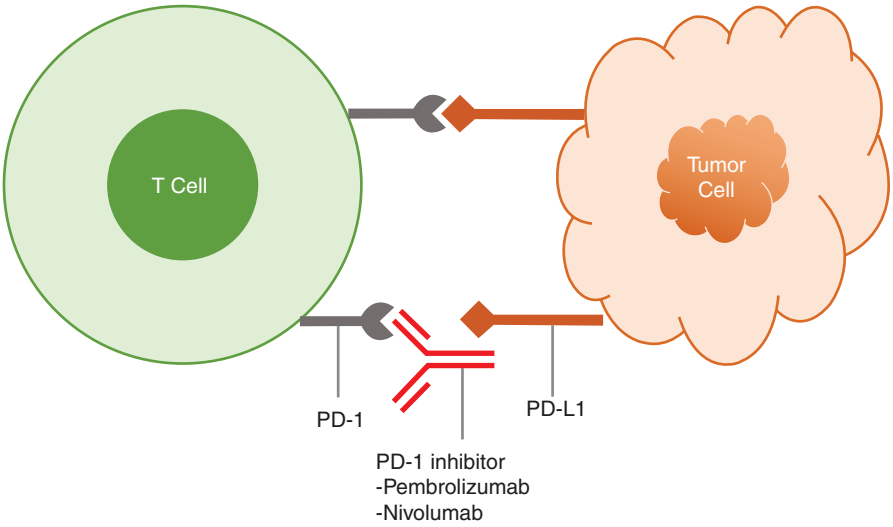


**Fig. 14.1** Simplified schematic drawing demonstrating the interaction between a tumor cell and T cell. Binding of PD-1 and PD-L1 results in the inhibition of the body's immune response to fight tumor cells. A PD-1 inhibitor binds to PD-1 and thus prevents binding of PD-L1, resulting in less T-cell inhibition and activation of an immune response

## *Nivolumab*

Nivolumab (Opdivo; Bristol Myers Squibb, Princeton, NJ) is a fully human PD-1 inhibitor that was developed as a strategy for cancer immunotherapy. In animal models, PD-1 knockout mice demonstrated late-onset strain and organ-specific lethality as opposed to early lethality that was seen in CTLA-4 knockout mice [18, 19]. This led, in 2006, to a phase I clinical trial of nivolumab (MDX-1106) in the United States for the treatment of advanced metastatic melanoma, colorectal cancer, castrate-resistant prostate cancer, non-small cell lung cancer (NSCLC), and renal cell carcinoma patients. Only 1 of 39 patients with metastatic ocular melanoma developed a serious adverse event (grade 3 inflammatory colitis) after five doses of treatment at 1 mg/kg. The most frequent treatment-related toxicity was a decrease in CD4+ lymphocyte count (14 patients, 35.9%). Overall, this PD-1 inhibitor was well tolerated and demonstrated evidence of antitumor activity [20].

In December 2014, nivolumab was approved for the treatment of metastatic melanoma. Subsequently, in 2015, it was also approved for patients with head and neck recurrent or metastatic oral mucosal squamous cell carcinoma with disease progression on or after platinum-based therapy. As of late 2017, nivolumab has additional US Food and Drug Administration (FDA) approval for

the treatment of renal cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer, and hepatocellular carcinoma. Nivolumab is also indicated for pediatric patients who are 12 years of age and older with MSI-H or dMMR metastatic colorectal cancer. Depending on the cancer type, nivolumab is given either at a dosage of 240 mg IV every 2 weeks or 3 mg/kg IV every 2 weeks. The most common adverse reactions in patients treated with nivolumab as a single agent included fatigue, rash, musculoskeletal pain, pruritus, and diarrhea [21]. Reports of various immune-mediated adverse events have included pneumonitis in 3.1% of patients, colitis in 2.9% of patients, hepatitis in 1.8% of patients, nephritis in 1.2% of patients, and hypophysitis in 0.6% of patients. Since nivolumab is infused intravenously, infusion reactions have been reported in 6.4% of patients in the clinical trials [21]. Based on the reported clinical data and concerns that persistent PD-1 inhibition might overstimulate alloreactive T cells, the FDA issued a new Warning and Precaution in the package insert (PI) for the potential development of severe immunologic complications, such as graft-versus-host disease in allogeneic hematopoietic stem cell transplant (HSCT) patients. A total of 17 patients underwent allogeneic HSCT after nivolumab, and 6 patients died from complications thought to be transplant related. However, these retrospective data are limited and did not account for patients' heterogeneous immunosuppressive regimens [22, 23]. In animal reproduction studies, administration of nivolumab to monkeys from the onset of organogenesis resulted in a higher abortion rate as well as premature infant death. For this reason, the PI indicated that females with childbearing potential should be advised to use effective contraception during treatment and for at least 5 months after the last dose of nivolumab [21].

The most common laboratory abnormalities seen in various trials include anemia, neutropenia, thrombocytopenia, lymphopenia, elevated aspartate aminotransferase, elevated alanine aminotransferase, elevated alkaline phosphatase, and hyponatremia. In two randomized, open-label, multicenter trials for the safety evaluation of patients ($n$ = 418) with NSCLC who were treated with nivolumab, seven deaths were caused by infection, four deaths were caused by pulmonary embolism, and one death was caused by limbic encephalitis. In the safety evaluation study of patients ($n$ = 266) with classical Hodgkin lymphoma who were treated with nivolumab, 11 patients died from causes other than disease progression [21].

Although not yet approved, PD-1 inhibitors such as nivolumab have been used off-label to treat advanced BCC. The first patient with metastatic BCC treated with nivolumab was described in 2016. This 58-year-old male patient had a recurrent BCC on the left posterior shoulder that metastasized to his axial skeleton, lungs, and liver. The patient developed metastasis to the right frontal lobe despite taking vismodegib. After undergoing stereotactic radiosurgery to the right frontal lobe lesion, the patient was initiated on chemotherapy

with cisplatin and paclitaxel. This regimen was discontinued after four cycles because he could not tolerate it, and his positron emission tomography/computed tomography (PET/CT) scan showed disease progression in his skeleton and liver. Subsequently, he was enrolled in a clinical trial with sonidegib combined with buparlisib (a pan-class I PIK3 inhibitor) and later switched to paclitaxel and vismodegib. Unfortunately, this therapy was discontinued due to lack of response. After exhausting available therapeutic options, he was started on nivolumab 240 mg intravenously every 2 weeks. His hepatic lesions responded within 2 months and were almost completely resolved per CT scan at 4 months. His mood and appetite improved as well [24].

Another case that was published around the same time described a 61-year-old female patient with BCC located at the left shoulder and axilla. The tumor infiltrated the chest muscle and bone and later spread to her lung. The patient had failed surgery and radiotherapy and could not tolerate vismodegib. She was then treated with paclitaxel combined with carboplatin and subsequently underwent left upper extremity amputation. Tumor pathology demonstrated invasive basosquamous carcinoma. The patient received four doses of nivolumab infusion, and her CT scan performed 3 months after immunotherapy initiation showed three pulmonary metastatic lesions that were stable in size and one that had decreased in size. Unfortunately, the patient died from acute bacterial pneumonia and adhesion-related postoperative ileus before the therapeutic response could be further assessed [25]. Currently, a phase II registered clinical trial to assess the overall response rate of patients with refractory T-cell and natural-killer cell lymphoma as well as various types of skin cancers, including BCC, is recruiting study patients (NCT02978625).

## *Pembrolizumab*

Pembrolizumab (Keytruda; Merck Inc., Kenilworth, NJ) is a humanized PD-1 blocking antibody first approved by the FDA in September 2014 for patients with ipilimumab (an anti-CTLA-4 antibody) refractory melanoma or patients with advanced melanoma who are carriers for BRAF proto-oncogene and who failed combination treatment with ipilimumab and a BRAF inhibitor. In late 2017, pembrolizumab was granted accelerated approval for NSCLC that meets certain criteria, recurrent or metastatic mucosal squamous cell carcinoma of the head and neck, classical Hodgkin lymphoma, urothelial carcinoma, MSI-H cancer, and gastric cancer. Pembrolizumab is typically administrated at a dosage of 200 mg every 3 weeks for adult patients and 2 mg/kg (up to 200 mg) every 3 weeks for pediatric patients. Pembrolizumab is indicated for pediatric patients with classical Hodgkin lymphoma and MSI-H cancer. The most common adverse reactions reported in a cohort study of 174 patients who received pembrolizumab

for the treatment of oral mucosal squamous cell carcinoma were fatigue, hypothyroidism, rash, decreased appetite, and dyspnea [26]. These adverse events were similar to those seen in the use of pembrolizumab for the treatment of melanoma or NSCLC. Similar to nivolumab, immune-mediated side effects, such as pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis, have been well documented. The most frequent serious adverse reactions include pneumonitis, dyspnea, confusion, vomiting, pleural effusion, and respiratory failure [26]. In theory, because human IgG4 immunoglobulins can cross the placenta, pembrolizumab has the potential to be transmitted from mother to fetus and cause potential fetal harm, although human data regarding the risk of embryo-fetal toxicity are lacking. Females with childbearing potential should be advised to use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose [21].

In November 2014, a 62-year-old female patient with metastatic BCC was treated with an unknown dose of pembrolizumab after failing vismodegib. After four cycles of treatment, her pulmonary lesions had increased in size before becoming stable. She had enlargement of her mediastinal lymph nodes, thought to be a sarcoid-like lymph node reaction secondary to immunotherapy [27]. Approximately 1 year later, in December 2015, a 67-year-old woman with metastatic BCC was given pembrolizumab at 2 mg/kg intravenously every 3 weeks after failing multiple therapeutic options, including Hedgehog pathway inhibitor, MEK inhibitor, and IGF-1R inhibitor. CT scans performed 4 months into her treatment showed a partial response that persisted 14 months into therapy. The patient was found to have subclinical hypothyroidism, likely induced by immunotherapy [28]. Reported cases of BCC treated with PD-1 inhibitor are summarized in Table 14.1. Currently, two registered clinical trials are investigating the efficacy of pembrolizumab in patients with difficult-to-treat BCC (Table 14.2).

One potential drawback of anti-PD-1 immunotherapy is the possibility of developing acquired resistance after treatment initiation. Approximately 25% of melanoma patients who had an objective response to PD-1 inhibitor subsequently stopped responding to the treatment and had disease progression [29]. During the active response to pembrolizumab in patients with metastatic melanoma, abundant intra-tumoral CD8+ T cells were found. Although these intra-tumoral CD8+ T cells were still present at the time of relapse, they were restricted to the tumor margin and no longer exerted cytotoxic effects on these tumor cells. When whole exome, next-generation sequencing of biopsy samples of paired baseline and relapsing lesions was performed, loss-of-function mutation within the genes encoding Janus kinase 1 or 2 (JAK1 or JAK2) were identified in two of four patients. JAK1 and JAK2 are critical intracellular signaling molecules that, when mutated, reduce the sensitivity of T cells to interferons. In addition, a mutation in the gene encoding beta-2-microglobulin—the protein product responsible for folding and MHC class I molecule transport—was also discovered. Thus, both insensitivity to interferons and MHC class I deficiency may play a role in anti-PD-1 resistance [30].

**Table 14.1** Reported cases of basal cell carcinoma treated with PD-1 inhibitor and CTLA-4 inhibitor

| Author, year | Age (years), sex | Risk factors | Tumor type and site(s) | Treatment history | Immunotherapy regimen | Response | Side effects/remarks |
|---|---|---|---|---|---|---|---|
| PD-1 inhibitor | | | | | | | |
| Lipson et al. [28] | 67, F | n/a | *BCC*, right posterior neck<br>Lung metastasis | WLE followed by adjuvant electron radiotherapy<br>Saridegib<br>AZD6244 (MEK inhibitor)<br>IMC-2A12 (a fully human IgG1 monoclonal antibody directed against insulin-like growth factor-1 receptor (IGF-1) | Pembrolizumab (PD-1 inhibitor) at 2 mg/kg IV every 3 weeks | Partial response per RECIST 1.1 and PR ongoing at month 14 | Subclinical hypothyroidism |
| Ikeda et al. [24] | 58, M | Frequent tanning salon visits | Recurrent *BCC* on the left posterior shoulder<br>Metastatic disease involving the axial skeleton, lungs, liver, and brain | Radiation<br>Vismodegib<br>Stereotactic radiosurgery to the right frontal lobe lesion<br>Four cycles of cisplatin and paclitaxel<br>Clinical trial with sonidegib combined with buparlisib | Nivolumab (PD-1 inhibitor) 240 mg intravenously every 2 weeks | Two months after nivolumab, CT scans demonstrated a marked decrease in size of the liver lesions 4 months after starting nivolumab, CT scans demonstrated near complete resolution in the hepatic lesions | n/a |
| Falchook et al. [40] | 66, F | n/a | Recurrent desmoplastic *BCC* on the left chin<br>Invasion into the left mandible<br>Lymph node metastasis (1/18)<br>Lung metastasis | Mohs surgery<br>Adjuvant radiation<br>Vismodegib | REGN2810 (PD-1 inhibitor) at 10 mg/kg IV every 2 weeks | Reduction in target lesion measurements of 37% at 24 weeks and confirmed at 32 weeks; partial response maintained 12+ months | Phase 1 study of REGN2810 |

(continued)

**Table 14.1** (continued)

| Author, year | Age (years), sex | Risk factors | Tumor type and site(s) | Treatment history | Immunotherapy regimen | Response | Side effects/remarks |
|---|---|---|---|---|---|---|---|
| Winkler et al. [27] | 72, F | Postnatal radiation of a hemangioma on the right back | *BCC* on the right flank<br>Lung metastasis | Vismodegib | Pembrolizumab (PD-1 inhibitor); no dosing regimen available | After four cycles of pembrolizumab, imaging revealed stable lung lesions without any further therapy | n/a |
| Borradori et al. [25] | 61, F | Liver transplant and polycythemia vera | *Basosquamous carcinoma* of left shoulder and axilla with infiltration of chest muscles and bones<br>Lung metastases | Surgeries (including amputation of the left arm)<br>Radiation<br>Vismodegib<br>Paclitaxel | Nivolumab (PD-1 inhibitor) at 3 mg/kg IV every 2 weeks; total of four cycles in 10 weeks | Stable disease of lung metastasis with progression-free survival of 5.5 months | Fatigue; patient passed from acute bacterial pneumonia and adhesion-related postoperative ileus 5.5 months after the treatment |
| CTLA-4 inhibitor | | | | | | | |
| Mohan et al. [38] | 60, M | n/a | Locally advanced *BCC* around the left external auditory meatus with infiltration of 7th CN, parotid gland, masseter muscle, and left pterygoid bone | Vismodegib | Ipilimumab (CTLA-4 inhibitor) at 3 mg/kg every 3 weeks for concurrent melanoma (vismodegib discontinued) | Advanced BCC had decreased in size from 9 cm × 8 cm to 5 cm × 7 cm after 8 weeks of ipilimumab. | Patient deceased from metastatic melanoma |

**Table 14.2** Registered clinical trials investigating PD-1 inhibitor on basal cell carcinoma

| Study title | NCT identifier | Phase | Status | Study design and treatment arms | Primary outcome measures |
|---|---|---|---|---|---|
| PD-1 in Patients with Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy | NCT03132636 | Phase 2 | Currently recruiting participants | Non-randomized, parallel assignment<br>Experimental: Group 1—metastatic BCC. Administration of REGN2810 in accordance with protocol dosing regimen<br>Experimental: Group 2—unresectable locally advanced BCC. Administration of REGN2810 in accordance with protocol dosing regimen | I. Overall response rate (ORR) for metastatic basal cell carcinoma (BCC) [time frame: baseline to 93 weeks]<br>ORR for metastatic BCC measured by RECIST version 1.1<br>II. ORR for unresectable locally advanced BCC [time frame: baseline to 93 weeks]<br>ORR for unresectable locally advanced BCC measured by composite response criteria |
| Pembrolizumab with or Without Vismodegib in Treating Metastatic or Unresectable Basal Cell Skin Cancer | NCT02690948 | Phase1b | Currently recruiting participants | Non-randomized, parallel assignment<br>Experimental: Arm I (pembrolizumab)<br>Patients experiencing disease progression during previous treatment with vismodegib receive pembrolizumab IV over 30 minutes on day 1. Courses every 21 days for 24 months in the absence of disease progression or unacceptable toxicity.<br>Experimental: Arm II (pembrolizumab, vismodegib)<br>Patients achieving partial response or stable disease during previous treatment with vismodegib may continue to receive vismodegib PO on days 1–21 per standard of care and pembrolizumab IV over 30 minutes on day 1. Courses repeat every 21 days for 24 months in the absence of disease progression or unacceptable toxicity | I. Determine the overall response rate (ORR) of unresectable or metastatic basal cell carcinoma (BCC) patients to pembrolizumab monotherapy after disease progression on smoothened inhibitor monotherapy.<br>II. Determine the overall response rate (ORR) of unresectable or metastatic BCC patients to pembrolizumab plus vismodegib after partial response or stable disease on smoothened inhibitor monotherapy |

## Cytotoxic T-Lymphocyte-Associated Antigen 4 Inhibitor

### *Background and Mechanism of Action*

Generally, cytotoxic T cells (CTLs) recognize antigens produced by cancer cells. When the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) receptor binds to the co-stimulatory protein receptor B7, the cytotoxic reaction produced by CTLs is switched off, permitting proliferation of cancer cells [31]. A previous study from more than two decades ago showed that mice deficient in CTLA-4 died from fatal lymphoproliferation, suggesting the immunologic role of CTLA-4 in cancer regulation [32]. Preclinical data also demonstrated antitumor immunity as a result of antibody blockade of CTLA-4 [33]. CTLA-4 was the first immune checkpoint receptor to be targeted for clinical purposes [34].

### *Ipilimumab*

Ipilimumab (Yervoy; Bristol Myers Squibb) is a monoclonal antibody CTLA-4 inhibitor that was approved by the FDA in 2011 for the treatment of unresectable or metastatic melanoma. In a phase I/II trial to determine the safety and pharmacokinetic profile of various dosing of ipilimumab for 88 patients with unresectable stage III or IV melanoma, approximately 86% of patients reported at least one treatment-related adverse event, with grade 1 or 2 fatigue (41%) and rash (40%) being the most common. Fourteen percent of study patients had a severe (grade 3 or 4) immune-related adverse event, with diarrhea and colitis being the most common. Ten percent of patients reported serious treatment-related adverse events. Of patients who had negative baseline antinuclear antibody (ANA), 29.5% were found to have ANA positivity during the study; however, no association between ANA status and toxicity was noted. Two patients died during the study, and both events were thought to be unrelated to the study drug. The half-life of ipilimumab was 359 hours [35]. A subsequent phase III trial in patients with advanced melanoma showed improvement in overall survival. In one phase III study of 676 patients with unresectable stage III or IV melanoma, the median overall survival of patients who received both ipilimumab and gp100 vaccination was 10.0 months and 10.1 months for patients who received ipilimumab alone, as opposed to 6.4 months for patients who received only the gp100 vaccine. Grade 3 or 4 immune-related adverse events were reported in 10%–15% of patients treated with ipilimumab and in 3% of patients treated with gp100 alone. Fourteen deaths (2.1%) were thought to be related to the study drug, and half of these deaths ($n = 7$) were thought to be caused by immune-related adverse events [36]. In 2015, a pooled analysis was published of overall survival data of 1861 patients with advanced melanoma from ten prospective studies (including two phase III trials) and two retrospective studies of ipilimumab. In 1861 patients, the median overall survival was 11.4 months, and 254 patients survived

at least 3 years. The authors also noted a plateau in the survival curve that began around year 3. This study further supports the durability of long-term survival in advanced melanoma patients treated with ipilimumab [37]. Currently, the recommended dosing for unresectable or metastatic melanoma is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four doses. For adjuvant melanoma therapy, the recommended dosing is 10 mg/kg every 3 weeks for four doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until disease recurrence or intolerable toxicity. Females of reproductive potential should use effective contraception during treatment with ipilimumab and for at least 3 months after the last dose of therapy, since animal reproduction studies in cynomolgus monkeys showed higher incidences of abortion, stillbirth, premature delivery, and infant mortality when ipilimumab was administered during pregnancy.

Literature regarding the use of anti-CTLA antibody in BCC is limited. A male patient in his 60s with advanced BCC regressed after incidental exposure to ipilimumab while being treated for concurrent metastatic melanoma. Despite 6 weeks of treatment with ipilimumab, the patient developed new intracranial metastases, and his melanoma grew. Interestingly, his advanced BCC had decreased in size from 9 cm × 8 cm to 5 cm × 7 cm after ipilimumab treatment, with significant granulation tissue replacing the previous BCC ulcer seen in histologic analysis (Table 14.1). Although the patient eventually died from metastatic melanoma, this observation suggests that anti-CTLA-4 may exhibit some activity against BCC [38].

## Discussion

Since immunotherapy has emerged as a therapeutic option for many types of cancer, efforts have been made to identify biomarkers that can predict a patient's treatment response. PD-L1 is an inducible receptor that is highly dynamic, so its expression alone has not been helpful in selecting metastatic melanoma therapy. PD-L1-positive tumor cells are found adjacent to tumor-infiltrating lymphocytes; therefore PD-L1 status may be misrepresented depending on the local tumor environment or the timing at which sampling takes place [39]. One study showed that 22% of patients (9/40) demonstrated PD-L1 expression on BCC tumor cells, and 82% (32/40) of patients demonstrated PD-L1 expression on tumor-infiltrating lymphocytes [28]. If the ongoing clinical trials confirm the efficacy of PD-1 treatment of advanced BCC, future studies will be needed to identify biomarkers that help guide clinical decisions regarding risk assessment, patient selection, staging/grading of disease, and disease progression, as well as current disease monitoring.

Another area of study focus would be to unravel the mechanism by which resistance develops in PD-1/PD-L1 blockade. Factors that contribute to resistance include lack of PD-L1 expression, insufficient number of tumor-infiltrating lymphocytes, the presence of severely exhausted CD8+ T cells, mutations of beta-2-microglobulin, and mutations of JAK1/JAK2 genes. A precise understanding of the resistance to checkpoint blockade can aid in the identification of methods to

enhance tumor sensitivity to PD-1 inhibitors, such as the use of radiotherapy to modify tumor microenvironment and convert a lymphocyte-poor tumor into a lymphocyte-rich tumor. It can also aid in the administration of an autologous cancer vaccination that primes a certain immune response with tumor-specific antigens.

## Conclusion

Patients with locally advanced or metastatic BCC, who are not candidates for surgery, continue to have a significant disease burden with limited treatment options available. After the development of Hedgehog pathway inhibitors, immunotherapy, such as PD-1 inhibitors and CTLA-4 inhibitors, has emerged as promising therapies for various types of cancer and is currently being investigated as potential therapeutic options for difficult-to-treat BCC. Future studies are necessary to optimize the treatment response of patients receiving immunotherapy by identifying key biomarkers, finding a solution to overcome treatment resistance, and exploring possibilities of combination therapy.

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# Chapter 15
# Treatment: Future Directions


**Egle Ramelyte, Gaetana Restivo, and Reinhard Dummer**

## Current Treatments and Future Directions

Despite having relatively good prognosis [1] in terms of mortality, the tumor growth and treatment-caused morbidity as well as treatment costs provide a reasonable rationale to further look for new treatment modalities or adjustment of existing ones. Several therapeutic options, approved for management of actinic keratoses, might be also used as monotherapy for superficial basal cell carcinomas (BCCs). It can be also used in combination with systemic therapies, in the setting of treatment-resistant solitary or multiple lesions. In this chapter, we discuss therapies currently used in clinical practice, those still in clinical trials and ways to improve them. Moreover, we discuss new putative treatments based on recent findings and preclinical models to test new possible drugs.

## Physical Modalities

### *Photodynamic Therapy (PDT)*

Conventional methyl 5-aminolevulinate (MAL)-PDT and 5-aminolevulinate (ALA)-PDT have been widely used as an effective treatment for actinic keratoses as well as for superficial BCCs. The reported recurrence rate for the BCCs is 9.3%

E. Ramelyte · G. Restivo
University Hospital Zürich, Dermatology Department, Zürich, Switzerland

R. Dummer (✉)
Faculty of Medicine, University of Zürich, Zürich, Switzerland
e-mail: Reinhard.Dummer@usz.ch



M. R. Migden et al. (eds.), *Basal Cell Carcinoma*,
https://doi.org/10.1007/978-3-030-26887-9_15

after 12 months [2] and 22% after 5 years [3], which is relatively high compared to 5-year recurrence rate after surgical excision (4.1%) or Mohs surgery (2.5%) [4]. However, additional PDT could be beneficial in patients undergoing systemic therapy for multiple BCCs, in whom solitary recalcitrant lesions are still observed. A combination of systemic vismodegib and ALA-PDT was evaluated in an open-label pilot study. Five patients with more than five BCCs were included in the study, three of which (19 lesions) have completed the full intervention phase, consisting of 3-month treatment with vismodegib and three ALA-PDT sessions. After 30 days of follow-up, one lesion was still showing clinical evidence of the disease, whereas others showed complete response [5]. A 30-day follow-up might be too short for complete resolution of the lesion, and thus longer follow-up is needed. This combinational therapy, however, could be a possible treatment option for patients with solitary Hedgehog (Hh) inhibitor-resistant lesions.

### *Daylight PDT*

Daylight (DL) PDT is a type of PDT, which uses daylight instead of artificial light sources. In contrast to conventional PDT, patients have to spend less time in the clinic, as it takes up to half an hour between application of photosensitizer (MAL) and initiation of 2-hour daylight exposure [6]. Recently, the daylight (DL)-PDT was shown to be as effective as conventional MAL-PDT and by far better tolerated for treatment of actinic keratosis [7] (pain 0.7 vs 4.4, respectively, $P < 0.001$). In an open, uncontrolled, prospective explorative study, 21 patients with 32 BCCs in total were treated with 2 sessions of DL-PDT. Although the therapy was well tolerated and provided excellent cosmetic results, the recurrence rate reported was higher than that reported with conventional PDT and reached 21% at 12 months. Larger studies are needed to define the role of DL-PDT in context of BCC [8].

## Topical Therapies

### *Ingenol Mebutate*

Ingenol mebutate is a substance found in the sap of the plant *Euphorbia peplus* that has been approved and used for treatment of actinic keratosis [9]. The mechanism of action is not fully clear, but it has been found to induce necrosis of the dysplastic cells as well as stimulate immune responses mediated by neutrophils [10]. A few case reports of BCCs treated with ingenol mebutate have been published [11, 12], all of which reported successful results. Such treatment option might be suitable for small superficial BCCs in aesthetically sensitive areas of the face; however, randomized clinical studies are needed to determine the role of ingenol mebutate in management of BCCs.

### *Intralesional Talimogene Laherparepvec*

Intralesional talimogene laherparepvec (T-VEC), an attenuated herpes virus approved for advanced melanoma, has shown clinical response in Merkel cell carcinoma, a highly mutated UV-induced non-melanoma skin cancer (NMSC) [13]. In a phase I clinical trial of intralesional T-VEC with following systemic anti-PD-1 therapy for metastatic melanoma, T-VEC led to an increase of $CD8^+$ infiltration in injected lesions and, possibly due to increased antigen presentation, contributed to clinical response even in lesions with low initial $CD8^+$ infiltration and PD-L1 expression [14]. A phase II clinical trial (NCT02978625) is currently investigating best overall response rate to T-VEC and, in cases without response, addition of anti-PD-1 antibody nivolumab in NMSC, including BCC (NCT02978625).

### *Topical Hh Inhibitors and Imiquimod*

The efficacy of topical SMO inhibitor LDE225 (sonidegib) was assessed in patients with NBCCS. When compared to the vehicle, 0.75% sonidegib gel reduced expression levels of GLI1, GLI2, and PTCH2 up to 16-fold in majority of the lesions tested and led to complete response in 3 and partial response in 9 lesions, whereas only 1 lesion showed no response [15]. An addition of topical imiquimod could be used to stimulate the immune response in cases of topical sonidegib-resistant cases, especially in patients with multiple comorbidities, when surgical or systemic therapy is contraindicated.

## Systemic Treatment

### *Non-Hh Pathway-Specific Therapies*

#### Immune-Checkpoint Inhibitors

After showing impressive response rates in melanoma and lung cancer, immunotherapy with immune-checkpoint inhibitors (CI) is being investigated in number of other malignancies. Within these, high mutational burden has been associated with clinical benefit from anti-programmed death-1 (anti-PD-1) antibodies [16]. Recently BCC has been reported to have the highest mutational load among cancers [17] which, along with inflammatory infiltrate usually surrounding tumor nests of BCC [18], could be considered good prerequisites for a successful treatment with CI. It is known that PD-L1 expression level has different predictive values among cancers (melanoma, lung, kidney), and it is yet not clear if it is the same in case of BCC.

To date no randomized clinical trials have been initiated, and the currently published case reports show controversial results. A case report of a patient with

metastatic BCC that received nivolumab has shown clinical response of the highly mutated tumor with amplification of PD-L1. However, while on the treatment, the patient developed new lesions, with lower mutation burden and no amplification of PD-L1 [19], thus emphasizing the importance of mutational load and PD-L1 expression. Another case of metastatic BCC with negative IHC staining for PD-L1 showed stable disease under anti-PD-1 antibody REGN2810 [20]. Multiple clinical trials are investigating anti-PD-1 as monotherapy (REGN2810 in NCT02383212, NCT03132636) or in combination to Hh inhibitors (pembrolizumab, NCT02690948).

However, the majority of these treatments are nonspecific, and more therapies, targeting BCC-specific pathways, are needed.

## *Hh Pathway-Specific Therapies*

The canonical hedgehog (Hh) pathway is involved in many aspects of fetal development and is tightly regulated in adult tissues; however it's misregulation is observed in many tumors [21]. Identification of Hh pathway mutations as being the main drivers of human BCC [22, 23] led to development of Hh pathway inhibitors (HhI), which proved to cause clinical response in Hh pathway-dependent tumors and are nowadays widely used in management of BCC or other cancers [24]. HhI include the Food and Drug Administration (FDA)- and the European Medicines Agency (EMA)-approved drugs vismodegib and sonidegib, along with other substances still in clinical trials. Various mechanisms of action have been described. Otsuka et al. reported that upon treatment with HhI, tumor regression is accompanied by a change of the microenvironment, involving influx of cytotoxic T cells ($CD4^+$, $CD8^+$) and alteration of the local chemokine/cytokine network [25]. Here we report some new Hh pathway-targeting drugs under evaluation.

### Hh Pathway Inhibitors Currently in Phase I/II Clinical Trials

A number of new Smoothened (SMO) inhibitors have been developed and showed positive results in solid tumors including BCC or medulloblastoma (Table 15.1).

#### LEQ 506

LEQ 506 is a second-generation SMO antagonist, proven to cause almost complete and sustained inhibition of Gli1 mRNA in medulloblastoma-bearing rats [26]. Phase I clinical trial in patients with solid tumors (including BCC) has been completed (NCT01106508), but the data have not been published yet (NCT01106508).

**Table 15.1** SMO inhibitors currently investigated in clinical trials for BCC [26]

| Compound | Company | Indication incl. BCC | Stage of development | Mechanism of action |
|---|---|---|---|---|
| LEQ 506 | Novartis | Solid tumors<br>Locally advanced or metastatic basal cell carcinoma | Phase I studies | SMO inhibition |
| BMS-833923 (XL139) | Bristol-Myers Squibb | Solid tumors<br>Basal cell nevus syndrome<br>Locally advanced or metastatic basal cell carcinoma | Phase I studies | SMO inhibition |
| LY2940680 | Eli Lilly | Solid tumors<br>Incl. BCC | Phase I study | SMO inhibition |
| TAK-441 | Millennium | Solid tumors<br>Incl. BCC | Phase I study | SMO inhibition |

### BMS-833923 (XL139)

Eighteen patients with advanced or metastatic solid tumors were treated with different concentrations of the drug (30, 60, 120, 240 mg). GLI1 expression was checked prior and after 21 days treatment. Only two patients with nevoid basal cell carcinoma syndrome (NBCCS) were included in the clinical trial with XL139. The drug was overall well tolerated by patients with only grade 2 adverse events. One patient with Gorlin syndrome developed pancreatitis, which resolved after discontinuation of the drug. The drug had caused adverse events, already reported with other SMO inhibitors and considered as on-target, including muscle spasms and dysgeusia [27] (NCT00670189).

### LY2940680

In vitro LY2940680 has been shown to inhibit growth in cell lines containing a mutation in the gene encoding SMO. In vivo, oral administration of LY2940680 to Ptch+/− p53−/− transgenic mice, which spontaneously develop medulloblastoma, significantly improved their survival [28]. In a phase I clinical trial that included 47 la/m BCC patients, LY2940680 treatment resulted in an overall good safety profile, even if a constant pattern of adverse reactions were observed during the therapy including dysgeusia, nausea, muscle spasms, decreased appetite, vomiting, alopecia, and weight decrease. These adverse events are probably caused by on-target effects of hedgehog pathway inhibition in affected tissues or organ systems. Overall, clinical responses were observed in patients that were naïve to Hh pathway inhibitors treatments and those who failed to respond to the treatment with other Hh pathway inhibitors (http://mct.aacrjournals.org/content/14/12_Supplement_2/B32). More advanced clinical studies should be performed, including a larger cohort of BCC patients.

Patidegib (TAK-441)

Patidegib (TAK-441) is a semisynthetic cyclopamine analogue, which inhibits the Hh pathway through binding to SMO. The effect of patidegib gel was evaluated in a double-blinded placebo-controlled, randomized clinical study in patients with Gorlin syndrome. Six months of topical application of patidegib led to reduction of surgically eligible BCCs, accompanied by reduction of GLI1 (NCT02762084). Based on these results, a phase II clinical trial in the setting of sporadic BCCs has been initiated (NCT02828111) [29]; however interim study results are not yet published.

### Hh Pathway Inhibitors in Preclinical Phase

GLI Antagonists (GANTs)

Another approach to block the Hh pathway is the inactivation of the downstream effectors. When Hh binds to PTCH1, SMO is not any longer inhibited, and this results in the nuclear localization of the GLI transcription factors [30]. GLI then activates the transcription of genes involved in Hh pathway feedback (GLI1 and PTCH1) but also genes involved in proliferation, angiogenesis, epithelial to mesenchymal transition, apoptosis, and stem cells renewal [31]. GLI antagonists, GANT-58 and GANT-61, were discovered in 2007 in a screen on HEK cells [32]. In vitro, GANT-61 was more specifically binding GLI1 and two transcription factors and showed a higher inhibitory capacity than GANT-58 in many cancer cell types including neuroblastoma and ovarian cancers [33, 34]. *In vivo* GANT-61 treatment induced tumor regression of xenografts of GLI1-positive prostate cancer cells [32] and of neuroblastoma cells injected in nude mice [33]. No clinical trials are ongoing with this inhibitor in any type of cancer.

## *Other Agents*

### Itraconazole

Itraconazole is a systemic antifungal that inhibits SMO by inhibiting its accumulation in the cilium [35]. In a suspended open-label exploratory phase II clinical trial, response to itraconazole was evaluated in 19 patients with BCC. The treatment regimen of oral itraconazole 200 mg/d for 1 month or 400 mg/d for an average of 2.3 months led to reduction of tumor size by 23%, reduction of tumor proliferation by 45%, and by 65% of Hh pathway activity [36]. In five patients, who experienced relapse after Hh inhibitor therapy, treatment with sequential treatment of oral itraconazole and arsenic trioxide was initiated. Three patients completed all three cycles of treatment. Arsenic trioxide prevents ciliary accumulation and destabilizes

GLI2, inhibiting the Hh pathway in such a manner [37]. Double inhibition of Hh pathway was expected to provide positive results; however despite reduction of *GLI1* messenger RNA by 75%, the best observed overall response was stable disease [38].

## Preclinical Experimental Models for BCC

Unfortunately, as previously described, some of the patients do not benefit from those treatments by failing to exhibit initial response, or developing drug resistance followed by recurrence of the tumor [39]. This is due to different reasons including the reactivation of Hh pathway through mutations and copy number alterations [40, 41] or due to possible activation of other molecular pathways. Indeed the huge variability of morphology, aggressiveness, and response to therapy highly suggests that Hh pathway is not the only one involved.

A recent genomic analysis on a BCC cohort has identified new driver mutations possibly involved in BCC onset and progression [17]. In this study, Bonilla et al. analyzed 293 BCCs: 23 vismodegib-resistant, 11 vismodegib-sensitive, and 259 vismodegib-naïve. They performed a whole exome sequencing (WES) and a RNA sequencing and observed that sporadic BCCs harbor 65 mutations/Mb – the highest rate ever found in tumors. As expected, 85% of BCCs had mutations in Hh pathway, followed by 65% in p53. Additionally, mutations in other possibly putative BCC driver genes, such as *MYCN*, *FBXW7*, *PTPN14*, *LATS1*, *LATS2*, and *PPP6C*, were identified. Interestingly, mutational load in *MYCN*, *PPP6C*, and *PTPN1* was higher in BCCs with high risk of recurrence, compared to those with low recurrence risk. Overall, this work demonstrates that new molecules and pathways (HIPPO, MAPK, PI3K, p53 cell cycle) could be potential target for new therapies to fight aggressive forms of BCC, resistant to conventional therapies.

The molecular analyses and testing of new treatment approaches necessitate appropriate and reliable experimental models. Attempts to create tumor xenografts have been not satisfactory for BCC [42]. Transplanted cells fail to grow in the host, and if they form a lesion, often they do not resemble the parental tumor [43, 44]. The explanation could be that the host response blocks the growth of BCC and that normal keratinocytes present in the mixture of cells could have an inhibitory effect. As an alternative, several genetic mouse models have been developed. As the main mutation in BCC is in the Hh pathway, mice models with genetic deletion of the tumor suppressor *Ptch1* have been created. Several mouse models have been described; the most widely used is with deletion of exons1 and 2 or 6 and 7 at the germline [45, 46]. The homozygous deletion of *Ptch1* results in embryonic lethality, thus only the mice with heterozygous deletion can be used for the experiments. Ultraviolet (UV) or ionizing radiation (IR) exposure is needed to induce BCC-like tumors in those mice. One year after chronic UV exposure, the mice started to develop tumors, but only 20% were BCCs [47], whereas a single dose of 1-4Gy IR radiation, applied at 2 months of age, resulted

**Table 15.2** Genetic mouse models and drug tested

| Compounds | Mouse model+BCC induction | Ref. |
|---|---|---|
| Cyclopamine, CUR61414, α-difluoromethylornithine, tazarotene, celecoxib, sulindac, MF-tricyclic, itraconazole | $Ptch1^{+/-}$ +UV or +IR | [59, 60, 61, 62, 63, 64] |
| CUR61414, itraconazanol, vitamin D3 | $Ptch1^{+/-}$K14-Cre-ER $p53^{fl/fl}$ +IR | [15, 65] |
| Calcitriol | $Ptch^{fl/fl}$ $ERT2^{+/-}$ | [66] |

in trichoblastoma-like tumors 1 year after the exposure. This mouse model was widely used to test drugs (Table 15.2); however a relatively long timespan between exposure and tumorigenesis drove the development of new mouse models. Additional deletion of the *p53* gene in keratinocytes (K14Cre-ET $p53^{fl/fl}$) was found to accelerate carcinogenesis. Deletion of the *p53* gene was induced at the age of 6 months by tamoxifen administration for 3 days, followed by IR exposure, which resulted in development of Gorlin syndrome-like BCCs. Conditional Ptch knockout mice have also been created. A targeting vector was designed to insert loxP sites in different parts of the genes. One of those types of BCC mouse model was obtained crossing the $Ptch1^{flox/flox}$ (deleting the exons 7–9) with Rosa26CreERT2 mice in which tamoxifen treatment led to deletion of *Ptch1* ubiquitously. All of those mice develop BCCs 45 days after tamoxifen injection on the tail and ears, but not on their body [48]. $Ptch1^{flox/flox}$ mice were also bred with mice expressing different types of Cre recombinase under specific skin promoters including $K14Cre^{ERT}$ [49]. Smo mutant mice (SmoM2) have also been described, in which a point mutation (W539L) has been inserted in Smo cDNA sequence, which lead to constitutive activation of the gene [49]. SmoM2 transcription is under a ROSA26 promoter, and the induction of the transcription of the mutant gene is controlled by tamoxifen because of a loxP-flanked stop codon placed between the promoter and the mutated sequence. Also in this model, BCC lesions develop 4 weeks after SmoM2 activation, only at the ears and tail [50]. A study using this mouse model showed that tumor formation can be suppressed by Sox9 depletion in a Wnt-dependent manner [51]. Although these mouse models represent valid experimental models for drug testing, they have important disadvantages: they do not fully recapitulate the human tumor onset and progression, and they fail to mimic the variety of BCC types present in human. In addition, the time to tumor development is relatively long and cost-consuming.

Although studies using adherent two-dimensional (2D) cell monolayers continue to provide valuable information and remain important in cancer research, their role remains limited due to inability to examine physiological interactions between tumor cells and the microenvironment. This interaction, same as for many other cancer types, plays a crucial role in BCC progression [52]. In order to overcome these limitations, new, fast, and reliable methods should be developed. One possi-

bility would be the establishment of in vitro skin equivalent models for BCC. In the last four decades, many researchers have been working on ways to reproduce the human skin by use of human skin cells [53]. The development of methods for human skin equivalents is mostly based on the work of Rheinwald and Green, which provided the possibility of isolating cells from human skin at a large scale [54]. Human skin equivalent models may contribute to a better pathophysiological understanding of skin diseases and moreover could reduce the need for in vivo mouse models. So far, human skin equivalent models have been extensively used to study melanoma tumor progression [55], role of fibroblasts in development of squamous cell carcinoma [56], and the biology of psoriatic disease [57]. Furthermore, human skin substitutes are used for in vitro drug testing [58].

In this light, we hypothesize that human skin equivalents could also be used as study model for BCC. Using this approach, BCC tumor biology could be recapitulated in a more physiological environment and could be used as tool for drug screening. Another option to test drugs and resistance mechanisms would be to establish BCC spheres, possibly in combination with fibroblasts. Tumor spheres are a reliable model to screen anticancer treatment in a more physiological situation [67]. In general, the limitation of these approaches is the difficulty to get good primary cells from BCC, because of the little amount of starting material. The use of mitomycin-treated feeder layer could overcome this problem [68]. Moreover, if the starting material is an aggressive BCC that is expected to have a very high mutational rate [17], the establishment of cells in vitro would be possible. Here we report a first attempt for BCC cell isolation with feeder layer and spheres and skin equivalent production (data not published) (Fig. 15.1).

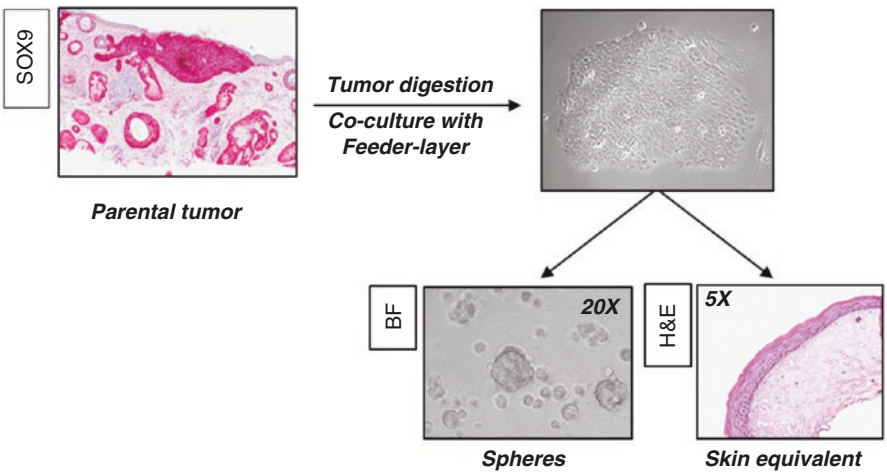


**Fig. 15.1** Test for establishment of BCC in vitro models

## Other Approaches for New Putative Therapy

### *T-Cell Therapy*

Two recent publications [69, 70] have shown that it is possible to activate immune response against melanoma with the use of vaccinations specifically targeting cancer epitopes expressed by the tumor cells. The idea behind this approach is that melanomas are highly mutated tumors, producing many mutated protein products that can be used to activate a cancer-specific immune response. In other words, these cancer-specific epitopes can be used as a basis to produce personalized vaccines. In two phase I clinical trials, small cohorts of patients (6 in the study by Ott et al. and 13 in the study by Sahin et al.) were treated with this approach, and most of them resulted in a complete remission of the disease at 24–36 months follow-up. Patients, who underwent a relapse, were successfully treated with anti PD-1 antibodies. We hypothesize that, due to the high mutational load of BCC, a similar approach could be undertaken as monotherapy or in combination with anti PD-1 therapies, in cases of very aggressive BCC subtypes resistant to conventional Hh pathway inhibitors.

## Conclusion and Outlook

Although most solitary BCCs can be easily treated by surgery or topical treatments, and there are approved systemic therapies for advanced disease, there is still an unmet need for sophisticated treatment options that would enable to overcome resistance and provide high efficacy with low rate of adverse events. Establishment of tissue and animal models that allow to investigate not only the tumor cells but also the microenvironment will first serve for understanding the pathogenesis and then for application of this knowledge for creation and investigation of new treatment modalities of BCC. The future of BCC lies in personalized treatment options, first by identification of driving mutation in the given tumor and then applying mutation-specific therapy. However, treatment combinations of approved immune therapies with topical or systemic Hh inhibitors could be used, while other treatments are being created.

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# Book Description

As a leader in cutaneous oncology and professor at the MD Anderson Cancer Center, senior editor Dr. Migden assembled a panel of authors with considerable expertise to participate in the writing of this book. *Basal Cell Carcinoma: Advances in Treatment and Research* provides the most comprehensive overview of evidence-based treatment approaches for the most common cancer worldwide – basal cell carcinoma. The first part of this book details the epidemiology, risk factors, pathophysiology, and different histologic subtypes of basal cell carcinoma highlighted with high-resolution histopathology images. The second part of the book provides an in-depth review of different treatment modalities including topical therapy, local immunotherapy with interferon, cryotherapy, electrodesiccation and curettage, radiotherapy, and surgical approaches with Mohs micrographic surgery, head and neck surgery, and oculoplastic surgery. The final part of the book highlights the utilization of innovative technology such as photodynamic therapy and laser for the treatment of basal cell carcinoma as well as emerging systemic therapeutic options utilizing hedgehog pathway inhibitors and immunotherapy for the difficult-to-treat disease state, advanced basal cell carcinoma. This book will serve as an informative practical guide for physicians, mid-level providers, and trainees for years to come.



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https://doi.org/10.1007/978-3-030-26887-9

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https://doi.org/10.1007/978-3-030-26887-9