Management of Advanced Basal Cell Carcinoma of the Head and Neck

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KEYWORDS

• Basal cell carcinoma • Management • Surgery • Radiation • Neoadjuvant • PD-1 • Immunotherapy

KEY POINTS

- Management of advanced basal cell carcinoma often requires a multidisciplinary team approach.
- Surgery remains the current standard of care for locally advanced basal cell carcinoma.
- Radiation or systemic therapy may be considered in patients who refuse or are not candidates for surgery.
- Hedgehog inhibitors are targeted agents against BCC, but have less efficacy than surgery or radiation, and should be reserved for patients who are not candidates for these treatments.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common human malignancy. While the exact incidence is unknown, BCC likely affects more than 2 million people in the United States each year.[1] The incidence is increasing despite efforts to mitigate risk factors. Patients with lighter skin tones (Fitzpatrick types I and II) who have significant sun exposures (ultraviolet radiation) account for most BCC cases, and these tumors tend to occur on sun-exposed areas of the head and neck.[2] Other risk factors include exposure to ionizing radiation; immunosuppression; and rarely, genetic syndromes (basal cell nevus syndrome, xeroderma pigmentosum).

Mortality from BCC is rare because most lesions are easily managed with surgical or nonsurgical treatments. However, the cost to patients and society to manage these

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cancers is substantial, given the high incidence.[3] A small subset of patients with BCC develop advanced tumors of the head and neck region that present unique management challenges and often merit a multidisciplinary approach. The focus of this article primarily is on the management of these high-risk cases, reviewing surgical and nonsurgical options to achieve cure wherever possible while minimizing morbidity and maximizing quality of life.

DISCUSSION

Management of Low-Risk Basal Cell Carcinoma

Most BCC are amenable to management with surgical techniques. Curettage with electrodessication is a destructive technique to remove low-risk BCC without assessment of margins. It is highly effective in experienced hands, but should be avoided for deeper lesions approaching subcutaneous fat, and lesions in areas with terminal hair growth (eg, scalp, beard, axilla, groin).[4] Simple excision with primary closure, secondary intention healing, or skin graft is also highly effective. Rotational flaps should be avoided unless frozen section margin clearance is achieved. A clinical margin of 4 mm is recommended to minimize risk of recurrence, and achieves negative margins in more than 95% of low-risk cases, obviating frozen section margin control or Mohs micrographic surgery (MMS) in appropriate cases.[5]

For patients who are not candidates for curettage with electrodessication or excision, a variety of nonsurgical treatments are available. Radiation is usually reserved for those patients older than 60 because of long-term sequalae, but achieves high rates of cure in low-risk cases. Topical therapies, such as imiquimod and 5-FU, although not as effective as surgical treatments, may have superior cosmetic outcomes in selected cases. Other options that may be considered are cryosurgery and photodynamic therapy.[6]

Management of High-Risk Basal Cell Carcinoma

Although most BCCs are considered low-risk and treated with simple excision or other local destructive measures as described previously, high-risk lesions are more likely to require a multidisciplinary approach. Any regionally or distantly metastatic tumor is considered high risk by default. For locally advanced tumors, several clinical and pathologic features are known to increase the risk of morbidity and/or recurrence and have been included in the definition for high-risk BCC contained in the National Comprehensive Cancer Network guidelines.[5] Within this definition, high-risk BCCs are those that include any of the following features: (1) recurrent; (2) poorly defined borders; (3) patient immunosuppression; (4) occurrence in site of prior radiotherapy; (5) demonstration of aggressive growth pattern (infiltrative micronodular, morpheaform, sclerosing, carcinosarcomatous, or basosquamous differentiation in any part of the tumor); (6) perineural invasion; and (7) size greater than or equal to 10 mm on the cheek, forehead, scalp and/or neck, or any in the H areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular, postauricular, temple, ear).

SURGICAL THERAPY

Surgery is the preferred curative treatment of locally advanced BCC.[5] Achieving negative margins is critical to preventing recurrence and associated morbidity and possible mortality. Two main strategies for intraoperative margin assessment are available: MMS and wide excision with intraoperative frozen section of circumferential skin and deep soft tissue margins. MMS is performed by a dermatologist with surgical

and dermatopathology training. The lesion is excised with small margins, in multiple layers if necessary. After each layer of excision, the entire margin of excision is examined in full by the Mohs surgeon to determine the need for further resection. This procedure is most often done in an office setting with local anesthesia. In contrast, in wide local excision the lesion is removed with a margin of normal-appearing tissue, and then the circumferential skin and deep margins are sampled by the surgeon and sent for intraoperative assessment by a pathologist using frozen sections. MMS was compared with wide local excision in a prospective randomized trial in the Netherlands.[7] After 10-year follow-up, the rate of recurrence in patients with high-risk facial BCC was lower in those treated with MMS compared with standard surgical excision, although this finding was only statistically significant for those patient with recurrent high-risk BCC.

Locally advanced BCC of the head and neck often presents unique challenges for surgical resection and reconstruction. Critical structures for function and cosmesis, such as cartilage, bone, cranial nerves, and sensory organs (eye, ear, nose), may be involved with cancer or need to be removed to achieve negative margins. Although MMS is most often used in an outpatient clinic setting under local anesthesia, there have been reports describing the successful use of MMS in the operating room setting under general anesthesia to remove larger/deeper tumors.[8]

Locally advanced tumors involving the skull base often require a multidisciplinary surgical approach. For example, advanced lateral skull base tumors might require a neurotologist to complete a temporal bone resection, a neurosurgeon if there is intracranial involvement, and a head and neck surgeon with capability to complete the reconstruction (**Fig. 1**). If cranial nerves (eg, facial, spinal accessory) are functional preoperatively, then they should be preserved unless gross disease will be left as a result. Similarly, tumors involving the anterior skull base might benefit from the involvement of an oculoplastic surgeon if there is orbital invasion but the eye is functional preoperatively and the goal is orbit preservation. In resections involving dura or brain, a reliable reconstruction, often using free tissue transfer, is important to minimizing postoperative morbidity (eg, meningitis, cerebrospinal fluid leak).[9] In tumors with high-risk features where adjuvant radiation is planned, using well-vascularized tissues for coverage of critical structures (eg, free tissue transfer or pedicled local/regional flaps), is important to prevent wound complications. These resections entail high risk of morbidity to the patient despite maximal reconstructive efforts; however, they may be justified given the likelihood of cure given the relative indolence of the pathology. Radical resections that would not be considered for other cancers because of the low likelihood of survival benefit, might be appropriate for BCC.[10]

Although surgery is the gold standard for the management of high-risk BCC, certain cases may benefit from alternative management strategies discussed later. Morbidity from surgery may be unacceptable to certain patients with locally advanced tumors. Patient preferences for quality and quantity of life must be elicited and respected. Other patients may not be good surgical candidates because of medical comorbidity. Surgery for locally advanced tumors requiring multidisciplinary surgical resection and reconstruction may take many hours with risk of significant blood loss, which may represent unacceptable perioperative risk of morbidity and mortality in some patients. Advanced age alone should not be a contraindication for proceeding with an aggressive surgery and reconstruction; rather careful risk stratification using assessments, such as frailty, should guide decision-making.[11] Thus, management of locally advanced head and neck BCC must be tailored to the individual patient. If surgery is not feasible or acceptable, then radiation or systemic therapy should be considered.

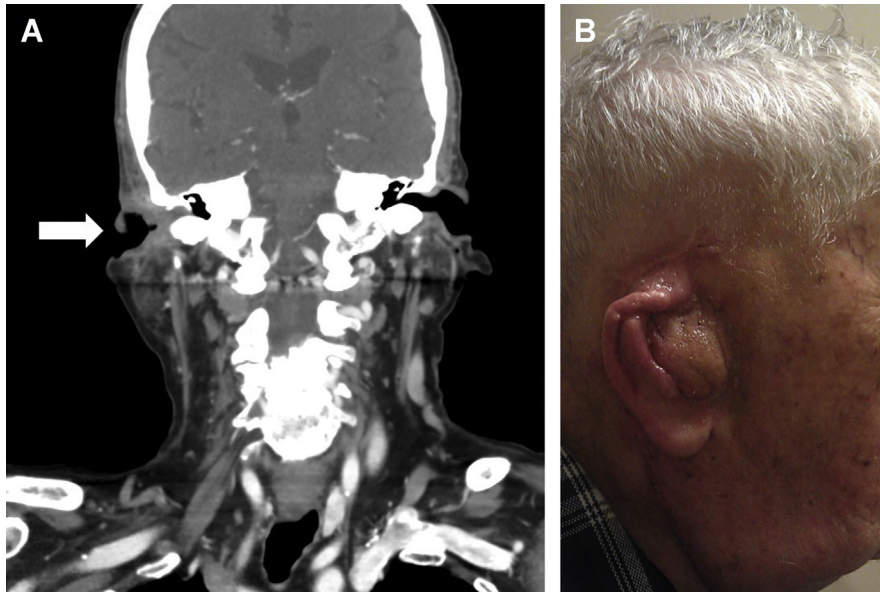

Fig. 1. An 86-year-old man presented with a basal cell cancer of the right ear, involving the conchal bowl and ear canal. He had undergone two previous surgical resections with positive margins at another institution, and subsequently underwent radiation therapy for local recurrence. Three months following the completion of radiation therapy he was noted to have persistent disease involving the ear canal. Imaging was obtained, showing tumor abutting but not invading the temporal bone and no evidence of perineural spread (*A, arrow*). Partial auriculectomy with lateral temporal bone resection was recommended, but the patient opted for therapy with vismodegib. There was no response to treatment, and he agreed to proceed with surgery 5 months later because of worsening ear pain. Surgical resection with submental artery island flap reconstruction was performed and negative frozen section skin and deep soft tissue margins were achieved (B). Final pathology revealed basal cell cancer, morpheaform type, with squamous differentiation. After being lost to follow-up, he returned 3 years later, age 89, with right otalgia and facial paresis. Imaging revealed likely recurrence along the skull base. He declined any further treatments and was alive with disease at last follow-up at age 91.

RADIATION

Primary Radiotherapy

Radiation therapy for advanced BCC of the head and neck is primarily considered when surgical resection is deemed unlikely to be curative, carries unacceptable surgery-related morbidity, or is deemed unsafe because of patient comorbidities and/or advanced age.

In the only randomized controlled trial to date comparing surgery with radiation therapy, surgical therapy demonstrated superior oncologic and cosmetic outcomes.[12] Avril and colleagues[12] compared surgical excision with frozen section margin clearance versus radiation therapy for BCCs of the head and neck less than 4 cm in size. Three radiation techniques were allowed, including interstitial brachytherapy to 65 to 70 Gy; superficial contact therapy with two, 18 to 20 Gy treatments; or conventional radiotherapy to 60 Gy. The primary end point of the study, cure rate at 4 years, was superior in the surgical treatment arm with 0.7% failure compared with 7.5% with radiotherapy. Cosmetic outcome as assessed

by a panel of five judges was also deemed superior with 87% of the surgically treated patients compared with 69% of the radiation-treated patients having a cosmetic outcome rated as good.

Data on radiation therapy control rates for more advanced BCCs are limited to case series. As might be expected, with increasing high-risk features, the effectiveness of primary radiotherapy decreases. In a study of 108 aggressive BCCs of the head and neck (defined as primary lesion >10 mm, >2 recurrences, or extracutaneous extension), primary radiation achieved a locoregional control rate of 87% and a recurrence-free survival rate of 82%.[13] Aggressive histologic subtypes and those in which delineation of the tumor margins is difficult, such as morpheaform BCC, are associated with lower rates of cure. In a series of 127 patients with morpheaform BCC, the 5-year cure rate was 81%.[14]

Adjuvant Radiotherapy

The use of adjuvant radiation therapy following surgical excision has been recommended when significant perineural invasion is noted or when surgical margins are positive and not amenable to further excision.[5,15] Recurrent disease with prior negative margins and invasion of muscle and/or bone have also been recommended as criteria for when adjuvant radiation therapy should be considered.[15] However, robust evidence to support these recommendations remains limited. No randomized trials have been conducted and evidence remains limited to small uncontrolled case series.[13,16]

SYSTEMIC THERAPY FOR BASAL CELL CARCINOMA

Cytotoxic Chemotherapy

Cytotoxic chemotherapy regimens reported in the literature typically involve a backbone of a platinum agent. Although these regimens are less frequently used today given the development of better-performing and better-tolerated targeted and immune-based therapies, they remain options in refractory disease or when a rapid response for symptom control is needed. In the largest reported series combining BCC and squamous cell carcinomas of the skin, Guthrie and colleagues[17] documented an overall response rate of 68% to the combination of cisplatin and doxorubicin. Rapid symptomatic response has been noted with the combination of cisplatin and paclitaxel or cisplatin and doxorubicin.[17–19]

Hedgehog Pathway Inhibitors: Vismodegib and Sonidegib

Initially discovered as the genetic cause of basal cell nevus syndrome, mutations in the hedgehog pathway have also been demonstrated to occur frequently in sporadic BCC. In a study of 42 BCCs, mutations in the sonic hedgehog pathway genes *PTCH*, *SMOH*, and *SUFUH* occurred in 67%, 10%, and 5%, respectively.[20] Mutations in PTCH and SMO, key receptor proteins in the hedgehog pathway, result in activation of GLI and downstream initiation of basal cell growth and proliferation. The two available hedgehog pathway inhibitors, vismodegib (Erivedge) and sonidegib (Odomzo), are small-molecule inhibitors that bind to SMO and inhibit downstream activation of these target genes.

In 2012 the Food and Drug Administration approved vismodegib for locoregionally advanced or metastatic BCC on the results of the ERIVANCE study.[21] This phase 2 trial evaluated vismodegib, 150 mg daily, in patients with metastatic or locally advanced BCC. For patients with locally advanced disease, inclusion criteria included

a size of 1 cm or more that was considered either inoperable or surgery was not advised because of a history of two or more recurrences or anticipated substantial morbidity. Patients were required to have had prior radiation therapy unless contraindicated. The primary end point of the study was an objective response of 30% reduction in visible or radiographic dimensions. In the initial report, of 33 patients with metastatic BCC, a response rate of 30% was noted. Of the 63 patients with locally advanced disease, 54% responded with a 21% complete response rate. The median duration of response was 7.6 months in both cohorts. In the final reported update, the investigator-assessed response rate was 48.5% in the metastatic cohort and 60.3% in the locally advanced. Twenty patients achieved a complete response. The median duration of response was 14.8 months.[22] Adverse events (AE) were common with more than 30% experiencing muscle spasms, alopecia, dysgeusia, weight loss, and/or fatigue. Approximately 25% experienced serious AE with seven reported deaths.

These results were replicated in the Safety Events In Vismodegib (STEVIE) trial,[23] an international open label study of vismodegib for patients with locally advanced or metastatic BCC. In the study of 1215 patients, investigator-assessed response rates of 69% for locally advanced and 37% for patients with metastasis were reported. Complete responses were reported in 34% of patients with locally advanced disease and 7% in the metastatic cohort. AE occurred in most patients (98%), with 24% experiencing serious AEs.

In 2015, sonidegib was approved for locally advanced BCC based on the results of the BOLT trial.[24] This trial was a multicenter randomized controlled trial comparing 200 mg and 800 mg of daily sonidegib. Inclusion criteria included a diagnosis of locally advanced BCC where surgery or radiation therapy was not indicated or metastatic. In all, 230 patients were randomized. With a 13.9-month median follow-up, an objective response was achieved in 43% of locally advanced patients and 15% of patients with metastasis in the 200-mg cohort. Only 5% of patients were noted to have a complete response. No improvement in response was noted in the 800-mg group (38% locally advanced, 17% metastatic, no complete responses) at the cost of a higher rate of AE. The most common AE included muscle spasms, alopecia, dysgeusia, nausea, and elevations of creatine kinase. Serious AE occurred in 14% of the 200-mg cohort and 30% of the 800-mg group.

Differences in outcome measures between the Erivance and BOLT studies complicate comparisons with regards to efficacy. A similar profile of adverse effects is present, although serious AEs were reported to be lower with sonidegib compared with vismodegib. For patients who initially fail vismodegib, significant response rates have not been noted with sonidegib,[25] suggesting that an agent with a different mechanism of action should be tried once patients fail to respond to one of the currently available hedgehog pathway inhibitors.

A significant criticism of both of these studies include ambiguity in the criteria used to define surgically unresectable disease. For these studies the decision was left up to the patient's surgeon, a group including Mohs, plastic, and head and neck surgical specialists. Given the significant differences in surgical extirpative training and experience among these surgical disciplines, it is reasonable to assume that the definition of surgically resectable might vary considerably. In both studies objective response rates were less than 50% for locally advanced disease and 30% or less for metastatic disease. Although higher rates of response were reported for follow-up studies,[22,23] these data are subject to potential bias given that they were determined by individual investigators and not

centrally reviewed. Given that these response rates remain significantly less than what has been reported for surgery and radiation therapy, these medications should not be viewed as equivalent treatment options in patients who are candidates for surgery and/or radiation.

The role of these therapies in a neoadjuvant setting remain exploratory. In a single-institution open label trial, 15 patients with BCC were given 3 to 6 months of neoadjuvant vismodegib at 150 mg daily before Mohs excision.[26] Eleven of the 15 patients completed the trial. Twenty-nine percent of patients were unable to complete more than 3 months of therapy because of treatment-related side effects. Vismodegib did reduce the surgical defect area by 27% from baseline. With a short-term mean follow-up of 11.5 months (range, 4–21), one patient recurred. Of seven patients with complete clinical response, only four demonstrated no residual tumor histologically following excision, underscoring the concept that complete clinical response does not equate to cure. Of concern, four patients in this trial did not complete standard of care surgical therapy because of either being lost to follow-up or experiencing side effects from vismodegib and withdrawing from the study. Although they might have received care subsequently, the potential for neoadjuvant vismodegib to hinder the delivery of curative therapy remains concerning and deserves further exploration.

Taken together, these data support the role of hedgehog pathway inhibitors as the current first-line treatment option in patients that are not deemed surgical or radiation candidates. Neoadjuvant hedgehog pathway inhibition should only be administered in the context of a clinical trial given the lack of long-term control data and concern regarding potential interference with curative therapy.

Immunotherapy

Based on the high mutational burden present in BCC,[27] and success with other cutaneous malignancies, immunotherapeutic strategies targeting the PD-1/PD-L1 pathway are currently being explored. In an investigator-initiated nonrandomized study of 16 patients, pembrolizumab was given with or without concurrent vismodegib.[28] In the nine patients receiving pembrolizumab monotherapy, four (44%) achieved a response, with a median duration of 67 weeks. This small series and other case reports demonstrating response to PD-1/PD-L1 inhibition[29,30] suggest that immunotherapy may become a viable treatment option. An ongoing multi-institutional phase II study of cemiplimab in advanced BCC has shown an objective response rate of 29% with locally advanced (n = 84) and 21% with metastatic (n = 29) BCC and 21% in an early press release of the data.[31] The final data from this study are anticipated to provide the most definitive picture regarding the usefulness of immunotherapy in this patient population.

SUMMARY

Locally advanced BCC requires a multidisciplinary treatment strategy. For most patients, surgery remains standard of care based on evidence demonstrating improved disease control. For patients in whom surgery is not possible because of patient comorbidities or unacceptable morbidity, radiation therapy remains a viable option with long-term disease control capabilities. Systemic treatments are available but are associated with inferior response rates to traditional therapies, such as surgery and radiation, and should be considered only for patients whom are not good candidates for these therapies.

CLINICS CARE POINTS

- Management of advanced BCC often requires a multidisciplinary team approach.
- Surgery with or without adjuvant radiation remains the current standard of care for locally advanced BCC.
- Radiation therapy has demonstrated long-term disease control potential that, although inferior to surgery, surpasses what is reported for systemic therapy and remains the second-line treatment of choice in patients with locally advanced BCC that are not surgical candidates.
- Hedgehog pathway inhibitors (vismodegib and sonidegib) are Food and Drug Administration approved systemic therapies with response rates ranging from 43% to 67% in locally advanced and 15% to 49% with metastatic disease. Complete responses to treatment occur in a minority of 20% to 30% with locally advanced and 7% with metastatic BCC. Complete clinical response correlates with histologic response in 57% of patients.
- PD-1/PD-L1 targeted immunotherapy approaches show promise in preliminary published evidence. Results of ongoing studies will clarify the role of these medications in the BCC treatment paradigm.

DISCLOSURE

M. Monroe has served on cutaneous squamous cell carcinoma advisory boards for Merck, Sanofi-Adventis, and Regeneron. He has research funding from the NIH (NIDCR), American Head and Neck Society, and Huntsman Cancer Institute. K. Kakarala has no disclosures.

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