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Aging and the treatment of basal cell carcinoma

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Abstract

Basal cell carcinoma (BCC) is the most commonly diagnosed type of skin cancer. BCCs are especially prevalent in the elderly population, given their association with cumulative sun exposure and other risk factors. In this contribution, we outline geriatric concepts related to the care of older adults with BCCs. We describe how a patient's life expectancy can be estimated and combined with tumor characteristics to determine lag time to benefit, a concept to better understand whether patients will experience the efficacy of a treatment within their life span. We also review the possibility of current BCC overdiagnosis and summarize the effectiveness, benefits, and risks of common treatments for BCCs, noting that all treatment modalities have special considerations when administered to older adults. In particular, nonsurgical treatments might be preferable for older adults with a limited life expectancy. Ultimately, we argue that the decision of whether and how to treat a BCC should be the result of shared decision-making between the provider and the patient and take into account not only tumor characteristics, but also patient values and preferences.

Introduction

Basal cell carcinoma (BCC) is the most commonly diagnosed cancer worldwide, with millions of new cases diagnosed annually in the United States,[1] and with a steadily increasing prevalence particularly among older adults.[2] BCC is typically a nonaggressive cancer: the tumors grow slowly and almost never metastasize (metastatic rate < 0.1 %),[3] making death due to BCC rare.[3] However, despite the fact that those diagnosed with BCCs will likely die of unrelated causes, each year more than 100,000 patients are treated for BCC in their final year of life.[4] In this contribution, we describe some of the geriatric concepts related to the care of older adults with BCCs, such as life expectancy, functional status, and lag time to benefit. In addition, we summarize the effectiveness, benefits, and risks of common treatments for BCCs, and outline special considerations in older adults. Overall, we

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argue that effective shared decision-making between the provider and patient is the key to understanding patient values and preferences and deciding whether and how to treat a BCC.

Life expectancy, functional status, and lag time to benefit in older patients

Several key concepts should be considered when treating any disease in older patients, including life expectancy, functional status, and lag time to benefit. Life expectancy is the probable additional number of years that a person is expected to live. Life expectancy in the United States can be crudely estimated based on national census data. In a sample of 80-year-old men, 25% are expected to live an additional 11 years, 50% are expected to live an additional 6.7 years, and 25% are expected to live fewer than an additional 3 years[5]; however, census data tables do not take someone's health status into account, and life expectancy for a particular individual may differ considerably from that predicted by age alone. Providers can therefore get a more individualized and accurate prediction of life expectancy by using programed life expectancy calculators that account for comorbidities and functional status.[6]

Combining information about a patient's tumor characteristics with a patient's life expectancy can help a provider assess whether a given intervention will positively affect a patient within an appropriate period, or whether the risks of an intervention outweigh the benefits in the patient's remaining years of life. This concept of "lag time to benefit" means we have to ask not only *how effective* a treatment is, but also consider *when* it will help in relation to the patient's life expectancy.

Overdiagnosis of BCCs

Overdiagnosis occurs when cancer screening identifies malignancies that would not have presented symptomatically in the patient's lifetime, either because the disease never progresses, spontaneously regresses, or is so slow-growing that the patient dies of another cause.[7] A well-studied example within oncology is low-grade prostate cancer. Although advancements in diagnostic technology led to the identification of more cases of prostate cancer, death rates attributed to prostate cancer remained unchanged, as identification of these additional cases did not reduce disease-specific mortality.[8] Current guidelines from the United States Preventive Services Task Force recommend against prostate-specific antigen screening for men 70 years and older.[9] Similarly, advancements in skin cancer detection have contributed to a significant increase in BCC incidence over the past several decades, especially among older patients[10,11]; however, these increased identification rates have not resulted in an improvement in disease-specific mortality from BCCs. Results suggest that most geriatric patients who are diagnosed with nonmelanoma skin cancers (NMSC), including BCC, die of unrelated causes. In one study of 1,360 patients treated for NMSC, 332 patients were classified as having a limited life expectancy; although 43% of patients with limited life expectancy died within 5 years, no deaths were due to NMSC.[12] In recognition of this potential for BCC overdiagnosis, the United States Preventive Services Task Force noted in its most recent recommendation on skin cancer screening that there is insufficient evidence to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults.[13]

BCC treatments

There are a variety of surgical and nonsurgical treatments for BCCs. In general, surgical methods[14] are employed more frequently due to their higher cure rate (Table 1). Nonsurgical treatments are typically reserved for high-risk tumors (eg, recurrent, poorly defined borders, aggressive histologic growth patterns)[23] in difficult-to-treat areas, for patients who cannot withstand or prefer not to undergo surgical treatment, and for patients with locally advanced or metastatic disease.[14] Although recommended treatment modalities are highly dependent on individual characteristics of both the patient and the tumor, in general, special considerations must be made for older patients when offering treatment options. In this next section, we summarize the effectiveness, benefits, and risks of common surgical and nonsurgical treatments for BCCs and describe special considerations for each option in older adults. Ultimately, we argue that nonsurgical options may be preferable for older patients with limited life expectancy.

Effectiveness, benefits, and risks of surgery in geriatric patients

Surgical treatment options include Mohs micrographic surgery, standard surgical excision, curettage and electrodessication (C&E), and cryosurgery. Surgical excision, C&E, and cryosurgery are all effective methods used to treat low-risk tumors (primary tumor, well-defined borders, nodular or superficial histologic subtype).[24] Excision has been reported to have a 5-year cure rate for BCCs as high as 98%.[20] If excised with a standard 4-mm margin (current National Comprehensive Cancer Network guidelines for a well-circumscribed BCC are less than 2 cm in diameter), complete tumor removal is achieved in 95% of cases.[14] C&E is another effective treatment, generally used for superficial or nodular BCCs on the trunk or extremities. Although it has been associated with cure rates as high as 97% to 98.8%,[15,16] the efficacy of C&E is highly operator-dependent because it relies on the ability of the physician to distinguish between a firmer dermis and a softer tumor.[25] C&E is a faster procedure than excision; in addition, it is cost-effective because it does not require a return visit for suture removal.[25] Similarly, cryosurgery can have cure rates as high as 99%; however, it is not commonly used to treat BCCs because it is ineffective for lesions that extend beyond the epidermis.[26] Cryosurgery is cost-effective and requires minimal anesthesia, but it has a high likelihood of permanent hypopigmentation or scarring.[25]

High-risk BCCs are most commonly treated with Mohs surgery.[24] These include BCCs on the central aspect of the face, as well as large, recurrent, or aggressive lesions in cosmetically or functionally important areas, where tissue sparing is important.[25] The cure rate for Mohs is estimated at 99%.[20]

When deciding between surgical modalities for geriatric patients, providers must take into account several special considerations in older adults. For example, wound healing after surgical procedures in geriatric patients is not as simple as it is in young healthy adults. One study found that patients older than 65 had a significant delay in epithelialization after a split-thickness wound compared with volunteers aged 18 to 55.[27] This delay can be attributed to diminished proliferation and migration of keratinocytes, fibroblasts, and endothelial cells; reduced collagen turnover; and increased fibroblast senescence. The delay

in wound healing leads to increased infection risk.[28] Epithelialization in the elderly can be further complicated by common comorbidities, such as diabetes mellitus, vascular disease, and venous insufficiency.[29] Aside from the potential medical complications, older patients' ability to tolerate the procedure must be evaluated. For example, a standard Mohs procedure may take several hours and require a staged repair involving multiple teams over several days. Notably, the consideration of age, comorbidities, and other variables that particularly affect the geriatric population are not included in the "Mohs Appropriate Use Criteria" published by the American Academy of Dermatology.[30] These variables require provider judgment and are essential in determining the appropriate treatment modality for a BCC, especially considering that the recurrence rate after Mohs surgery is only slightly lower than the recurrence rate after destruction or excision.[31]

It is also possible that postsurgical complications for BCC are underreported. In a prospective cohort study of 866 patients with an average age of 66 years who were treated for NMSC via mostly surgical modalities (99%), more than a quarter of patients (27%) reported a complication after treatment. Ten percent of the cohort reported "moderate, very, or extremely serious" complications. Fourteen percent of the patients who reported a postoperative issue described a medical complication, but only 3% of the cohort had complications noted in their medical charts. Problems that were described by patients included pain, numbness or itching (7%), infection or swelling (5%), and need for additional treatment (8%).[32]

Effectiveness, benefits, and risks of nonsurgical treatment in geriatric patients

Nonsurgical BCC treatments include topical therapies, such as imiquimod and 5-fluorouracil, radiotherapy, vismodegib and sonidegib, and intralesional therapy. These are employed to treat patients who want to avoid operative risks, are not good surgical candidates, or prefer the improved cosmesis of nonsurgical treatments.

Imiquimod and 5-fluorouracil are topical creams that have been approved for treatment of low-risk superficial BCCs.[25] The antitumor effects of 5-fluorouracil are exerted via a competitive inhibition of thymidylate synthetase, which prevents DNA synthesis and halts rapid cell proliferation.[33] Imiquimod enhances the immune system by upregulating levels of interferon alfa, leading to antitumorigenic effects via increased natural killer cell activity.[34] It has been reported that 5-fluorouracil has a 5-year cure rate of 80%, whereas imiquimod has a cure rate of 83%.[20] Scarring can, however, still occur in a significant percentage of users (9%−16% of 5-fluorouracil users, 15% of imiquimod users).[35] Additional common adverse reactions include local skin irritation, xeroderma,[36] persistent telangiectasias, and cardiac ischemia if systemically absorbed.[25]

Patients with higher-risk BCCs, who wish to avoid surgery, can also be treated with radiotherapy or intralesional therapy. Radiotherapy is noninvasive and painless, and unlike surgical treatments it is more likely to preserve cosmesis and functionality of uninvolved structures; however, it does not allow for histologic assessment of clear margins and involves a long period of treatment, because it is typically delivered in a fractionated schedule of four

or more sessions.[23] Studies suggest that radiotherapy has a 5-year cure rate for BCC of 93% to 96%, which is comparable to the surgical 5-year cure rate of 98% (excision) to 99% (Mohs).[20] Radiotherapy is also more expensive than other treatments, with radiation oncologist hospital based radiotherapy for one lesion costing between $3,300 and $8,000 and outpatient electronic brachytherapy costing between $1,950 and $2,340.[37] In comparison, the cost of surgical excision is significantly lower ($361-$1,000).[38] Additionally, radiotherapy can cause long-term side effects such as permanent alopecia at the treatment site and chronic radiation dermatitis.[23]

An alternative to radiotherapy is intralesional therapy with agents such as methotrexate, 5-fluorouracil, bleomycin, and interferon. Although data are limited, the BCC cure rate with intralesional 5-fluorouracil and bleomycin has been reported to be as high as 96% and 100%, respectively; however, all therapies can result in local pain, erythema, and crusting of the injection site, with potential progression to ulceration and necrosis, and require multiple visits over several weeks for proper delivery of therapy.[39] Intralesional therapies are typically not administered as first-line treatments because these agents are used off-label, and there are no large, well-designed trials that have provided sufficient data on their efficacy.

Locally advanced or metastatic BCC in nonsurgical candidates can be treated with Hedgehog-pathway inhibitors such as vismodegib or sonidegib.[40] Both drugs have shown promising response rates (percentage of patients whose BCCs decreased or disappeared) at 43% for vismodegib and 56% for sonidegib[22,41]; however, there are considerable side effects with these medications, including muscle spasms, alopecia, dysgeusia, fatigue, and nausea.[42,43] In particular, vismodegib may increase the risk of developing cutaneous squamous cell carcinoma,[44] although this is highly debated.[45–47] Vismodegib and sonidegib are also expensive, with an average wholesale price of $120,000 for 30 tablets.[48]

Nonsurgical treatment options also require special consideration when treating older patients. Targeted therapies, such as vismodegib or sonidegib, in particular, should be used with caution in the elderly. Prescribing information for vismodegib notes that the drug's clinical studies did not include a sufficient number of patients older than 65, and, therefore, it is unclear whether vismodegib is safe to administer in a geriatric population.[42] Although clinical trials for sonidegib did include older adults, the drug was found to have a higher incidence of serious adverse events in patients older than 65, leading to increased necessity of dose disruption or discontinuation in the geriatric population.[43]

Applying geriatric principles to BCC treatment

Current BCC clinical practice guidelines focus on the curative intent of removing as much malignancy as possible and lack recommendations for a tailored approach for older patients who may have unique needs and priorities. A team of Dutch researchers recently' to: In 2016, a team of Dutch researchers Change 'six of the 13' to: six of the thirteen.[49]

Ultimately, patients and providers should engage in shared decision-making to decide on a treatment modality that accounts for a patient's values and preference in the context of their

life expectancy. Shared decision-making involves prioritization of patient-centered communication in treatment discussions, which was ranked as the top priority of the Institute of Medicine during the delivery of cancer care.[50] In a focus group assessment of patients with skin cancer, the most important need identified was to "receive all relevant, tailored information" and the second was that "a physician takes you seriously and communicates well."[51] When a decision is made to pursue BCC treatment, it is imperative that the physician and patient discuss the following:

- What is the patient's goal in treatments?
- What are the treatment options?
- What is the cost, duration and risks versus benefits of each of those options?
- Will the treatment likely help the patient during their expected lifetime?

In some instances where lag time to benefits extends beyond a patient's lifespan, intervention might *still* be warranted to improve the patient's quality of life (eg, large tumor affecting functional ability such as interfering with vision and tumors that bleed or are painful.) The input of family members and caregivers is often essential in this process. It is, therefore, our responsibility to use shared decision making to foster a dialogue that combines a physician's medical expertise with a patient's understanding of the clinical manifestations and psychosocial effect of his or her disease, using the central principle of patient autonomy.[52]

Conclusions

The incidence of BCC is high and continues to increase. Our aging population will make this an even bigger problem in the future, especially among older adults. There is no one-size-fits-all recommendation for the care of these tumors; instead, providers must work with patients and their families to find the best option for the individual patients. To better care for our patients, we need to incorporate principles of gseriatrics into the practice of dermatology.

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Table 1

Reported cure rates for BCC treatment options

Treatment	5-year BCC cure rate *
Surgical treatments	
Curettage and electrodessication	97%–98.8%[15–17]
Cryosurgery	99%[18,19]
Standard excision	98%[20]
Mohs	99%[20]
Nonsurgical treatments	
Radiotherapy	93%–96%[20]
Topical therapies	
Imiquimod	83%[20]
Fluorouracil	80%[20]
Targeting therapies	
Vismodegib	28%[21,†]
Sonidegib	21%[22,‡]

BCC, basal cell carcinoma.

* Reported cure rates are for 5 years and tumor types are primary BCCs unless otherwise specified.

† 9 months, locally advanced and metastatic.

‡ 3 months, locally advanced.