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GERIATRIC ONCOLOGY (AR MACKENZIE, SECTION EDITOR)

Non-Melanoma Skin Cancers in the Older Patient

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Abstract

Purpose of Review The incidence of non-melanomatous skin cancer (NMSC) increases with age and there are specific considerations regarding management of NMSC for the older patient population. Here we will review current data regarding treatment considerations and options for older patients with NMSC.

Recent Findings Hypofractionated regimens and high-dose brachytherapy may be non-surgical treatment options for older patients with NMSC. Other less aggressive strategies such as active surveillance can also be considered in some settings.

Summary Management of NMSC in the older patient population requires a thorough assessment of comorbidities, frailty, and life expectancy. Additionally, discussions regarding goals of care and quality of life (QOL) issues are especially important in this population. Older patients with NMSC in particular may benefit from a tailored treatment plan based on current available data rather than a broad application of general treatment guidelines for NMSC.

Keywords Non-melanoma skin cancer · Geriatric oncology · Skin cancer · Surgery · Radiation therapy · Radiotherapy

Introduction to Non-melanoma Skin Cancer

Non-melanoma skin cancer (NMSC), also referred to as keratinocyte cancer, is the most common cancer diagnosed in the USA; it includes squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Approximately five million cases of NMSCs were treated in the USA in 2012 [1]. BCC is at least twice as common as SCC and approximately two million cases of BCC are diagnosed each year [1, 2]. NMSCs are infrequently metastatic, but can cause significant local destruction and disfigurement. NMSCs overall have a favorable prognosis and are often curable with surgical excision [3]. There are data to suggest increased mortality after a diagnosis of cutaneous SCC [4].

SCCs of the head and neck are at higher risk of recurrence and lymph node metastases as compared with SCC located on the trunk and extremities [5–7]. BCCs of the head and neck are also more likely to recur than those on the trunk and extremities. BCCs are much less likely to metastasize than SCC [8]. NMSC lesions are classified as either low-risk or high-risk. High-risk lesions include those with poorly defined borders, recurrent NMSC, perineural, lymphatic, or vascular involvement, poorly differentiated lesions, Clark's level IV–V or depth greater than 2 mm (mm) [5, 9]. Additionally, high-risk lesions include those located on the trunk or extremities and larger than 20 mm; those located on the cheeks forehead, scalp, neck, and pre-tibia area and greater than 10 mm; and those located in the "mask" area (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, pre/postauricular, temple, and ear), genitalia, and hands/feet greater than 6 mm [5, 9].

Low-risk NMSC may be treated with curettage and electrodessication (C&E), cryotherapy, wide local excision (WLE), or Mohs microscopic surgery (MMS) [10]. C&E is a cost-effective treatment which involves scraping away tumor tissue with a curette and denaturing the area

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by electrodessication. A disadvantage of this technique is that it does not allow the evaluation of histologic margins. Likewise, cryotherapy is a convenient treatment that can be used for low-risk lesions but does not allow for margin assessment. Both of these procedures can also create significant scarring. WLE can be performed for small SCCs and BCCs in non-critical areas. WLE should be followed by postoperative pathologic evaluation of margins. For well-circumscribed SCCs, low-risk lesions < 2 cm (cm) should be excised with 4 mm margins. For low-risk lesions > 2 cm, 6 mm margins are necessary [5, 11]. Larger margins may be needed for larger tumors or with risk factors including poor differentiation, high-risk location, and perineural invasion [12]. Low-risk BCC should be excised with 4 mm margins for lesions < 2 cm [13]. Re-excision with margin assessment is recommended for positive margins.

MMS can also be used for treatment of NMSC and is the preferred technique for high-risk lesions. Meta-analyses report a 5-year recurrence rate of 1.0% for BCC and 5.6% for recurrent BCC [14]. Five-year recurrence rates for SCC are 3.0% and 10% for recurrences [7]. Advantages of MMS include complete evaluation of deep and peripheral surgical margins while conserving uninvolved tissue [15]. Reconstruction is performed only after negative surgical margins are confirmed. MMS is typically a single-day outpatient procedure and involves tumor excision and mapping followed by immediate histologic evaluation of frozen, horizontal sections. The process is repeated until negative margins are obtained, which is on average 1.6–1.9 times depending on the histology and location [16]. Potential disadvantages include prolonged surgical days for some patients, inability to perform the procedure on patients who cannot tolerate surgery under local anesthesia, and challenges in obtaining clear margins for tumors involving deep structures including bone or the parotid gland [15, 17]. Complication rates are low for MMS with an overall rate of 0.72% and 0.2% for serious events and no deaths in one large, prospective study [18].

Radiation for NMSC may be delivered in the definitive or adjuvant setting. Although the majority of NMSC can be treated with surgical excision or ablation, a recommendation for definitive radiation may be made in settings where cosmetic or functional outcome would be better with radiation as a form of local therapy [19]. Areas of the face where primary radiation may be more commonly utilized, in lieu of surgery, include the eyelids, nose, and lips [20]. Radiation may also be used for patients with contraindication to surgical excision or for patients who may not tolerate excision. Local control rates for definitive radiation for BCC are around 90–95% and approximately 90% for SCC [20–22]. Additionally, adjuvant radiation may be recommended for SCC or BCC with high-risk pathologic features such as extensive perineural or large nerve involvement and for positive margins after definitive surgery [5, 9]. Adjuvant radiation is commonly offered for pathologic findings of positive lymph nodes, invasion of bone or cartilage, and extensive skeletal muscle infiltration [20].

NMSC Epidemiology in the Older Patient Population

The incidence of NMSC increases with age. Rates of skin cancer have been reported between 9 and 12% in cohorts of older patients in dermatology clinics; however, it is difficult to accurately determine the incidence of skin cancer in the older patient population. This is due to selection bias of patients referred for suspicious skin lesions and because skin cancer is not reported in most cancer registries [23, 24]. White patients in the 65–70 years and over 80 years age groups have had the highest increase in the incidence in BCC [2]. More than 80% of cases of SCC occur in older patients and the mean age at diagnosis is 70 [25].

NMSC is a common skin condition in elderly patients residing in nursing homes [26]. The prevalence of skin cancer is estimated to be close to 5.0% in acute and long-term geriatric units [27, 28]. Based on these findings, close collaboration has been encouraged between geriatricians managing patients in these settings and those who treat skin cancers.

The most common anatomic location of NMSC in older patients from observational studies is the head and neck [29]. Additionally, older patients may frequently have multiple synchronous SCC lesions due to field cancerization effect [30]. One population study of an elderly population of patients with NMSC showed that patients were majority female, from low socioeconomic status, and predominantly worked in occupations with ultraviolet radiation exposure without daily sunscreen use [31]. Commonly associated comorbidities in this particular study included hypertension and diabetes.

Given the rising incidence of NMSC, appropriate strategies for prevention and management should continue to be evaluated [32–35]. This is especially important for older patients with NMSC due to longer life expectancy of the general population and increased incidence of NMSC with age [36, 37]. The older patient population often has more comorbidities and increased physiological fragility and may tolerate treatment differently than younger patients. Therefore, a discussion of the specific considerations for treatment of older patients with NMSC is warranted.

Specific Considerations for the Elderly Population with NMSC

Comorbidities

A retrospective study of 241 patients with skin cancer > 75 years old found that over half of patients had > 3 comorbidities [38•].

A systematic review of comorbidity indices used for patients with NMSC identified three comorbidity assessment tools commonly used: the Charlson Comorbidity Index (CCI), the American Society of Anesthesiologists risk classification system (ASA), and the Adult Comorbidity Evaluate-27 (ACE-27) [39]. A study of nonagenarians undergoing Mohs micrographic surgery for NMSC showed that CCI scores ≥ 3 predicted for shorter survival [40]. However, a separate study with patients over the age of 90 undergoing Mohs micrographic surgery (MMS) found no significant differences in survival based on comorbidities and concluded that older patients may safely undergo MMS [41].

The ACE-27 includes more comorbid conditions than the CCI and is more specific to cancer patients. This assessment has been shown to be more accurate than standard medical history taking in patients with NMSC [42]. In a retrospective review of 488 patients over the age of 85, comorbidities were assessed with ACE-27 and an age-adjusted Charlson comorbidity index (ACCI). Scores from these indices were associated with overall survival; however, the cohort presenting for MMS had improved survival despite similar intercohort comorbidity [43]. Based on this information, comorbidities and age alone may be insufficient when making treatment decisions for older patients with NMSC. Given the increasing number of aging patients and increasing incidence of NMSC, tailored assessments for this population may be beneficial.

Hypertension is a common comorbidity among older patients and may contribute to bleeding and hematoma formation during and after cutaneous surgery [44]. Hypertension may affect blood supply to flaps and grafts which, if these procedures fail, may lead to poor functional and/or cosmetic outcomes [45]. Guidelines regarding appropriate cutoffs for systolic and diastolic pressure for deferment of cutaneous surgery have been employed [44]. However, it is up to the surgeon to perform a risk/benefit analysis in each specific clinical scenario.

In a large study of elderly patients with NMSC, 52% were taking anticoagulant or antiplatelet agents [38•]. Treatment with anticoagulant and antiplatelet agents was not a significant risk factor for postoperative complications. Current review of the literature supports continued use of warfarin and aspirin during minor cutaneous surgery [46]. Increased attention to hemostasis during procedures in this group of patients may eliminate the need to discontinue anticoagulation and hence prevent putting patients at risk for thromboembolic complications. Given the large proportion of older patients with NMSC being treated with anticoagulant and antiplatelet agents, this is an important consideration when managing patients with NMSC surgically.

Diabetes is another common comorbid condition among older patients with NMSC [29, 31, 38•]. Diabetes has been implicated in delayed wound healing after procedures for other medical conditions aside from NMSC. Therefore, further exploration into the impact of diabetes as a comorbid condition among older patients with NMSC may be beneficial.

Comprehensive Geriatric Assessment

The comprehensive geriatric assessment (CGA) is an evaluation of general health status using validated geriatric scales and tests and is intended to allow for the development of individualized geriatric interventions [47]. The CGA has been shown to identify numerous health conditions in older patients with cancer and can be utilized to help with treatment decisions. Additionally, associations between comorbidities and treatment-related toxicity and overall survival have been made. As such, it may be of more use in the population of older patients with NMSC than comorbidity indices alone. However, only a small numbers of patients with skin cancer have been included in studies evaluating the use of the CGA in older cancer patients [48, 49]. Therefore, its utility in the older patient population with NMSC has not yet been determined. NMSC is unique from other malignancies in that it is usually not a fatal condition, however, can cause significant morbidity when left untreated. As such, development of a unique geriatric assessment that assists clinicians in balancing benefits with unwanted side effects of treatment of NMSC may be warranted.

Limited Life Expectancy

Although an assessment of comorbidities may provide information about survival after treatment of NMSC in older patients, accurately assessing life expectancy may be of more importance for this group. In a study of 2,702 patients ≥ 65 years treated for NMSC, rates of treatment were no different among patients with limited life expectancy compared with those with normal life expectancy [50•]. Specifically, there were similar rates of Mohs surgery and higher rates of excision in patients who died within 1 year of treatment compared with patients who lived longer. Another study demonstrated that most NMSCs were treated surgically regardless of life expectancy and many patients with limited life expectancy died within 5 years; however, none of these deaths were attributed to NMSC [51]. Furthermore, 20% of patients with limited life expectancy in this study reported complications of therapy. Therefore, it is important for clinicians to recognize that patients with limited life expectancy may not live long enough to benefit from intensive treatments and may be more affected by adverse effects of treatment. As such, in cases of limited life expectancy, observation may be an appropriate treatment strategy when patients are asymptomatic from NMSC.

Assessing Frailty

Frailty affects many older patients and is defined as a state of vulnerability secondary to poor resolution of homeostasis after a stressor and is a result of a cumulative decline among many of a patient's physiological systems over his or her lifetime [52]. Minor stressor events can then lead to disproportionate changes

in health status. Treatment-related morbidity from NMSC is indeed a minor stressor and therefore assessment of frailty should be considered an important component of managing older patients with NMSC. The Groningen Frailty Index (GFI) is one tool that may be used to screen for frailty [53]. In a study of patients over the age of 65 undergoing surgical treatment for head and neck cancer, including skin cancer, analysis of frailty using the GFI identified older patients who had worse subjective postoperative experiences [54]. Furthermore, the integration of frailty-related consideration into clinical practice guidelines may encourage a more personalized approach to care for older patients with NMSC [55].

Post-operative Complications

Post-operative complications from cutaneous surgery can include dehiscence, infection, and hematoma. There are no reports directly comparing post-operative complications from cutaneous surgery between older and young patients. Some data suggest rates of complications may not be different while other data suggest complication rates following cutaneous surgery for NMSC may be higher among older patients. The postoperative complication rate among elderly patients undergoing cutaneous surgery in a study from Bouhassira et al. was reported as 20%, which is higher than the complication rate of 3–6% reported in similar studies with patients with no age restriction [38•, 56, 57]. Male sex, histological type, and insufficient initial resection margins were identified as significant postoperative risk factors in this group of patients > 75 years. In an observational study of 247 patients older than 85 years of age undergoing cutaneous surgery, 7.9% of patients experienced complications [29]. Necrosis and cellulitis were the most common complications. Length of surgical procedure, area of skin removed, and reconstruction with skin graft were found to be risk factors for post-operative complications. In a large, multi-center prospective study of over 20,000 cases of MMS performed, the mean of age of patients with complications was > 70 years and half were male [18]. Most complications were associated with MMS performed on the face. Additionally, those with postoperative bleeding had been receiving anticoagulation.

While a direct comparison between older and younger patients may further elucidate whether age is an independent risk factor for post-operative complications following cutaneous surgery, the data currently available may still assist clinicians in identifying older patients at higher risk for such complications and those for whom other treatment strategies may be appropriate. A summary of risk factors for post-operative complications for the older patients is summarized in Table 1.

Table 1 Risk factors for post-operative complications in the older patient after dermatologic surgery

Age > 75 [38•]	Male sex
	Histologic type
	Insufficient initial resection margins
Age > 85 [29]	Length of surgical procedure
	Area of skin removed
	Reconstruction with skin-graft

Radiation Therapy as Primary Treatment

Radiation can also be used in the definitive or adjuvant setting. Lesions may be treated to a dose of 50–60 Gray (Gy) with a fraction size of 2–2.5 Gy in the definitive setting to achieve local control with acceptable toxicity [19]. Hypofractionated regimens have been used in the definitive setting [19]. Given the convenient treatment schedule, hypofractionated radiation may be a suitable treatment option for older patients in whom surgical excision may produce unacceptable cosmetic/functional outcomes or are at high risk of post-operative complications. In a phase II study of 31 patients ages 70–90 with NMSC, Ferro et al. demonstrated a course of definitive radiation with a total dose of 30 Gy in 5 fractions produced greater than 90% local control with only grade 1 acute and late skin toxicity [58]. In another series of older patients over the age of 80 with life expectancy ≤ 5 years in 90.5%, two hypofractionated schedules were administered: 6 Gy in 10 bi-weekly fractions and 5 Gy in 12 bi-weekly fractions [59•]. The overall response rate in this study was 96.1% with 92.4% complete responses and all patients experienced an improvement of symptoms. A reduction in the number of pain medications during the course of radiation proportional to the improvement of the lesion was also observed.

Brachytherapy may be preferred for older patients with limited mobility in whom positioning for daily treatment may be challenging. Brachytherapy may be advantageous over external beam radiation therapy (EBRT) when treating large lesions or convex surfaces. In a series of 19 patients ≥ 75 years old, Lancellotta et al. demonstrated a personalized method of delivering high-dose rate (HDR) brachytherapy utilizing a double-layer mold of thermoplastic mask material applied to each patient's skin resulted in effective and tolerable treatment [60•].

A retrospective case series of 57 lesions in 39 patients > 70 years reported on high-dose rate brachytherapy (HDR-BT) using a Valencia applicator; this resulted in a 96% complete response rate [61]. The regimens used were 40 Gy in 8 fractions or 50 Gy in 10 fractions. The biological effective dose (BED) was 60 Gy and 75 Gy, respectively. The authors conclude that a hypofractionated regimen using a surface applicator was safe and effective in elderly patients. Additionally, treatment of NMSC with high-dose rate electronic brachytherapy (EBT) has been compared with outcomes of treatment with MMS [62•]. In this matched-pair cohort study, the median age of those undergoing treatment with EBT and MMS was 80.7 and 76.8, respectively. EBT was found to be an effective non-surgical treatment option for NMSC with equivalent

Table 2 Studies evaluating non-surgical treatment of NMSC with radiation

Treatment	Study Design	Patients (*n*)	Patient Age	Outcomes	Toxicity	Reference
HF EBRT (electrons or photons)	Phase II trial; 30 Gy in 5 fractions over 6 consecutive days	31	Median age 79; (range 70–90 years)	96.8% complete response rate; 93.2% 2-year LC; 3-year LC 88.3%; 9.7% died of other causes	Grade 1 acute and late skin toxicity; 12.9% hyperpigmentation, 35.5% skin atrophy, 3.2% grade 1 fibrosis	Ferro et al. [58]
HF EBRT (electrons or photons)	Phase II trial; 6 Gy in 10 bi-weekly fractions and 5 Gy in 12 bi-weekly fractions	21	Median age 88 (range 77–100 years); 90.5% life expectancy < 5 years	96.1% overall response rate; 92.4% complete response rate; 95% 1-year and 2-year CSS; 42.7% died of other causes	61.% with acute toxicity (46.2% with grade 1–2 toxicity and 15.3% (with grade 3);	Valeriani et al. [59•]
HDR-BT	Phase II trial; 36 Gy with 4 Gy/fraction BID for recurrent or de novo disease and 57.5 Gy with 2.5 Gy/fraction for adjuvant RT or critical area	19	Median age 86; (range 75–96 years)	100% complete response rate with median follow-up of 6 months	100% with grade 2 epidermolysis which resolved; late toxicity include central hypopigmentation and alopecia in treatment field	Lancellotta et al. [60•]
HDR-BT (Valencia surface applicator)	Retrospective review; 40 Gy in 8 fractions and 50 Gy in 10 fractions delivered 2/3 times per week	39	Median age 84 (range 70–96)	96.5% complete response rate; 0 recurrences with 12 months median follow-up	58% with acute grade 1 toxicity; 5.3% acute grade 2 toxicity; 17.5% with late grade 1 toxicity; 1.9% with late grade 2 toxicity; 86% with excellent cosmesis	Delishaj et al. [61]
EBT (Xoft® Axxent® Electronic Brachytherapy System®)	Matched pair cohort study; 40 Gy in 8 bi-weekly fractions	369 (188 patients treated with EBT and 181 patients treated with MMS)	Median age 81 (range 61–89 years)	99.5% treated with EBT free of recurrence at 3 years	59.6% with hypopigmentation; 31.4% with telangiectasia; 97.6% with excellent or good cosmesis	Patel et al. [62•]

HF EBRT hypofractionated external beam radiation therapy, *LC* local control, *CSS* cancer-specific survival, *HDR-BRT* high-dose rate brachytherapy, *BID* two times daily, *RT* radiation therapy, *EBT* high-dose rate electronic brachytherapy, *MMS* Mohs micrographic surgery

recurrence rates and cosmetic outcomes. Data from recent studies for non-surgical treatment of NMSC with radiation are summarized in Table 2.

Hypofractionated radiation may be an especially important alternative treatment option to consider for older patients with NMSC at higher risk for post-operative complications. Furthermore, brachytherapy may provide additional advantages such as decreased number of treatments, personalized treatment plans, and decreased dependence on patient positioning.

Systemic Therapy

Systemic therapy is used in the management of advanced NMSC including metastatic disease or advanced lesions not amenable to local therapy. Its use in the post-operative setting has also been investigated [5, 9]. In a randomized phase III trial investigating concurrent carboplatin with postoperative radiation in high-risk cutaneous SCC of the head and neck, carboplatin was found to offer no additional benefit over post-operative radiation alone [63].

Immune modulators and monoclonal antibodies are also of growing interest for the treatment of advanced NMSC [64]. A phase II study investigating the use of cetuximab as first-line therapy for cutaneous SCC demonstrated a 69% disease control rate at 6 weeks [65]. In a retrospective study of older patients with refractory locally advanced or metastatic NMSC, neoadjuvant cetuximab alone, or combined with cisplatin and 5-fluorouracil demonstrated that 92% of unresectable tumors became amenable to surgery and complete histological response was observed in 65% of patients [66]. A phase I and phase II study of cemiplimab, an immune checkpoint inhibitor, demonstrated a response in approximately half of patients [67].

Additionally, the sonic hedgehog (SHH) signaling pathway has been shown to be an important part of BCC carcinogenesis [68]. Vismodegib has been approved for the treatment of advanced BCC base on phase II clinical trial data which demonstrated response in 30% of patients with metastatic BCC and 43% of patients with locally advanced BCC [69]. Sonidegib is another SHH inhibitor that was shown to be effective for advanced BCC [70]. The median age of patients on a phase II trial which tested sonidegib was 67.

As additional clinical trials provide more data related to the use of systemic therapy and immunotherapy for advanced NMSC, understanding the impact of age on adverse events caused by these therapies will become even more important. Future investigations related to use of these therapies for NMSC should consider the tolerability of these treatments for the older patient population in order to maximize therapeutic gain for these patients. Furthermore, geriatric assessments related to the treatment of NMSC may need to consider unique adverse events associated with systemic therapy and immunotherapy in older patients as continued progress is made in treatment of advanced NMSC.

Active Surveillance

Active surveillance for low-risk NMSC in older patients is another viable treatment strategy that has more recently been a part of the discussion in medical literature [51, 71, 72]. Similar to active surveillance as a strategy in the management of other non-aggressive tumors, a thorough discussion between clinician and the patient should take place in order to outline goals of care and treatment preferences. Other factors such as functional status and mental capacity of the patient should also be considered [73]. As previously discussed, older patients often have other comorbid conditions that are a greater risk to their health or put them at high risk for post-operative complications and these patients may also have limited life expectancy. For those patients who are incapable of understanding the situation, a thorough discussion with the legal power of attorney is critical. Thus, the guideline recommendations to cure patients of their NMSC with either surgical resection or other definitive treatment may not be applicable to every patient. Furthermore, the need for surgical re-excision in all cases of positive microscopic margins may not be merited in every case of older patients with NMSC given that this could lead to a higher risk of complications and does not necessarily lead to an improvement in survival [71, 74]. Additionally, there are some data to suggest that there may be regression of residual NMSC after shave biopsy [75]. Although rates of regression may not be high enough to recommend against re-excision in all patients, observation after biopsy may be an appropriate treatment strategy for the older adult with NMSC in certain settings [76].

Moreover, as a proposed solution to overdiagnosis and overtreatment in cancer, some have even suggested a change in the terminology used for cancerous lesions that distinguishes between indolent and fast-growing lesions [77]. Such a change in semantics could arguably decrease the urge to aggressively treat all malignancies. NMSC is among the cancers believed to be a candidate for such a change in terminology given that it is infrequently fatal and could be observed in certain situations such as in the older, frail patient with limited life expectancy. Whether such a change in terminology from cancer to the proposed "indolent lesion of epithelial origin" would change management for NMSC cannot yet be determined. However, this idea does emphasize the notion that clinicians should be judicious when determining which clinical situations warrant aggressive treatment for older patients with NMSC.

Treatment of NMSC and Quality of Life

Quality of life (QOL) issues in the setting of NMSC include scarring and disfigurement from treatment as well as anxiety about future skin cancers [78, 79]. Improvements in emotional and mental health well-being following treatment of NMSC have been demonstrated [80]. Interestingly, patients younger

than 65 years old showed a greater improvement in emotional well-being after treatment than their older counterparts which may be in part due to the possibility that younger patients are more sensitive to the potential disfigurement and scaring related to the disease process [80]. This suggests some differences in how older and younger patients may be affected by NMSC QOL issues. Additionally, several studies have assessed QOL issues related to the surgical treatment of NMSC [78, 79]. Aside from reports of cosmetic outcomes, less data specifically related to QOL after treatment with radiation are available. An understanding and acknowledgment of the specific QOL concerns for older NMSC patients and how different treatment options affect QOL is needed when developing an appropriate treatment plan for older patients with NMSC. Thus, future research related to both surgical and non-surgical treatment of older patients with NMSC should also analyze QOL.

Conclusion

NMSC is common among older patients. A complete evaluation including comorbidities, frailty, and predicted life expectancy is warranted in order to balance potential benefits from treatment with unwanted treatment-related side effects. A discussion related to goals of care including QOL issues is important. Several geriatric assessments are available to assist clinicians when making treatment-related decisions. Although several of these have been validated in the older patient population with NMSC, none are specific to NMSC. Specific geriatric assessments for older patients with NMSC may be important and further research is warranted. Ideally, such assessments may be used to determine which patients may benefit from each treatment approach.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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