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Systematic Review

Recommendations of the International Society of Geriatric Oncology on skin cancer management in older patients

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ABSTRACT

Introduction: Non-melanoma skin cancer (NMSC) is becoming ever more prevalent among older adults. However, older adults with NMSC are often underrepresented in clinical trials and guidelines on effective management is still unclear. The International Society of Geriatric Oncology (SIOG) created a multi-disciplinary task force to explore the potential in developing practical guidelines for the treatment of older patients with basal cell carcinoma (BCC) and skin (cutaneous) squamous cell carcinoma (cSCC).

Materials and Methods: A systematic literature search to identify relevant and up-to-date literature on treatment of NMSC in older adults was conducted on various databases including MEDLINE, Embase, CINAHL, Cochrane, and PubMed. The resulting papers were discussed by an expert panel, leading to a consensus recommendation.

Results: A total of 154 articles were identified for the expert panel to utilise in generating consensus recommendations. A major focus on geriatric assessment and management options including surgery, radiotherapy, systemic therapy, clinical monitoring, and medical/medicophysical therapy were reviewed for recommendations.

Discussion: Patient age should not be the sole deciding factor in the management of patients with NMSC. Assessment from a multidisciplinary team (MDT) is crucial, and the decision-making process should consider the patient's lifestyle, needs, and expectations. A comprehensive geriatric assessment should also be considered. Patients should feel empowered to advocate for themselves and have their views considered a part of the MDT discussion.

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1. Introduction

Skin cancers can be divided into cutaneous melanoma or non-melanoma skin cancer (NMSC). The world age standardised incidence of NMSC is 15.1 per 100,000 in males and 7.9 per 100,000 in females [1]. NMSC encompasses a broad category of tumour types with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) being the most frequent types but rarely fatal [2,3].

The proportion of older people (aged ≥65 years) within the global population is increasing [4,5]. An ever-increasing prevalence of skin cancer is reaching epidemic levels due to prolonged lifetime sun exposure in correlation to an ageing population. Skin cancer poses a significant burden on healthcare systems across the world. Due to ultraviolet (UV) light exposure, up to 95% of these cancers occur in the head and neck region. Aging is an indisputable risk factor for developing skin cancer [6].

For the purposes of appropriate treatment, it is advisable to consider the age ranges 65–74, 75–84, and ≥ 85 years in assessing older adults [7] who may present with treatable cSCC and BCC [2]. Older adults may have specific needs that make them dependent on other family members or carers. Assessment from a multidisciplinary team (MDT) needs to account for holistic patient care.

Current clinical practice guidelines for skin cancer provide minimal guidance in cancer care for the older population [8]. Ultimately, older patients are prone to increased odds of being untreated due to factors such as loss to follow-up, geriatric comorbidities, and treatment compliance [9]. Literature indicates possible overtreatment and over-diagnosis issues in older patients, specifically with BCC, and postulates that active surveillance may be an excellent alternative for patients with a limited life expectancy [10]. Some skin cancers without treatment may continue to grow and cause symptoms whilst other patients, especially those with short life expectancy, may not live long enough to benefit from active anticancer treatment [11].

The definition of an older patient based purely on their "chronological" age is not an objective reflection of every individual in the older population [12]. As a result, most studies use variable definitive cut-offs such as 65, 75, or 85 years to define an older patient cohort. Thus, there is still disparity in the clinical management of skin cancer in older patients worldwide. With no consensus on the definition of age at which an individual is defined as an older patient, standardised management guidelines are hard to establish [8,13]. Therefore, a greater need for clinical practice to become more streamlined in tackling the rising epidemic of skin cancer in older patients is warranted. The below recommendation paper refers to BCC and cSCC.

1.1. Methodology and Search Strategy

A multidisciplinary task force (TF) of international experts in skin cancer management was formed within the International Society of Geriatric Oncology (SIOG) to review current guidelines in NMSC. The TF consisted of one dermatologist, one surgeon, two radiation (clinical) oncologists, two medical oncologists, one geriatrician, one skin cancer nurse, one patient representative, two young SIOG members, and one senior librarian. The latter three TF members were also on a methodology team.

An electronic scoping search to identify relevant current literature on the management of NMSC was conducted. Online databases including CINAHL, The Cochrane Library, EMBASE, MEDLINE, and PubMed were searched for English language publications. Search terms were identified using the PICO (Patient/ Problem, Intervention, Comparison, and Outcome) framework (Appendix A, Supplemental Table 1) and the key concepts included: "squamous cell carcinoma", "basal cell carcinoma", "surgery", "radiotherapy", "dermatology", "brachytherapy", "immunotherapy", "systemic therapy", "palliative therapy", "therapy/treatment", and "older people." Additional Medical Subject Headings (MeSH) terms were identified in each of the individual databases. The full search strategy can be viewed in supplementary data (Appendix A, Supplemental Table 2). An 'English Language' limit was implemented into the search. The search was not limited to a period of date, due to the nature of the topic of interest. The total result of records identified from the initial search underwent rigorous primary and secondary screening via the Rayyan systematic review tool. Initial titles and abstracts were used for primary screening, while secondary screening adhered to inclusion and exclusion criteria. Both phases of screening were performed by two different experts from the TF.

Records excluded by reviewers during screening are visible in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Fig. 1). Articles were excluded from the review if they were editorials, commentaries, letters, news articles, case reports, conference abstracts, or narrative reviews.

Included studies were then shared with the whole TF for discussion and formulation of expert consensus to address the literature with current clinical practice and experiences in older patients with NMSC.

A. Inclusion criteria

- English language
- Aged 65 and over
- BCC and cSCC

B. Exclusion criteria

- NOT "Head and Neck" or "tongue" or "laryngeal" or "oesophageal" or "lip" or "throat" or "oropharynx" or "hypopharynx" or "oral" in the title.
- Reviews (including narrative), commentaries, case reports, letters, news articles, editorials, and conference abstracts.

C. Aim

- By reviewing current literature, consensus-based guideline and recommendations are proposed by TF experts accordingly.

1.2. Results

From Fig. 1, a total of 154 articles were identified and utilised by the expert panel from the TF. Each member reviewed relevant literature on the treatment of NMSC in older adults to form general insight into current practice in older NMSC patients. The data obtained from these articles gave insight and aided the TF to generate consensus recommendations.

2. Expert Recommendations

2.1. Geriatric Assessment

The geriatric assessment (GA) is characterized by a series of tools able to evaluate multiple aspects of a patient and by a "forma mentis" for which the clinician can more easily identify some problems and manage patients defined as complex [14–16]. It is, therefore, essential that clinicians be familiar with some geriatric aspects for appropriate management.

The most distinctive aspects of the GA are represented by assessing patients' care needs [17]. Specifically, in the oncological scenario, it involves an assessment tool(s) capable of identifying the risk of toxicity to a given treatment and developing a personalised approach. It is essential to consider two fundamental aspects of GA [1]: it must be adaptable because frailty is a dynamic process, and [2] it must change according to the treatments and oncological disease [18]. Due to the everchanging frailty status, it is advisable to consider ongoing evaluations rather than a single assessment before treatment. It should also be stressed that frailty assessment should not solely justify palliative

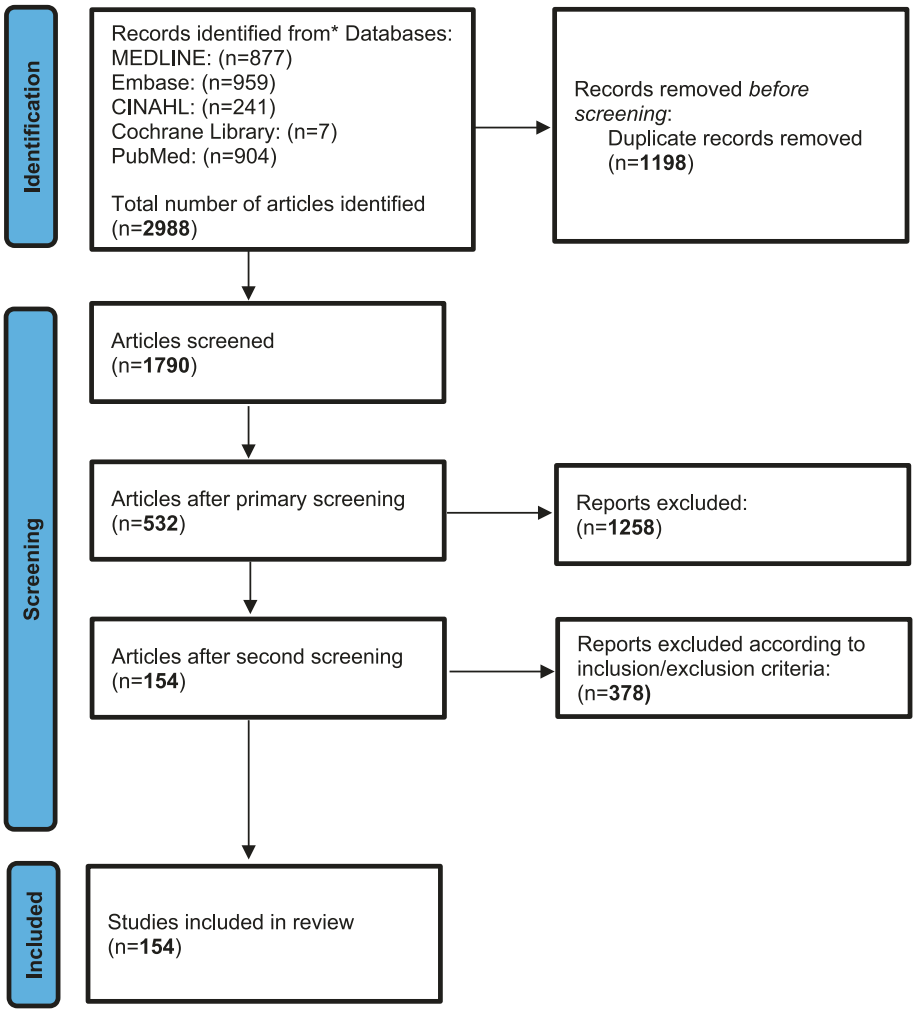

Fig. 1. Adapted PRISMA flow diagram to illustrate search strategy and included studies for review.

treatment which needs to be personalised in any given scenario.

2.2. Constitutive Aspects of GA in Skin Cancers

2.2.1. Age

In geriatrics, it is preferred not to consider the chronological age but rather the biological age and, even better, the patient's life expectancy [12,19]. In the Western world, a GA is recommended for people over 75. In the context of skin cancers, it is recommended to raise this age group to at least 80 years. All patients >80 years of age should be evaluated through a screening test [20–22]. Currently, the most recommended screening tool is the Geriatric 8 (G8) score [23]. If the screening test highlights a frailty risk, the patient should undergo a comprehensive geriatric assessment (CGA) [24].

A two-step approach has been proposed by a geriatric oncology task force to improve the management of older patients with cancer [22]. The first step consists of a screening process for every older patient with cancer to roughly estimate their biological and clinical resilience (i.e., vulnerability to stressors). Older patients screening as "fit" from this assessment should not be considered differently from younger patients. If regarded as "unfit" or "frail" they would require the second step, a CGA. "Unfit" patients at the screening (stage one) phase of the process represent the target population of the geriatrician [25,26]. This classification should not be restrictive of considered treatments, but allows for prevention of severe toxicities to treatments or to calculate the risk of toxicities.

In the case of systemic treatments or surgery requiring general anesthesia, it is recommended to use an assessment focused on performance (i.e., Short Physical Performance Battery [SPPB], Timed Up and Go [TUG], walking speed, grip strength) and cognition (i.e., Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], Mini-COG™ tool). At least one initial screening test should be performed [27]. A correct pre-treatment evaluation prevents the risk of delirium, infections, and prolonged hospital stay for these patients [28]. In local treatments, there are no contraindications to the therapy, and the older patient should receive the same treatment opportunities as the younger one.

2.2.2. Physiological Age-Related Changes

Compared to younger patients, older patients present physiological changes in the absorption, pharmacodynamics, and pharmacokinetics of drugs [29], so it is advisable to evaluate these aspects before starting a systemic treatment. This is not a contraindication to systemic treatments but a warning.

Older patients often present with polypharmacy (taking multiple medicines or drugs, sometimes defined as taking five to nine drugs), which correlates directly with adverse drug reactions (ADR), rather than chronological age. In patients >80, greater attention must be paid to the treatments in place, including a careful medication review [30].

2.2.3. Compliance and Social Networks

If the treatment choice involves systemic anticancer therapies that must be repeated in cycles and/or radiotherapy (RT) delivered over several sessions, a careful assessment of the patient's compliance and

social network is essential. Understanding whether the patient has subjective or objective difficulties in continuing treatment is crucial. This data should not represent a limitation, but rather an invitation to refer patients with difficulties to a geriatric center and activate social assistance programs that allow the treatment to be carried out [31].

2.2.4. Aesthetic Aspects and Quality of Life

Any patient, regardless their age, deserves a treatment that maximises aesthetic results. Cosmesis can significantly impact quality of life (QoL) [32]. In patients with reduced life expectancy related to other causes or comorbidities, pain control, aesthetics, and maintenance of the QoL should be privileged.

2.3. Management of NMSC in Older Patients

The main management options of NMSC in older patients are presented in Fig. 2.

3. Dermatology (Medical and Medicophysical) Treatment

Apart from surgical and RT of NMSC, clinicians have physical, medical-physical, and medical treatments available to treat BCC and cSCC [33,34].

Cryotherapy (destruction by cold which induces necrosis of the targeted lesion) is the main mode of physical treatment [35]. For substantial tumour damage to occur, tissue must be treated to a temperature of −60 °C [36] and needs two freeze-thaw cycles to decrease the number of recurrences [35]. This is typically accomplished with liquid nitrogen. Cryotherapy is mainly used for hyperkeratotic actinic keratosis (AK). To destroy a full tumour, cryotherapy will require local anesthesia because the procedure is painful, as well as directed healing in a second phase which may take several weeks and therefore require local care. A major disadvantage of this technique is the absence of histological control, which does not ensure the absence of residual neoplasia following healing. Other destructive methods include electrodesiccation and curettage, and ablative laser treatment [37].

Photodynamic therapy (PDT) involves the application of a photosensitizing agent (i.e., aminolevulinic acid) on the skin followed by irradiation with a light source [34]. This requires a longer clinic visit as the photosensitizing agent needs to be applied for at least a few hours on the affected skin before the red-light source is applied. The procedure itself can produce some pain. Additionally, patients with mental or physical limitations may have difficulties with the tight physical constraints of the light unit. Most patients cite erythema, irritation, and pain in the week following the procedure, but minimal wound care is required. These treatments are mainly applied in AK, the precursor lesions of cSCC. PDT is usually applied once in AK but requires two applications at two-week intervals in carcinoma in situ (Bowen's disease) or in superficial BCC. PDT can offer broader cure rates of up to 70–90% in both BCC and in situ cSCC [38,39]. A small study has shown that PDT is not less effective in patients >65 years old [40]. While a single-center study [41] showed that the combination of aminolevulinic acid and interferon alpha-2B had a better efficacy, a lower recurrence rate, and caused a smaller wound, indicating that it was a more effective method for the treatment of superficial BCC in older patients. However, cryotherapy and PDT are limited by the depth of penetration and cause local destruction hence no pathology can be obtained after the treatment.

Medical treatments in NMSC involve immune action (i.e., imiquimod) and local chemotherapy (5-fluorouracil) [34]. Imiquimod is a synthetic imidazoquinolinamine, that exhibits immunomodulatory, antiviral, and antitumoral effects by the induction of cytokines, and activation of both innate and humoral immunity. Application of imiquimod should occur five times weekly for six weeks. Imiquimod is regarded as the most effective of the three topical therapies for superficial BCC (imiquimod, 5-fluorouracil, and PDT) but may have late clinical effects [42]. 5-fluorouracil is an antimetabolite that stops the cancer cell from repairing their DNA. Topical 5-fluorouracil should be applied twice daily for 6 to 12 weeks. Both medications typically cause erythema and inflammation of the treated area, and patients must be monitored for adequate therapy. These treatments are applied to precancerous lesions such as AK, and Bowen's disease, but also to superficial BCCs. Although medical treatments can be curative, without pathological control to check the eradication of these lesions, relapse may occur. The application of these molecules requires multiple courses of treatment, and some patients tend to abandon the application prematurely due to side effects, mainly inflammation reactions. This results in the induction of redness, erosion, and crusts which can be disfiguring and last for the whole duration of the treatment. Systemic side effects associated with topical treatments are rare, but an influenza-like syndrome may accompany imiquimod-based treatment following interferon induction. Regarding 5-fluorouracil, even in local application, may lead to resorption and interaction in older patients who are poly-

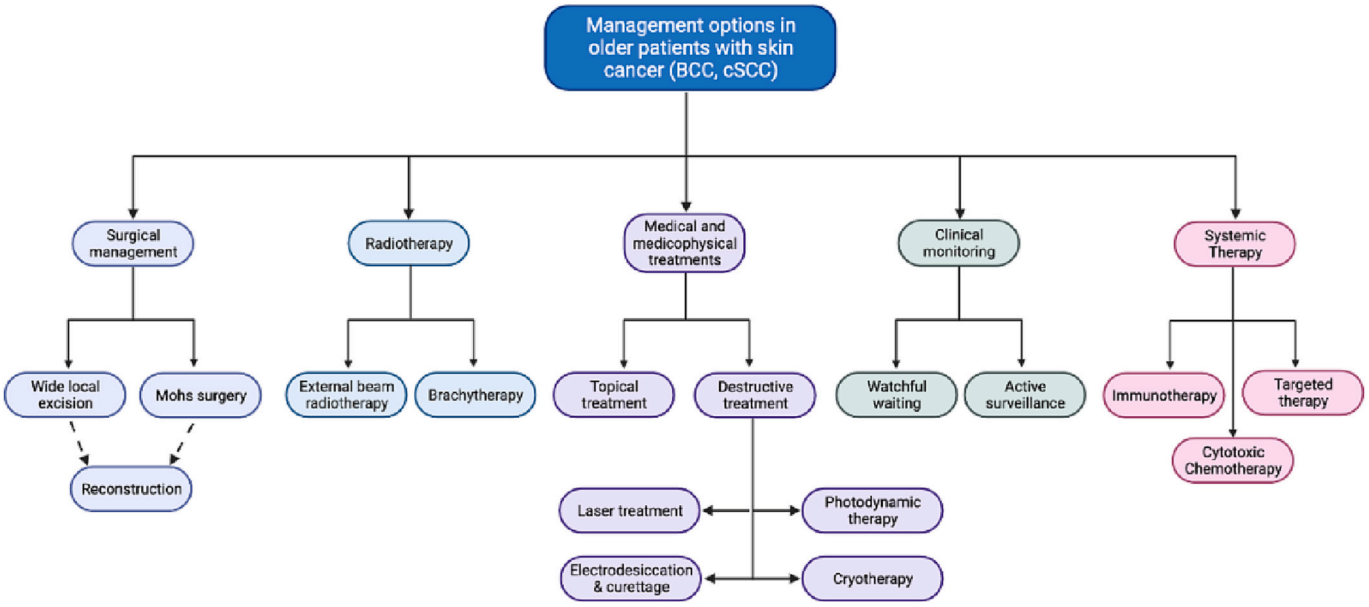

Fig. 2. Management options in older patients with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).

medicated.

Very few studies have been published on the effectiveness and relevance of adapting physical, chemical, or medical treatment in older patients. They present a valid alternative to more invasive treatment options and provide satisfactory local control of skin cancer with adequate cosmesis [43,44].

4. Surgical Management, Including Mohs Micrographic Surgery, and Reconstruction

Surgical treatment of NMSC aims to completely remove the tumour while minimising functional and cosmetic impairment. This goal does not change in older patients. Most NMSCs can be safely treated in an outpatient setting which reduces the stress of the procedure for most older patients [45]. In surgical consultation, it is important to assess the lesion, its anatomic location, and the general condition of the patient as older patients represent a very heterogeneous population. Previous treatments, especially RT in the planned surgical site, can also influence future treatment plans. Treatment must be individualised for each patient. Medications that the patient is taking must be reviewed and modified accordingly, specifically anticoagulants.

4.1. Basal Cell Carcinoma

Surgical excision with a margin of clinically normal skin is regarded as a gold standard, even in older patients. The recommended excision margin is 4 to 5 mm as smaller excision margins can lead to an increased risk of local recurrences. The depth of excision is as important as the lateral margins and should follow the same recommendations [46,47]. Mohs micrographic surgery consists of the excision of the tumour with immediate histologic control of horizontal sections of tissue. The excision and evaluation are repeated until the tumour is completely removed. Although, this procedure is time-consuming and requires special training and equipment. It has a very low recurrence rate and the advantage of reduced surgical margins in preserving aesthetically important areas [48,49]. Therefore, Mohs can improve the treatment outcome in selected patients with larger tumours or those with an aggressive subtype [50,51]. This still holds true for older patients, hence age is not a contraindication for Mohs surgery [51].

4.2. Cutaneous Squamous Cell Carcinoma

Surgical excision with a margin of clinically normal skin is also the best option for treatment in older patients. The recommended excision margin for low-risk tumours is 4 mm and for high-risk tumours, a margin of at least 6 mm is recommended [52]. The depth of excision depends on the structures involved. Scalp, ears, eyelid, nose, and lip were found to be associated with deeper penetration of the tumours at the time of diagnosis requiring resection of deeper structures [53]. Intraoperative assessment with frozen sections is not found to be reliable in assessing resection margins [54]. In high-risk cSCC, delayed reconstruction is usually recommended following the results of standard histology. Mohs micrographic surgery is also regarded as less reliable than in BCC excisions due to the possibility of skip and in transit metastases but can be considered in high-risk tumours pending MDT discussion [55]. Before surgery of larger or more aggressive tumours, regional lymph node status must be assessed by palpation and with ultrasound. Suspicious lymph nodes on clinical examination and/or ultrasound are usually assessed further in CT or MRI scan and by fine needle cytology or core needle biopsy.

4.3. Reconstruction

Reconstruction of defects after excision of BCC or cSCC depends on the size of the excision and the area that is involved. As skin laxity is a characteristic of older patients, most often the defect can be closed directly using a standard 2-layer closure. In defects that cannot be closed directly split or full-thickness skin grafts can be used with good results. This can be further augmented with the use of dermal substitutes. In other cases, local skin or fasciocutaneous flaps can be used. Regional or free flap reconstruction is reserved for the most complex cases where large defects or defects requiring a 3D reconstruction are the results of tumour resection. Even complex reconstruction is not contraindicated in older patients when the general condition and patient-related factors allow it [56,57]. In cases where the margin status is unclear, definitive reconstruction is postponed until the definitive pathological result is available.

5. External Beam Radiotherapy and Brachytherapy (Interventional Radiotherapy)

RT is an excellent non-invasive alternative to surgery in older patients. It can achieve very good disease control with cosmesis and functional outcomes rate. As in the wider population, the intent of RT in older patients can be radical (definitive or adjuvant, postoperative) or palliative. In NMSC, RT is delivered as superficial or orthovoltage x-rays, electron beams, megavoltage photons, or brachytherapy (BT). However, RT for cSCC and BCC is contraindicated in genetic conditions such as Gorlin's syndrome, Ataxia Telangiectasia, or Li-Fraumeni syndrome. It is also relatively contraindicated in poorly controlled connective tissue disorders and sites of previous RT. [3]

5.1. Specific Considerations for Radiotherapy in Older Adults

The prevalence of co-morbidities in older adults, such as hypertension, diabetes, and anticoagulant therapy (as well as potentially many others) makes surgical management of NMSC challenging [58]. Additional parameters that add to the complexity of managing older adults with NMSC include frailty status, limited life expectancy, and limited physiologic reserve. In many cases, a less invasive alternative to surgery, namely RT, should be considered.

RT for NMSC is typically administered in an outpatient setting. Inpatient admissions can pose a significant health challenge for an older adult due to the risk of hospital-acquired infections and relative immobilisation. RT compared to surgical intervention can deliver better cosmetic outcomes of NMSC treatment at certain anatomical locations with function preservation such as in-ear or nose location. RT is also preferable for older adults who present with multiple BCC or cSCC for which multiple surgical excisions may not be appropriate.

Older adults with NMSC can be treated with definitive RT where adequate surgical excision is not appropriate or possible or in patients who decline surgery. Postoperative RT can be offered to older adults with NMSC who have involved or close surgical margins. Adjuvant RT is also indicated in a patient with negative prognostic factors such as pT4 staging, perineural, or perivascular invasion [59].

Standard RT doses and fractionations should be considered in all fit

Table 1
Recommended standard dose and fractionation of EBRT in NMSC*.

Field size < 3.5 cm	Field size 3.5–6.0 cm	Field size > 6.0 cm	Number of Fractions
18–20Gy	N/A	N/A	1
32.5-35Gy	32.5-35Gy	N/A	5
45Gy	40-45Gy	N/A	10
N/A	45-50Gy	50Gy	15
N/A	50-55Gy	50-55Gy	20
N/A	60Gy	60Gy	30
N/A	66Gy	60-66Gy	33

EBRT – external beam radiotherapy, NMSC – non-melanoma skin cancer, Gy -gray.

* cSCC merits a higher dose than BCC although is it not commonly applied in clinical practice.

patients, regardless of their age (Table 1). Non-standard fractionation (i.e., hypofractionation) or dose modifications should be applied to address specific challenges such as travel to RT centres. Co-morbidities, such as anticoagulation, poorly controlled diabetes mellitus, peripheral vascular issues, and peripheral oedema could potentially have an impact on RT-related toxicity. There is no convincing evidence for the use of concurrent chemotherapy in the adjuvant setting or exclusive chemo-RT for high-risk cSCC [59,60].

Older patients with cSCC or very rarely with BCC that metastasised to lymph nodes should be appropriately assessed and undergo lymphadenectomy followed by adjuvant RT [3], pending their performance status and co-morbidities.

Hypofractionated RT with 5-7Gy per fraction delivered in 1–3 fractions per week up to a total of 30-40Gy results in high local control and tolerable toxicity. This schedule in an older patient with NMSC can be considered on a case-by-case basis and based on practitioner/institutional experience [59,61].

5.2. Brachytherapy

BT offers hypofractionated schedules and is associated with high radiation dose conformity within the target volume and rapid dose fall-off in surrounding normal tissues [62]. There are several techniques and fractionation schedules in which skin BT can be performed in older patients [62]. BT is delivered in a relatively short treatment time and offers excellent cosmetic and good functional outcomes with often fewer visits than external beam RT. [62] These advantages are particularly important in older and/or frail patients, who may be less compliant with prolonged treatments, daily attendance, and complex set-up required for external beam RT.

BT is often the treatment of choice for older patients with poor performance status and/or severe comorbidities when surgery is not a viable option (e.g., on anticoagulation). As the BT applicator is placed directly on the affected skin and treatment time remains relatively short, it can be used in primary and postoperative treatment in patients with mental health issues (e.g., dementia, significant anxiety) or mobility (e.g., Parkinson's disease). Therefore, BT improves inter-fraction reproducibility, reduces set-up errors, and allows to compensate for moving targets in patients with poor patient compliance [63]. Age should not be regarded as a limiting factor in skin BT [64].

5.3. Palliative Radiotherapy

Palliative RT is an excellent option for patients where there are no viable curative options. These include older adults with medically and/or technically inoperable cutaneous squamous cell carcinoma that may metastasize to nodal basins such as neck, axilla, and groin regions. Palliative RT aims at durable local control, reduction of local symptoms, and prevention of disease-related complications such as bleeding or ulceration. It should be minimally invasive and of shorter duration, especially for patients with poor performance status, short life expectancy, and those unable to travel for multiple hospital visits. Palliative RT can be used in primary skin cancer, nodal metastases, or in skin and subcutaneous metastases from non-skin primaries. Almost all these scenarios are well palliated with hypo-fractionated RT (e.g., 20-36Gy in 5–6 fractions with options of daily, 2–3 times a week, or weekly treatment) which is well tolerated with excellent response rates and with patients often dying from their comorbid disease and rarely from their skin cancer [61,65–67].

5.4. Follow-up Arrangements

Post-RT follow-up arrangement to assess treatment effectiveness is crucial for determining management directions. Furthermore, consistent data collection for local service audits is important for improving and streamlining patient care. Effective communication between healthcare professionals in the MDT to develop shared follow-up pathways that embody holistic medicine is the utmost priority for patients. Remote consultation via telemedicine should be considered where appropriate for greater access to continuity of care.

6. Systemic Anticancer Treatment

The advent of immunotherapy has completely changed the therapeutic possibilities for patients with cSCC and especially for the older population. The first trial published in 2018 showed tremendous results with anti-programmed cell-death protein 1 monoclonal antibody (anti-PD1) cemiplimab in locally advanced or metastatic disease with objective response rates of about 50%, durable response rates of 60% and <20% of patients having progressive disease [68]. In the case of the initial response, which is mostly reached within two months, patients had no relapse in about 80% of the cases at the time of data cut-off of the trial, suggesting long-lasting responses once a clinical response is achieved. In contrast to other trials, 75% of patients were older than 65 years, and patients until the age of 93 were included. It was not reported whether the response rate was maintained among the oldest or frail population.

Side effects of immunotherapy are called immune-related adverse events (irAEs) and in the registration trial grade 3 or higher serious adverse events were described in 29% of cases. In most cases, however, the toxicities were very manageable, which is in contrast with prior conventional therapies such as chemotherapy and anti-epidermal growth factor (EGFR) therapy.

To find the right systemic treatment for the patient, working closely together with the general practitioner and the family around the patient is of the utmost importance to best fulfil the patient's needs. A CGA is advised to guide treatment decisions.

6.1. Basal Cell Carcinoma

Systemic therapy for advanced BCC utilises hedgehog inhibitors (HHI), such as sonidegib and vismodegib, which target the Wnt pathway. These targeted agents have been shown to exhibit antitumoral potential and sustained efficacy with manageable safety profiles [69,70]. However, the long-term side effects such as ageusia and anorexia may complicate therapy adherence. The incorporation of immune checkpoint inhibitors (ICI) into BCC management has been explored. A phase 2 trial investigating the efficacy of cemiplimab post-HHI therapy showed that the overall response to ICI was less [71] compared to the response in spinocellular carcinoma (6% of patients had a complete response and 31% had a partial response). Combination treatment strategies are also being researched. Currently, it remains unclear whether the response rate to ICI is maintained among the geriatric population. Patients >65 years may be more prone to treatment discontinuation with combination therapy of ICI and hedgehog inhibitors due to cumulative toxicity but efficacy seems similar [72].

6.2. Cutaneous Squamous Cell Carcinoma

In the registration trial, patients with a lower performance status or compromised immune system were excluded, but this group makes up a large part of our daily practice. Since 2020, multiple retrospective reviews have been published describing a 'real-world' population and the authors mostly conclude that efficacy and safety are maintained. A French group published data of 240 patients treated with cemiplimab with a mean age of 77 years, including 24% of patients that were immunocompromised (59 patients with chronic haematological diseases and 7 organ transplant recipients) and 27% of patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or higher. After a median follow-up of 12.6 months, they report objective response rates in 50% of patients with disease control in 60% and only 9% of patients experiencing a serious adverse event of grade 3 or higher, with

two transplant rejections. They found a significantly lower response rate in patients with poorer performance status (≥2) but emphasize that even in this cohort of patients, responses were seen in 37% [73]. The second largest retrospective multicentre study described 131 patients being treated in Italy and found a disease control rate of 71% with comparable rates of adverse events [74]. These retrospective real-world reviews suggest that ICI is safe and efficacious even at an advanced age, consistent with a recent review on the impact of age on the toxicity of ICI demonstrating the safety of therapy regardless of age, with no appreciable increase in irAEs in older patients [75].

There is an ongoing debate in ICI regarding the duration of such treatment. As 80% of the patients have a durable response after an initial good response, one can presume that in those patients the immune system is recognizing the tumor and will continue to do so as an immune memory has been formed. In treating older patients, there is a stronger focus on symptom control than on life-prolonging measures, leading to many patients asking to stop ICI upon achieving a complete response in our clinic. Up to now, only very few have relapsed and in case of relapse, most respond well to rechallenging of immunotherapy, which is consistent with published data [73] showing very few relapses in complete responders after cemiplimab discontinuation.

Some older patients have an underlying autoimmune disease (AID) which can be reactivated while giving immunotherapy [76,77], making communication and collaboration with the organ specialist treating the AID essential to determine the necessity for immunosuppressive treatment and the risk of starting ICI, knowing that in several tumour types, the tumour response may be impaired if ICI is given alongside systemic immunosuppression [78]. Retrospective analyses of patients treated with cemiplimab have shown comparable toxicity rates among immunosuppressed and immunocompetent patients. Although this has not been studied so far in this setting, stopping, or switching immunosuppression might also have an anti-tumoral role as is the case in patients with renal transplantation who develop cSCC.

In conclusion, cSCC is an immunosensitive disease and we hypothesize that only a few ICI injections can restore the immune system, as illustrated by rapid and often long-lasting responses. The acceptable toxicity profile, even in the older, frail, and comorbid population, support the choice of ICI as the gold standard for systemic therapy of cSCC.

7. Nursing Care and Input

Cancer nurses provide medical interventions to people in healthcare settings. Depending on the treatment method, patients with NMSC can be looked after by dermatology nurses, surgical nurses, and RT nurses. A dermatology nurse provides patient education on skincare and skin cancer prevention, removing stitches post-biopsy, or attending to complex wound care dressings. A surgical nurse in the hospital setting will care for a patient post-procedure from tasks like activities of daily living to wound care and preventing postsurgical infection. Once safe discharge from the hospital is facilitated the community nursing team can assist with the management of the wound at home if required post-surgery. Patients undergoing RT with skin as the target organ benefit from a patient-centered, integrated model of care, with nurses playing a vital role in the MDT.

Early identification and clear communication with patients about side effects are important for patients to manage symptoms and receive optimal treatment [79]. Nursing consultations include psychosocial discussions, clinical assessments, and management of treatment side effects (e.g., post-surgical healing, radiation-induced skin reactions). Integrated care is patient-centered but also includes families and caregivers involved across the cancer experience from diagnosis, treatment, and survivorship to end-of-life care [80]. Nurses deliver this level of care by educating, counseling, and driving support functions needed to assist the patient and family to cope with their treatment plan.

RT nursing is a relatively young subspeciality. Nurses are trained and educated to understand how RT interacts with the skin to treat NMSC [81]. Patients are assessed by the nurse before commencing RT to identify any risks or concerns that might limit them while on treatment. Social circumstances, well-being, mobility, cognition, and skin integrity are some examples of areas discussed and a plan implemented to facilitate their treatment journey.

Weekly nurse-led clinics during treatment address patient side effects such as fatigue, pain, or skin irritations as part of the patient-centred care model ensuring all needs including holistic are met. Nurse-led consultations can empower patients to better cope with side effects, leading to a high level of patient satisfaction [82]. Skin is graded using scoring tools (i.e., CTCAE v.5) and dressings are initiated based on this grading outcome. A skincare pathway is followed as the aim is to reduce variation in clinical practice and therefore provide consistent skincare advise to our patients while enhancing nurses to work as efficient caregivers. Clinical photography of any skin change is attended to over the course of the patient's treatment plan. Thus, enabling active monitoring of any skin reaction that may occur. Nurse-led clinics are an opportunity to provide support and to identify challenges that might impact the safe and effective delivery of care to the patient.

On the final day of treatment, the nurse implements a discharge plan adopting an integrated care model which will see patient, family, and caregivers' involvement. The nurse also educates patients on effective wound management to promote confidence and patient participation with dressings, if required. The nurse remains a key component of the patient's treatment journey following up with the patient after treatment and attending to wound care if required until satisfied the patient is safe to be discharged from care. Escalation to the clinician is attended to by the nurse as necessary but otherwise, the patient's treatment journey can be predominantly nurse-led and patient-focused.

8. Deciding Not to Treat and Clinical Monitoring

Skin cancer is often slow growing and may never cause any symptoms or problems, apart from awareness of cosmetic appearance. Older patients with predominantly low-risk skin cancer may benefit from clinical monitoring (active surveillance or watchful waiting). It involves monitoring skin cancer that is not causing any symptoms or is minimally symptomatic with the view of consideration of the active anticancer treatment of cancer that grows locally and/or worsening of symptoms. The active surveillance approach is more proactive and involves regularly scheduled follow-up consultations with the medical team. Watchful waiting (deciding on treatment when symptoms are troubling with consultation usually initiated by the patient) may be a suitable option for patients who may not fully benefit from either surgery or RT. In a prospective cohort study by Linos et al. [83], researchers noted that one-quarter of patients with NMSC were classified as having limited life expectancy either because they were at least 85 years old or suffered from significant comorbidities. Nearly half of the patients with limited life expectancy died within five years of surgery, but none of the deaths were attributed to skin cancer. Interestingly, it was reported that a fifth of treated patients reported significant treatment-associated complications. Thus suggesting that active treatment options may pose risks that may outweigh potential benefits [83]. Chauhan et al. [84] advocate that appropriate counseling may prevent surgery among older patients (>90 years) who may never see a benefit from facial nonmelanoma skin cancer excision. As a result, future studies are needed to investigate whether clinical monitoring in selected older patients with skin cancer is cost-effective and generates higher patient satisfaction than surgical excision [84].

Many older patients with skin cancer on clinical monitoring may never experience problems related to their skin cancer and may not need any treatment. The decision to treat or not to treat should always be taken jointly with the patient and his carers and consider the patient's lifestyle, expectations, comorbidities, and polypharmacy together with the patient's needs, wishes, and compliance.

9. Concept of Easy-to-Treat and Difficult-to-Treat NMSC

The vast majority of NMSCs are regarded as relatively easily treatable by the common therapies discussed below. There is no agreed definition of easy-to-treat and difficult-to-treat NMSC [85]. The 2019 European consensus-based interdisciplinary guidelines introduced the concept of easy-to-treat and difficult-to-treat BCC based on the low and high risk of recurrence [86]. More recently, a team of NMSC experts has differentiated groups of difficult-to-treat NMSC by cluster subdivision [87]. The clusters included different criteria such as size, number of lesions, risk of disfigurement and the need for general anesthesia specifically in frail patients, patient capacity, and wishes.

10. Patient Advocacy – Patient's Voice is Very Important

Chuck, Patient Advocate: *"I was asked to write about why a patient advocate, in particular a geriatric advocate, was asked to partner with this task force looking at NMSC.*

My answer would be the same for any advocate partnering with any research in cancer. Unless you have had cancer or been a caregiver for someone with cancer it's hard to know what 'we' think about. I'm not a researcher or doctor or statistician - what I am is a person willing to ask questions. If you write a report on your work and I don't understand what you said then, as a patient, it isn't doing me any good.

As a patient trying to investigate what is right for me, I need to be able to understand what your paper says in language that makes sense to me as a layperson. Without an advocate like me partnering with you, you probably don't know what I can or cannot discern from your work.

By including advocates, you will be better informed on our feelings, perceptions, and what we as patients with cancer want to know about your work. As researchers, you need to know what is important to us: the patient with cancer, cancer caregiver, or cancer survivor.

We don't want to just be a cog in the wheel, a checkbox that says you included an advocate, we want to be a partner in your research. When it comes time to share your work or results, we can help with that as well.

I would also advise patients to have written down questions before consultation, do your Google search if needed but please use only well recognised websites, ask for a copy of the clinic letter or letter to the patient, including an easy-to-read / accessible format if needed. If you need any special arrangements, please contact your medical team before the consultation so they can accommodate it for you.

How can you find your older adult advocate?

There are many cancer advocacy groups, some working at international levels, others at national or local. Examples of such advocate groups include in US: the American Cancer Society, National Cancer Institute and one of the larger groups is the Southwest Cancer Chemotherapy Study Group (SWOG https://www.swog.org/), in Europe: the European Cancer Organisation https://www.europeancancer.org/ and in Australia: Cancer Council https://www.cancer.org.au/. Patient advocate groups can be integrated as a part of such organizations or exist as a separate entity example being the US National Coalition for Cancer Survivorship (NCCS https://canceradvocacy.org/) or the European Cancer Patient Coalition (ECPC https://ecpc.org/). Many groups have cancer advocates. Unfortunately, there are not many groups that are exclusively older adult advocates. The examples are the International Society of Geriatric Oncology, also called SIOG *(Société Internationale d'Oncologie Gériatrique https://siog.org/) and Stakeholders for Care in Oncology & Research for our Elders Board (SCOREboard https://www.mycarg.org/?page_id=148). SCOREboard is part of the Cancer Aging Research Group (CARG), an international consortium of geriatric oncology investigators https://www.mycarg.org/.*

11. Conclusions

Age should not be the sole deciding factor in the management of older patients with NMSC. The decision-making process should consider the patient's lifestyle, needs, and wishes, as long as they understand what the course of the cancer management entails. In patients with limited or no capacity, such discussion should include their family and/or carers. There are a variety of options available for managing NMSC and each modality presents its advantages and disadvantages (Table 2). Patients/carers should feel empowered to advocate for themselves or for the individual that they are caring for and to take an active role in guiding treatment.

12. General Recommendations

- **Age** alone is an **inadequate** factor in the decision-making process in NMSC
- Treatment decisions should be based on a **comprehensive approach** including health status (comorbidities, nutritional status, dependence) and patient's preference
- **High cure rates** should not necessarily guide the management of frail older patients who might not want to undergo invasive procedures in their final years of life
- **Cognitive evaluation** is mandatory to assess the patient's capacity to evaluate information and make informed decisions
- In patients with **cognitive impairment,** determine whether an adjustment in the environment (i.e., longer consultation time, easy-to-read patient information, non-standard treatment approach, virtual consultation with family/cares present) could improve the patient's compliance with the proposed treatment
- For patients aged 80 and over, a **frailty screening test** is recommended. If the screening test highlights a frailty risk, the patient should undergo a complete geriatric assessment
- Careful evaluation of **polypharmacy, potential drug interactions, and proactive management of treatment side effects** is needed in older patients
- **Remote consultation** with pictures sent by the patient/family/carers should be considered where appropriate.
- **Surgery** option depends on general performance status and comorbidities. It is rarely contraindicated as it can most often be performed under local anaesthesia. Complex operations even free tissue transfer can be safely done in older patients who are in good biological condition and with more extensive preparation.
- **Radiotherapy/brachytherapy** is an excellent alternative treatment for older patients with NMSC, especially when surgery is not a viable option.
- In retrospective series **immunotherapy** and **targeted therapy** in advanced and metastatic skin cancer, their antitumor activity was not impaired in very older patients

Table 2
Advantages and disadvantages of non-melanoma skin cancer management options in older patients.

Management options	Advantages	Disadvantages
Medical and medicophysical	Non-invasive	Lower cure rates than in surgery No pathology
Surgery	High chances of cure Excision provides pathology	Surgical complications, cosmetic and functional impairment
Radiotherapy	High chances of cure Noninvasive	Multiple hospital visits Radiotherapy related side effects
Systemic anticancer treatments (targeted therapy and immunotherapy)	High chances of regression in BCC Long lasting responses (years) can be expected if good initial response	Not curative Ultimately therapy has often to be stopped due to side effects Unsure which patients will have side effects
Clinical monitoring	No treatment related side effects No stress related to treatment	Lesion can progress, become more symptomatic and more challenging to treat

- If **clinical study participation** is an option, it should be discussed with patients and their caregivers as older patients are underrepresented in skin cancer research
- **Future studies are needed** to investigate if a no-treatment option in selected older patients with skin cancer is cost-effective and has higher patient satisfaction than active treatment
- **As the patient or the caregiver**, if you don't understand what you are hearing ask for explanations. Advocate for yourself or the person you are caring for. It is okay to speak up.

12.1. Low-risk/Localised/Early-stage BCC and cSCC

- Any active treatment option should be considered if felt appropriate
- Active clinical monitoring could be considered in patients with asymptomatic NMSC, especially with BCC and/or short life expectancy

12.2. Advanced Disease/Palliative Treatment in BCC and cSCC

- Treatment burden, especially in extensive treatment, should be carefully considered against the patient's fitness and wishes
- Early palliation and supportive care should be implemented
- Palliative treatments include debulking, radiotherapy, systemic treatment, and medical treatments for pain and symptoms
- In selected cases, best supportive care only should be considered

Author Contributions

Agata Rembielak: Conceptualization, Methodology, Funding acquisition, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Thomas Yau:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Baran Akagunduz:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Sandrine Aspeslagh:** Investigation, Writing – original draft, Writing – review & editing. **Giuseppe Colloca:** Investigation, Writing – original draft, Writing – review & editing. **Aoife Conway:** Writing – original draft, Writing – review & editing. **Falalu Danwata:** Investigation, Writing – original draft, Writing – review & editing. **Veronique del Marmol:** Writing – original draft, Writing – review & editing. **Chuck O'Shea:** Writing – original draft, Writing – review & editing. **Marthe Verhaert:** Writing – original draft, Writing – review & editing. **Rado Zic:** Writing – original draft, Writing – review & editing. **Dan Livesey:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

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Appendix A. Supplementary data

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