Effect of Patient Characteristics on Treatment Decisions Regarding Keratinocyte Carcinoma in Elderly Patients: A Review of the Current Literature

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There are straightforward guidelines for treatment of keratinocyte carcinoma (formerly known as non-melanoma skin cancer); however, there are no clear recommendations specifically for elderly patients. The aim of this review was to provide an overview of the current literature about the effect of patient characteristics, specifically life expectancy, frailty and comorbidity, on treatment decisions in elderly patients with keratinocyte carcinoma, by searching PubMed database. It was found that the literature is limited and based mostly on small retrospective studies. Therefore, it is difficult to give firm recommendations about how to treat elderly people who have keratinocyte carcinoma. A “one-size-fits-all” approach to this population is not sufficient: life expectancy and frailty need to be considered in the decision-making process regarding treatment for elderly people with keratinocyte carcinoma. Among the comorbidity scores, Adult-Comorbidity-Evaluation-27-index seems to have the best prognostic value. Prospective studies are needed to generate more individualized recommendations for this increasing and often vulnerable group.

Key words: keratinocyte carcinoma; elderly people; treatment; patient characteristics.

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UV radiation cumulatively damages the skin, and therefore non-melanoma skin cancer, currently termed “keratinocyte carcinoma” (KC), affects a significant number of patients with advanced age (1). In the Netherlands, for example, approximately half of the patients with basal cell carcinoma (BCC) were 70 years old or older and almost 3/4 of patients with squamous cell carcinoma (SCC) were 70 years or above (2). Confirming the theory of cumulative damage to the skin by UV radiation, KC occurs mostly in the sun-exposed head and neck region (2). This fact, together with the substantial increase in the elderly population, results in an excessive number of elderly patients with KC, especially in the head and neck area (KCHN).

There are straightforward clinical guidelines for the treatment of both BCC and SCC, and in some cases individualized treatment can be applied, as alternatives are given for the increasing population of elderly people, who may benefit from a different approach than their younger counterparts.

The aim of the present review is to provide clinical recommendations on how to assess the most relevant patients’ characteristics, specifically in elderly patients with KC, after reviewing the literature on life expectancy, frailty and comorbidity. The effect of age on treatment outcomes and alternative treatment schedules for elderly patients are discussed in another review article (5).

METHODS

A literature search was performed using PubMed database in March 2020. The following issues were systematically reviewed from the literature: life expectancy; frailty; and comorbidity.

A search term was created for each individual topic, as described in Table I. Full-text English manuscripts about KC and patient characteristics, especially in elderly people, were eligible for inclusion and have been retrieved, reviewed and checked for references by at least 2 authors.
RESULTS

Life expectancy

This section reviews literature regarding all relevant articles about the influence of limited life expectancy (LLE) on treatment decisions in elderly people with KC (the results are summarized in Table II).

The most obvious difference between young and elderly patients with KC is their life expectancy. KC, especially BCC, but also SCC in early stage, is in most cases not life-threatening; therefore, a wait-and-see policy can be considered in vulnerable elderly patients with a short life expectancy. Esserman et al. (6) proposed the term “indolent lesion of epithelial origin” (IDLE), drawing attention to the danger of the overdiagnosis and overtreatment of cancer. KC is one of the targeted IDLEs, a candidate for change in terminology and to bring wait-and-see policy to the foreground, instead of surgery. These suggestions harmonize with the large prospective study by Linos et al. (7). Based on more than 1,500 cases of KC, this study showed that choice of surgery was not influenced by the patients’ diagnosis, even after adjusting for tumour and patient characteristics. They suggest that clinicians consider less invasive treatment in patients with KC and LLE because of the low recurrence rates and high mortality rates unrelated to KC. On the other hand, these tumours can cause long-term significant morbidity, such as pain and cosmetic or functional impairment, when left untreated, which may necessitate (major) treatment in a more advanced stage. In some cases, it is extremely difficult to make a proper prediction as to whether these patients live long enough to benefit from the treatment. This dilemma is often referred to as “time to benefit”.

Another more recent study by Linos et al. (8), which included 9,653 KC in patients aged ≥65 years, showed that type of treatment was not influenced by the patient’s life expectancy.

As emphasized in the review of Lubeek et al. (9), not only medical aspects, but also personal preferences of the patient and their family should be involved in the decision-making process, weighing potential benefits and risks of treatment in patients with a LLE. However, the definition of LLE is not straightforward and data on the prediction of life expectancy in KC patients based on comorbidity is inconsistent.

Charles et al. (10) found, in a retrospective study on nonagenarians undergoing Mohs micrographic surgery (MMS) for KC, that patients without comorbidities (measured by the Charlson Comorbidity Index; CCI) survived longer. On the contrary, another study which included patients of 90 years and older, did not find any association between CCI and survival and confirmed a substantial survival time of these patients without morbidity or mortality after surgery (11). Subsequently, a prospective study in patients with KC who were 80 years and older, found CCI to be a predictor of increased overall mortality (12). According to a recent study, the comorbidity indexes Adult Comorbidity Evaluation-27 (ACE-27) and age-adjusted CCI can predict LLE in the very elderly (≥85 years) (13). The different outcomes of these studies can be explained by the differences in the inclusion criteria (i.e. age, type of surgery), as highlighted by the study of MacFarlane & Goldberg (14).

Based on the above-mentioned studies, we can conclude that type of treatment does not seem to be influenced by LLE; however, it should be involved in the decision-making process.

Table I. Literature search method performed in PubMed

| Topic             | Last search date | Search term                                                                 | Results                                                                 |
|-------------------|------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Life expectancy   | 8 March 2020     | (“Skin Neoplasms”[Mesh] OR skin cancer*[tiab] OR keratinocyte carcinoma*[tiab]) AND (“Carcinoma, Basal Cell*[Mesh] OR “Carcinoma, Squamous Cell*[Mesh] OR nonmelanoma*[tiab] OR non-melanoma*[tiab] OR basal cell carcinoma*[tiab] OR squamous cell carcinoma*[tiab] OR keratinocyte carcinoma*[tiab] OR Planocellular Carcinoma*[tiab]) AND (“Aged*[Mesh] OR elder*[tiab] OR older patient*[tiab] OR older person*[tiab] OR older people*[tiab] OR older adult*[tiab] OR older cancer patient*[tiab] OR old patient*[tiab] OR old person*[tiab] OR old people*[tiab] OR geriat*[tiab] OR old age*[tiab] OR octogenarian*[tiab] OR nonagenarian*[tiab]) AND “Life Expectancy*[Mesh] OR “Quality-Adjusted Life Years*[Mesh] OR “life[tiab] AND expect*[tiab]) OR life year*[tiab] OR qaly*[tiab] OR life table*[tiab] OR LLE*[tiab]) | This search identified 53 articles, and after cross-referencing, a total of 6 articles were found relevant (Table II) |

Frailty

| Topic             | Last search date | Search term                                                                 | Results                                                                 |
|-------------------|------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Frailty           | 8 March 2020     | (“Skin Neoplasms”[Mesh] OR skin cancer*[tiab] OR cutaneous head and neck malignancies*[tiab]) AND (“Carcinoma, Basal Cell*[Mesh] OR “Carcinoma, Squamous Cell*[Mesh] OR nonmelanoma*[tiab] OR non-melanoma*[tiab] OR basal cell carcinoma*[tiab] OR squamous cell carcinoma*[tiab] OR keratinocyte carcinoma*[tiab] OR cutaneous head and neck malignancies*[tiab] OR head and neck cancer*[tiab] OR Planocellular Carcinoma*[tiab]) AND (“Aged*[Mesh] OR elder*[tiab] OR older patient*[tiab] OR older person*[tiab] OR older people*[tiab] OR older adult*[tiab] OR older cancer patient*[tiab] OR old patient*[tiab] OR old person*[tiab] OR old people*[tiab] OR geriat*[tiab] OR old age*[tiab] OR octogenarian*[tiab] OR nonagenarian*[tiab]) AND (“Frailty*[Mesh] OR “Frail Elderly*[Mesh] OR “Geriatric Assessment*[Mesh] OR Frail*[tiab] OR vulnerab*[tiab] OR geriatric assessment*[tiab] OR geriatric*[tiab] OR g-9*[tiab]) | This search resulted in 37 hits and 3 relevant studies (Table III) |

Comorbidity

| Topic             | Last search date | Search term                                                                 | Results                                                                 |
|-------------------|------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Comorbidity       | 8 March 2020     | (“Skin Neoplasms”[Mesh] OR skin cancer*[tiab] OR keratinocyte carcinoma*[tiab]) AND (“Carcinoma, Basal Cell*[Mesh] OR “Carcinoma, Squamous Cell*[Mesh] OR nonmelanoma*[tiab] OR non-melanoma*[tiab] OR basal cell carcinoma*[tiab] OR squamous cell carcinoma*[tiab] OR keratinocyte carcinoma*[tiab] OR Planocellular Carcinoma*[tiab]) AND (“Aged*[Mesh] OR elder*[tiab] OR older patient*[tiab] OR older patient*[tiab] OR older person*[tiab] OR older people*[tiab] OR older adult*[tiab] OR older cancer patient*[tiab] OR old patient*[tiab] OR old person*[tiab] OR old people*[tiab] OR geriat*[tiab] OR old age*[tiab] OR octogenarian*[tiab] OR nonagenarian*[tiab]) AND (“Comorbidity*[Mesh] OR comorbid*[tiab] OR co-morbidity*[tiab] OR co-exist*[tiab] OR multi-morbidity*[tiab]) | This search identified 208 articles. After cross-referencing, a total of 11 relevant articles were included (Table IV) |
Therefore, we recommend assessing life expectancy in elderly people, especially before major treatment is performed. Predicting life expectancy is complex; however, comorbidity (measured by ACE-27 or age-adjusted CCI) is an important factor in the very elderly and should therefore be considered. In case of LLE, minimal invasive treatment can be recommended. Nevertheless, the personal preferences of the patient and their family should always be considered in the decision-making process.

**Frailty**

This section reviews literature regarding all relevant articles about the influence of frailty on treatment decisions in elderly with KC (results summarized in Table III).

In recent decades, the concept of “frailty” has been widely investigated, reflecting a major impact on the physical state of a vulnerable patient by a minor stressor (15). A comprehensive geriatric assessment (CGA) is the current gold standard in detecting frailty by thoroughly screening for possible impairments in multiple domains of life in elderly patients. Functional, nutritional, cognitive and psychological state, social support and physical performance needs to be analysed (16). A CGA is time consuming and therefore not commonly used in clinical practice, especially for patients with KC. Several shorter screening instruments have been developed and tested in various patient cohorts, but their predictive value seems disappointing (17, 18).

The study by Bras et al. (19) primarily analysed the relation between frailty (measured by the Groningen Frailty Indicator, GFI) and postoperative complications, including, beside skin malignancies, also mucosal and salivary gland malignancies of the head and neck. No separate analysis was performed on patients with skin cancer. The total GFI score was not predictive for complications; however, its dimension “health problems” was related to complications. Other predictors of complications were advanced tumour stage and prolonged surgery. The study also analysed the subjective experiences of the recovery by the patients and the surgeons. Interestingly, frail patients experienced more often difficult recovery, but the surgeon often underestimated this. Based on this study, it is not possible to evaluate the role of frailty screening in elderly patients with KC.

A recent study by De Vries et al. (20) prospectively analysed the value of geriatric assessment for predicting postoperative complications in patients undergoing surgery for cutaneous head and neck malignancies. This study identified the Geriatric 8 (G8) frailty screener as the strongest independent predictor of postoperative complications. However, almost three-quarter of the patients were scored as frail according to this test, questioning the value of this frailty screener in daily practice.

In another recent study of patients diagnosed with KC undergoing excision and reconstructive surgery, frailty was scored using the FRAIL scale, which includes 5
comorbidities are increasing with age. This finding has
already been verified in patients with KC (26). Inflam-
matory bowel disease (IBD), rheumatoid arthritis (RA),
extra-cutaneous malignancies, solid organ transplantation,
alcohol consumption and various skin disorders
were significantly more often observed in patients with
BCC compared with patients without BCC. Smoking
and obesity do not seem to be risk factors for BCC (27).
Furthermore, older people (≥60 years) with diabetes mel-
litus (DM) had increased incidence rates of KC compared
with patients without DM (28).

The systematic review by Connolly et al. (25) aimed
to identify comorbidity instruments used in the KC
population and prefers comorbidity instead of age in
treatment decision-making. The most commonly used
comorbidity score is the CCI, followed by ACE-27 and
American Society of Anesthesiologists risk classification
system (ASA score). This review concludes that there are
only small and heterogeneous studies available. ACE-27
seems to be superior to the other scoring systems, as it
analyses the most conditions and at the same time allows
for comorbidity grading. However, larger studies are
needed to judge its real value.

There is a correlation between comorbidity and
postoperative complications; however, it is not obvious
whether comorbidity scores could be used as predictive
instruments to forecast treatment-related adverse events.

Comorbidity

This section presents literature regarding all relevant
articles about the influence of comorbidity on treatment
decisions in elderly patients with KC, among which a
systematic review about comorbidity indices used in
patients with KC (25) (results summarized in Table IV).

It is known that both the number and severity of
comorbidities are increasing with age. This finding has

### Table III. Overview of literature on frailty

| Study            | Type          | Participants/age                                      | Treatment | Frailty tool | Outcome                                                                 | Limitations                                                                 |
|------------------|---------------|------------------------------------------------------|-----------|--------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Bras et al. (19) 2015 | Retrospective study | Patients aged ≥65 years with head and neck cancer | Surgery   | GFI          | - Frail did not predict postoperative complications                     | - Both mucosal and cutaneous head and neck cancer were included             |
| De Vries et al. (20) 2019 | Prospective study | Patients with cutaneous head and neck malignancies Mean age 78.9 years | Surgery   | G8, GFI      | - Frail measured by the G8 was the strongest predictor of postoperative complications | - Retrospective character, with no information about the decision-making of both the patient and surgeon Study performed in a tertiary care hospital, which included a high amount of complex patients and tumours |
| Valdatta et al. (21) 2019 | Retrospective study | Patients with massive KC, aged ≥65 years, mean age 81 years | Plastic/reconstructive surgery | FRAIL scale | - The GFI section ‘health problems’ was a significant predictor for postoperative complications |- Frail patients experienced more often difficult postoperative recovery - Frail patients experienced more often difficult postoperative recovery |

GFI: Groningen Frailty Index; G8: Geriatric 8.
Table IV. Overview of literature on comorbidity

| Study                  | Type                      | Participants/age                   | n       | Treatment                                      | Comorbidity score system | Outcome                                                                 | Limitations                                                                 |
|------------------------|---------------------------|------------------------------------|---------|-----------------------------------------------|--------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Connoly et al. (25)    | Systematic review         | Patients with KC                   | 22 studies | n/a                                           | CCI, ASA, ACE-27         | - The most commonly used comorbidity score was the CCI, followed by the ACE-27 and the ASA score  
- The ACE-27 seems to be superior to the other scoring systems, as it analyses the most conditions and allows for comorbidity grading | The included studies were small and heterogeneous |
| Dhiwakar et al. (26)   | Retrospective study       | Patients with KC of the head and neck ≥80 years | 152 patients (208 NMSC) Compared to 311 patients (430 NMSC aged <80 years) | Surgery | CCI, ASA | - CCI and ASA scores were higher in elderly patients  
- Lesion size at presentation was larger in elderly people (required also larger defect)  
- Disease-free survival and wound complication rate were comparable in the younger and elderly patients | Non-surgical options were not included  
- Retrospective character |
| Reinau et al. (27)     | Retrospective case control study | Patients with BCC, mean age 69.5 years | 57,123 patients | n/a                                           |                          | Inflammatory bowel disease, rheumatoid arthritis, extracutaneous malignancies, solid organ transplantation, alcohol consumption and various skin disorders were significantly more often observed in patients with BCC compared with controls |                          |
| Tieng et al. (28)      | Retrospective cohort study | Patients with DM, compared with non-DM mean age 57.41 years | 41,898 patients with DM and non-DM | n/a                                           | DM and non-DM            | - The risk of developing skin cancer was significantly higher in older patients with DM, compared with non-DM.  
- Males and having chronic obstructive pulmonary disease were also significant risk factors for KC in older adults with DM | Several information facts were not available, such as body mass index, details of smoking, alcohol consumption, exposure to ultraviolet etc. |
| Chossat et al. (29)    | Retrospective study       | Patients with BCC >75 years mean age 81.75 years | 158 patients | Surgery (reconstructive and cosmetic plastic surgery) | n/a                      | Statistical significant risk factors for major postoperative complications were:  
Age >85 years, ≥1 comorbidities, long-term use of anticoagulant treatment, conventional hospitalization and the use of general anaesthesia | The retrospective character of the study |
| Chen et al. (30)       | Prospective cohort study  | Patients with KC                   | 633 patients | EDB&c, excision, or MMS | CCI | Less comorbidity (measured by CCI) and better mental health predicted better QOL outcomes | Only patients who responded to the pretreatment questionnaire were included |
| Basu et al. (31)       | Retrospective study       | Patients with KC                   | 927 biopsied KC | No treatment, Cryotherapy, EDB&c, MMS, excision, topical therapy | n/a                      | - Patients with ≥4 comorbidities and elderly patients (≥85 years) had significant higher chances of no treatment  
- No treatment was most likely in patients with impairment in activities of daily living, neurocognitive impairment and hemiplegia | - The single centre retrospective design  
- Exclusion of non-biopsied cancers  
- Potential selection bias; i.e. influences by distance from the hospital and insurance status |
| Bouhassira et al. (32) | Retrospective study       | Patients aged ≥75 years with BCC, SCC and melanoma, mean age 84.7 years | 241 patients | Surgery | n/a | - Complication rate was 20%  
- No relation between the number of comorbidities and complication was found  
- Male gender, histological type (SCC, melanoma) and positive surgical margins were independent predictors for complication after surgery | Lack of statistical power of the study |
| Arguello-Guerra et al. (33) | Retrospective study | Patients undergoing surgery for skin cancer | 655 patients | Surgery | n/a | - Complication rate was 4.2%  
- Dermatological surgery was found to be safe in patients with multiple comorbidities, without discontinuing antithrombotic therapy or antibiotic prophylaxis | - The retrospective single centre study design  
- The number of cigarettes consumption before surgery and the size of tumour and surgical defect were not available |
| Lubeek et al. (34)     | Retrospective study       | Patients with KC, median age 71 years | 401 patients | Conventional excision, PDT, imiquimod, MMS, radiotherapy, other | CCI | Guideline-adherence/management was not influenced by comorbidity or high age | The single centre retrospective design; population and management differences can occur between different hospitals and countries, non-reporting bias might occurred |
| Linos et al. (8)       | Cross-sectional study     | Patients with KC, aged ≥65 years, mean age 79 years | 2,702 patients, 9653 KC | MMS, simple excision or electrodessication and curettage | CCI | Comorbidity status, advanced age, functional status and life expectancy did not influence the choice of treatment | - KC treated with topical therapies, radiotherapy and untreated KC were not included  
- Information about patient preferences was not available |

KC: keratinocyte carcinoma; n/a: not applicable; CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists risk classification system; ACE-27: Adult Comorbidity Evaluation-27; DM: diabetes mellitus; MMS: Mohs micrographic surgery; EDB&C: electrodessication and curettage; QOL: quality of life; SCC: squamous cell carcinoma; PDT: photodynamic therapy.
(QoL) (measured by Skindex 16). However, tumour factors and age were not prognostic for QoL change (30). Harmonizing with these findings, a recent retrospective study including 927 KC found that patients having ≥4 comorbidities were significantly more likely to receive no treatment (31).

In contrast, several other studies found that the complication rate after treatment of KC was not different between young and elderly patients with more comorbidities, suggesting that (surgical) treatment is safe in this group, despite the higher comorbidity rate in elderly patients (26, 32, 33).

A different question is whether advanced age or multi-comorbidity influence treatment decision. Lubeek et al. (34) found that comorbidity (measured by CCI) and high age (≥80 years) did not have a significant influence on guideline-adherence in both BCC and SCC. Similarly, the study by Linos et al. (8) confirmed that comorbidity status (measured by CCI), together with advanced age, functional status and life expectancy did not influence the choice of treatment in patients with KC. In this study, for example, no significant difference was found in the treatment rate of MMS between patients who died within one year after treatment and patients who lived longer (15% vs 17%, respectively).

In conclusion, CCI is the most commonly used comorbidity score in elderly patients with KC; however, ACE-27 seems to be superior, based on a systematic literature search. Studies are contradictory regarding the influence of comorbidities on complication rate and treatment decision.

We recommend registering comorbidities according to one of the validated comorbidity scores, especially before major treatment. More and larger prospective studies are needed to evaluate the prognostic value of different comorbidity scores.

Conclusion

The “one-size-fits-all” approach to the elderly patients with KC is not sufficient; beside tumour characteristics, life expectancy, frailty and comorbidities have to be considered. Therefore, it is recommended that these items are registered before treatment according to one of the validated scoring systems, especially before major treatment modalities.

As seen in the present review, literature data is sparse; therefore, prospective studies including elderly patients with KC are needed to draw firmer clinical recommendations and to reach a consensus, in order to avoid improper treatment of this increasing and potentially vulnerable patient group.

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