

## REVIEW ARTICLE

# Treatment of keratinocyte carcinoma in elderly patients – a review of the current literature

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## Abstract

A large percentage of the patients with keratinocyte carcinoma (KC, formerly known as non-melanoma skin cancer) is of advanced age and often too frail for standard therapies. However, no specific treatment recommendations are given for this population. This review aimed to give an overview of the current literature on the best practice for the treatment of elderly patients with KC. A literature search was performed in MEDLINE, using 'keratinocyte carcinoma', 'elderly', 'treatment' and various synonyms. Case reports, reviews, comments, non-English literature and studies with a sample size <15 were excluded. After selection, a total of 47 studies were reviewed. Two types of studies were identified, focusing on (I) the effect of age on treatment outcomes and (II) alternative treatment schedules for elderly patients. Studies on surgery, the gold standard, describe larger lesions and defect size in the elderly population. Recurrence rate, complication rate and disease-specific survival were not affected by age. Depending on the expected morbidity of a suggested (re-)excision and patient preferences, a conservative watchful waiting policy can be agreed upon as a shared decision. Other common treatment modalities, such as adjuvant radiotherapy, photodynamic therapy and systemic therapy for basal cell carcinoma (BCC), show comparable results in the elderly and younger population. Alternative treatment schedules for elderly patients include primary hypofractionated radiotherapy, which seems effective and well-tolerated, although research is limited to case series. Additionally, localized and topical treatments seem safe and effective especially for low-risk tumours. Data are lacking on the efficacy of systemic therapies of metastatic KC in elderly patients. Efficacy of most treatments (with the exception of photodynamic therapy) is not dependent on age. There is need for more research on the efficacy of adjusted treatment modalities, such as hypofractionated radiotherapy and palliative or curative systemic treatment.

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## Introduction

Keratinocyte carcinoma (KC, formerly known as non-melanoma skin cancer) affects a significant number of patients with advanced age; the most diagnoses are made in patients aged 70 or above.<sup>1</sup> In addition to cumulative ultraviolet (UV) radiation due to age, the most dominant factor contributing to the

increased incidence is a change in UV exposure behaviour, such as longer vacations and more body exposure. Climate change and the use of artificial tanning devices may also contribute.<sup>1–3</sup>

The gold standard for the treatment of KC is surgery, which is often considered too aggressive in frail elderly patients. Lubeek *et al.*<sup>4</sup> recently discussed that due to shorter life expectancy, patients may not live long enough to benefit from treatment, while treatment complications could result in a reduced quality of life. On the other hand, tumour progression can also deteriorate quality of life if patients live long enough. Prediction of

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treatment outcome in the elderly can be difficult. In a study on over 1200 cases, age itself was found not to be a predictor of postoperative outcome after major head and neck surgery.<sup>5</sup> Since there is no consensus on 'elderly', the definition or threshold differs per study. The National Institute on Ageing produced the most accepted classification, with patients between 65 and 74 defined as 'young old', 75–84 as 'older old' and 85 or older as 'oldest old'.<sup>6</sup>

The aim of the present review was to summarize the current literature on the best practice for the treatment of elderly patients with KC. We will discuss differences between curative treatment outcomes in elderly and younger patients, as well as non-invasive treatment options and their applicability for the elderly patient.

## Methods

To systematically identify the available literature in MEDLINE, a search term was created in October 2018 (Appendix S1, Supporting Information). A total of 3821 potentially relevant articles were found based on the title and abstract. After removal of non-English literature, case reports, reviews, comments and application of inclusion criteria (KC in elderly or frail patients), 166 articles were subjected for full-text review. After exclusion of papers without age- or frailty-related outcomes, 47 articles were included for analysis (Fig. 1). These publications were reviewed by at least two authors and processed in the current paper. We

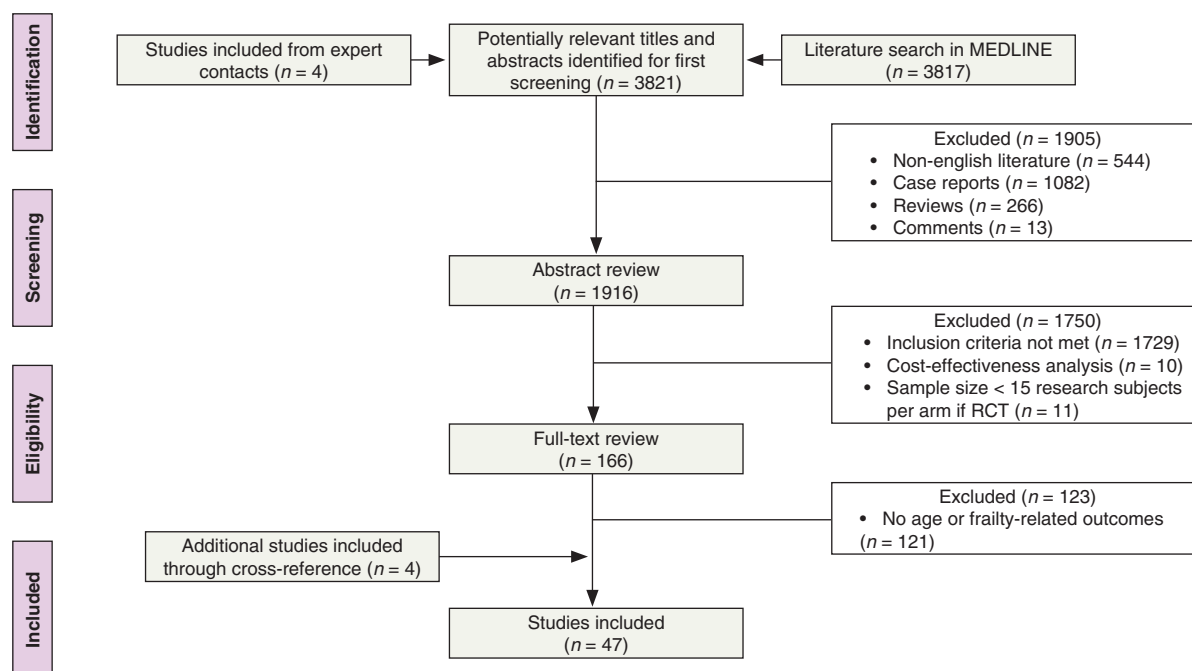
found two types of original papers: papers analysing the effect of age on treatment outcomes and papers describing alternative treatment schedules for inoperable, frail elderly patients.

## Results

### Effect of age on treatment outcomes of common treatment modalities

**Surgical treatment** Surgery is the gold standard treatment for KC. As opposed to simple excision, Mohs' micrographic surgery (MMS) is characterized by fewer recurrences, and with the possibility of sparing healthy skin.<sup>7–9</sup> Both treatments use local anaesthesia and are well-tolerated by elderly patients.<sup>10,11</sup> Several studies analysed whether surgical treatment outcomes differ in elderly patients when compared to younger patients, as shown in Table 1.

All four studies on defect size conclude that higher age is associated with a larger lesion and defect size in MMS and conventional surgery.<sup>12–14</sup> Studies on complexity show no association between age and the number of MMS stages necessary to achieve complete excision.<sup>15,16</sup> Only one study found that patients over 80 years old were almost twice as likely to need more than one MMS stage compared with patients under 80.<sup>17</sup> Four studies focusing on recurrence rate concluded that age is not predictive for the recurrence of KC.<sup>12,18–20</sup> Nonetheless, the follow-up



**Figure 1** Flow chart depicting the search algorithm.

**Table 1** Overview of literature on surgical treatment outcomes in elderly patients

Study (year), type	Participants	Intervention and follow-up	Primary outcome
<b>Complexity</b>			
Batra <i>et al.</i> <sup>15</sup> (2002), retrospective	N = 1131 KCs. Age groups: <35, 35–44, 45–54, 55–64, 65–74, 75–84, ≥85	MMS, 3-year inclusion, 3-year FU	Age under 35 years protective for ≥3 stages MMS, multivariable OR: 0.12 (95% CI: 0.01–0.98)
Hoorens <i>et al.</i> <sup>17</sup> (2016), retrospective	N = 1062 HNBCCs. Age groups: <60, 60–69, 70–79, ≥80	MMS, 14-year inclusion, FU not specified	Age ≥80 years predictive of >1 stage MMS, univariable OR: 1.9 (95% CI: 1.0–3.5)
Sahai <i>et al.</i> <sup>16</sup> (2012), retrospective	N = 231 KCs. Age complex cases (≥4 stages): 69.0 ± 14.6 years, age non-complex cases: 66.0 ± 14 years	MMS, 3-year inclusion, FU not specified	No effect of age on complexity
<b>Defect size</b>			
Camarero-Mulas <i>et al.</i> <sup>12</sup> (2017), prospective cohort	N = 2575 pts with KC. Age groups: <80, ≥80	MMS, 3-year inclusion, 1-year FU	Larger tumours in elderly group
Dhiwakar <i>et al.</i> <sup>14</sup> (2007), retrospective	N = 463 pts with 638 HNKCCs. Age groups: <80, ≥80	Conventional surgery, 10-year inclusion, average FU: 26 months (range: 1–70)	Larger tumours and defect sizes in elderly group
Dinehart <i>et al.</i> <sup>13</sup> (1992), retrospective	N = 2728 BCCs. Age groups: 15–30, 56–70	MMS, 11-year inclusion, median FU in young group: 4.2 years (range: 6 months–9.9 years), older group: 4.4 years (range: 5 months–10.7 years)	Larger tumours and defect sizes in elderly group
Eide <i>et al.</i> <sup>84</sup> (2005), retrospective	N = 860 pts with KC. Age groups: <40, 41–50, 51–60, 61–70, 71–80, 81–90, >90	MMS, 1-year inclusion, FU not specified	Age is predictive for defect size, $P < 0.014$ , partial $R^2 = 0.019$
<b>Recurrence rate</b>			
Camarero-Mulas <i>et al.</i> <sup>12</sup> (2017), prospective cohort	N = 2575 pts with KC. Age groups: <80, ≥80	MMS, 3-year inclusion, 1-year FU	No effect of age on recurrence rate
Dzubow <i>et al.</i> <sup>18</sup> (1982), retrospective	N = 414 pts with primary cSCC. Age groups: 1–39, 40–59, ≥60	MMS, 15-year inclusion, mean FU: 18.6 months (range: 1–136)	No effect of age on recurrence rate
Maghami <i>et al.</i> <sup>19</sup> (2007), multicentre retrospective cohort	N = 120 pts with KC. Age groups: ≤50, >50	Craniofacial surgery, 44-year inclusion, median FU: 27 months (range: 1–279)	No effect of age on recurrence-free survival
Mueller <i>et al.</i> <sup>20</sup> (2010), retrospective case-control	N = 101 pts with facial BCC. Age groups: ≤70, >70	Ablative surgery, 4-year inclusion, 1-year FU	No effect of age on recurrence rate, univariable OR: 1.4 (95% CI: 0.5–4.1)
<b>Survival</b>			
Delaney <i>et al.</i> <sup>26</sup> (2013), retrospective	N = 214 pts with KC. All pts ≥90 years	MMS, 9-year inclusion, FU until 4 months after last inclusion	No difference in survival compared with general US population. Perioperative mortality not increased
Dhiwakar <i>et al.</i> <sup>14</sup> (2006), retrospective	N = 463 pts with 638 HNKCCs. Age groups: <80, ≥80	Conventional surgery, 10-year inclusion, average FU: 26 months (range: 1–70)	No effect of age on DFS
Maghami <i>et al.</i> <sup>19</sup> (2007), multicentre retrospective cohort	N = 120 pts with KC. Age groups: ≤50, >50	Craniofacial surgery, 44-year inclusion, median FU: 27 months (range: 1–279)	No effect of age of DSS or OS
Pascual <i>et al.</i> <sup>27</sup> (2013), prospective	N = 130 pts with KC. All pts ≥80 years	Surgery, minimum FU: 24 months	Age predictor for mortality, $P = 0.002$ (univariable)
Linós <i>et al.</i> <sup>28</sup> (2016), cross-sectional	N = 2702 pts with 8064 KCs and 9653 distinct treatments. LLE vs. normal life expectancy	Excision, MMS and C&ED, 20-year inclusion, minimum FU: 1 year	No different treatment rates between groups
<b>Postoperative complication rate</b>			
Bras <i>et al.</i> <sup>29</sup> (2015), retrospective cohort	N = 90 pts with head and neck cancer. Age groups: 65–74, ≥75	Conventional surgery, 15.5-year inclusion, median FU: 12 months	No effect of age or frailty on complication rate

Table 1 Continued

Study (year), type	Participants	Intervention and follow-up	Primary outcome
Bouhassira <i>et al.</i> <sup>30</sup> (2016), retrospective	N = 241 pts with cSCC, BCC or melanoma. Age groups: 75–85, >85	Conventional surgery, 3-year inclusion, 2-week FU	No effect of age on complication rate, P = 0.084 (univariable)
Camarero-Mulas <i>et al.</i> <sup>12</sup> (2017), prospective cohort	N = 2575 pts with KC. Age groups: <80, ≥80	MMS, 3-year inclusion, 1-year FU	No effect of age on complication rate
Dhiwakar <i>et al.</i> <sup>14</sup> (2006), retrospective	N = 463 pts with 638 KNKCs. Age groups: <80, ≥80	Conventional surgery, 10-year inclusion, average FU: 26 months (range: 1–70)	No effect of age on complication rate
Mueller <i>et al.</i> <sup>20</sup> (2010), retrospective case–control	N = 101 pts with facial BCC. Age groups: ≤70, >70	Ablative surgery, 4-year inclusion, 1-year FU	Older pts 2.7× more likely to develop wound healing disorders than younger pts, univariable OR: 2.7 (95% CI: 1.1–7.0)
Pascual <i>et al.</i> <sup>33</sup> (2015), prospective	N = 260 pts with 320 KCs Age groups: <80, ≥80	Surgery, inclusion or FU not specified	Haemorrhagic complications more common in older pts
Pascual <i>et al.</i> <sup>31</sup> (2015), prospective	N = 144 pts with 180 KCs. All pts ≥80 years	Conventional surgery, 28-month inclusion, FU 7 and 30 days after surgery	ADL not affected after surgery
Sclafani <i>et al.</i> <sup>32</sup> (2012), retrospective	N = 446 pts with skin tumours. Age groups: <60, ≥60	Repair of facial defects after MMS, 10-year inclusion, average FU 7.74 months (SD: 11.97)	Age < 60 years associated with higher risk of overall complications
<b>Postoperative radiotherapy</b>			
Terra <i>et al.</i> <sup>39</sup> (2017), retrospective	N = 90 pts with 99 HNCSCCs. Median age: 76 years (range: 39–106)	PORT in different regimens, 14-year inclusion, median FU: 24 months (95% CI: 24.9–35.8)	No effect of age > 50 (univariable, HR: 0.486; 95% CI: 0.048–4.513) or age > 70 (univariable, HR: 0.864; 95% CI: 0.113–6.628) on local recurrence rate
Ebrahimi <i>et al.</i> <sup>40</sup> (2012), retrospective	N = 229 pts with nodal metastatic HNCSCC. Age groups: ≤65, >65	Surgery in all pts, adjuvant RT in 88%, 30-year inclusion, median FU: 3.8 years	Increased age associated with short DFI
Amoils <i>et al.</i> <sup>35</sup> (2017), retrospective	N = 80 pts with regional metastatic HNCSCC. Age groups: ≤70, >70	Surgery alone, surgery with adjuvant RT, or surgery with adjuvant CRT. 15-year inclusion, FU not specified	No effect of age or treatment modality on survival, univariable HR: 1.2 (95% CI: 0.6–2.4)
Givi <i>et al.</i> <sup>36</sup> (2011), retrospective	N = 61 pts with nodal metastatic HNCSCC. Median age: 73 years (range: 43–90)	Surgery in all pts, adjuvant RT in 40 pts. 14-year inclusion, median FU: 15 months	No effect of age on OS. Adjuvant RT associated with longer OS, univariable HR: 0.24 (95% CI: 0.09–0.68)
Wang <i>et al.</i> <sup>37</sup> (2011), retrospective	N = 122 pts with nodal metastatic HNCSCC. Median age: 66 years (range: 18–95)	Surgery in all pts, adjuvant RT in 102 pts. 28-year inclusion, minimum FU: 24 months, median: 57 months	No effect of age on DFS. Adjuvant RT associated with longer OS

ADL, activity of daily living; BCC, basal cell carcinoma; C&ED, curettage and electrodesiccation; CI, confidence interval; COD, cause of death; CRT, chemoradiotherapy; DFI, disease-free interval; DFS, disease-free survival; DSS, disease-specific survival; FU, follow-up; Gy, grey; HNBCC, head and neck basal cell carcinoma; HNCSCC, head and neck cutaneous squamous cell carcinoma; HNKCC, head and neck keratinocyte carcinoma; HR, hazard ratio; KC, keratinocyte carcinoma; LLE, limited life expectancy; MMS, Mohs' micrographic surgery; OR, odds ratio; OS, overall survival; PORT, postoperative radiotherapy; RT, radiotherapy.

might be too short to detect recurrence after MMS.<sup>7,8</sup> Codazzi *et al.*<sup>21</sup> describe a cohort of 3957 excisions of BCC. Patients with complete excisions had a recurrence rate of 5.9%, whereas incomplete excisions recurred in 26.8%. However, only 50.7% of the patients complied with follow-up for a year or longer, so longer-term recurrences are underestimated in this study. Discussion of these data with patients might aid shared decision-making on performing re-excision vs. watchful waiting.

Data about recurrence rates in patients with cSCC and close or positive margins are lacking, probably because of the standard

clinical practice to perform a re-excision in those cases.<sup>22</sup> The incomplete excision rate of cSCCs is about 6–16%; localization in the head and neck area, larger tumour diameter and deeper tumour invasion are risk factors for positive margins.<sup>23,24</sup> In the cohort described by Bovill *et al.*<sup>23</sup>, the patients with residual tumour cells in the re-excision were slightly, but not significantly older compared to the patients with negative re-excisions (78.9 years vs. 73.3 years). Residual tumour cells were found less in patients with longer delay between first and re-excision. Nevertheless, since only a small percentage of the tissue is examined

during histopathological examination of conventionally excised tumours, tumour cells could be present without being detected.<sup>25</sup>

Five papers on survival after surgery strongly indicate that skin surgery in the elderly population does not increase mortality.<sup>14,19,26–28</sup> In the majority of these studies, age was not a predictive factor for disease-specific survival (DSS). Furthermore, most of the studies involving postoperative complication rate show no difference in the occurrence of complications between age groups.<sup>12,14,29–32</sup> On the contrary, Mueller *et al.*<sup>20</sup> found that patients >70 years of age were 2.7 times more likely to develop postoperative wound healing disorders compared with younger patients ( $P = 0.03$ ) and Pascual *et al.*<sup>33</sup> describe more haemorrhagic complications in the higher age group ( $P = 0.04$ ). On the other hand, an age of <60 years was found to be associated with a higher risk of postoperative complications by Sclafani *et al.*<sup>32</sup> ( $P = 0.01$ ) (Table 1).

**Surgery with adjuvant radiotherapy** According to the European guideline<sup>22</sup>, adjuvant or postoperative radiotherapy (RT) should be considered in the case of cSCC with substantial perineural involvement, and when surgical margins are not free and re-intervention is not possible or unlikely to completely remove the tumour. Also, in the case of metastatic disease, adjuvant RT could improve survival compared with surgery or RT alone.<sup>22,34</sup> In most reviewed studies, advanced age was not associated with recurrence, poorer overall or disease-free survival (DFS) after surgery with adjuvant RT (Table 1).<sup>35–39</sup> Only one study found that patients with a shorter disease-free interval (DFI) were significantly more likely to be aged >65 years.<sup>40</sup> However, DFI was probably influenced by a subgroup of patients with delayed presentation of advanced nodal disease, which may bias the results.

**Systemic treatment for BCC** For patients with locally advanced or metastatic BCC, treatment options are limited. Vismodegib is the first approved Hedgehog pathway inhibitor, which is indicated for these complicated cases of BCC. In the study of Chang *et al.*<sup>41</sup>, vismodegib showed similar efficacy and adverse effects in different age groups. Systemic therapy targeting cSCC will be addressed in part II. All studies concerning systemic therapy are summarized in Table 4.

### Treatment modalities adjusted for the treatment of (frail) elderly patients

Alternative therapeutic strategies for elderly patients are used in several case series (Tables 2 and 3). Moreover, elderly patients with KC are more often not treated than younger patients.<sup>42</sup>

**Local destructive therapy** Several localized treatments could be used as an alternative to treat elderly patients. Generally, it is only recommended for patients with low-risk KC. Characteristics for high-risk tumours are described in Samarasinghe *et al.*<sup>43</sup>

A practical and cheap therapeutic option is curettage with electrodesiccation (C&ED). A study by Lubeek *et al.*<sup>44</sup> showed a 6% recurrence rate of BCCs treated with C&ED after a median follow-up period of 21 months. Increasing age and high-risk BCCs were not associated with a higher recurrence rate, indicating that C&ED may also be a good option for high-risk BCCs. A study by Yakish *et al.*<sup>45</sup> found a 97% local control rate of 89 cSCCs after treatment with curettage alone. Recurrence after a median follow-up of 6 years was not associated with increasing age.

Two studies on the effectiveness of intralesional cryosurgery for nodular and superficial BCCs in elderly patients found low recurrence rates (0% and 5%, respectively).<sup>46,47</sup> In a study by Kuflik *et al.*<sup>48</sup>, 4406 new and recurrent KCs were treated with curettage and cryosurgery in a period of 30 years with an overall cure rate of 98.6%; however, follow-up period (5 years) is only mentioned for a subgroup of patients.

Stewart *et al.*<sup>49</sup> assessed elderly patients with KCs thought to be small enough for complete removal by shave biopsy. Examination of the surgical specimens taken after shave biopsy showed that 42% of the BCC specimens and 73% of the cSCC specimens were negative for residual tumour. Despite these high percentages, shave biopsy cannot be considered as a curative treatment for KC.

**Primary radiotherapy** Primary RT is an alternative for surgery and is widely used for the treatment of KC with curative intent, also in elderly patients, although its efficacy is lower than that of surgery.<sup>50</sup> In the case of inoperable tumours, when surgical defects would give functional or cosmetic problems, or patients with severe comorbidities, primary RT is even favoured over surgery. RT should also be taken into consideration when a patient refuses surgery.<sup>22</sup> Older age has been identified as a risk factor for refusing surgery in breast cancer patients.<sup>51</sup>

Most studies on primary RT in elderly patients assessed the effectiveness of treatment schedules that were less intensive than traditional schemes, such as hypofractionated RT (weekly irradiation as opposed to daily fractions) and found that hypofractionated RT was effective and well-tolerated in elderly patients<sup>38,52–55</sup>, as summarized in Table 2. However, these results should be handled with care as the studies suffer from the lack of control groups and short follow-up. Studies that compared different age groups found no significant differences in recurrence rates.<sup>39,56</sup> Pampena *et al.*<sup>38</sup> compared elderly disabled patients treated with weekly irradiation with other patients treated with daily irradiation. No differences were found in overall survival, DFS or cosmetic outcome.

**Topical and intralesional treatment modalities** Topical therapy is generally used for the treatment of superficial BCC (sBCC) or cSCC *in situ*. However, it may also be used for nodular BCC (nBCC) when surgery or RT is unfeasible.

A study with imiquimod in 11 elderly patients who were unfit for surgery, with nBCC, superficial multicentric BCC and

**Table 2** Overview of literature on alternative primary radiotherapy schedules and outcomes in elderly patients

Study (year), type	Participants	Intervention and follow-up	Reason for alternative treatment	Primary outcome
Cognetta <i>et al.</i> <sup>56</sup> (2012), retrospective	N = 1149 pts with 1715 non-aggressive KCs. All pts >65 years	Superficial X-ray therapy (80 kV) with 35 Gy in 5 fractions, three times per week. 10-year inclusion, average FU: 31.5 months (range: 1–120)	Patient preference	No effect of age on recurrence, multivariable HR: 0.99 (95% CI: 0.95–1.02)
Ferro <i>et al.</i> <sup>85</sup> (2015), prospective phase II	N = 31 pts with KC. All pts ≥70 years	Electrons (6–9–12 MeV) or photons (6MV) with 30 Gy in 6 daily fractions. Median FU: 30 months (range: 8–72)	Unfit for other local treatments	Local control after 2 years 93.2%
Kouloulis <i>et al.</i> <sup>52</sup> (2013), retrospective	N = 38 pts with HNBCC. All pts ≥64 years	Electrons (6 MeV) or photons (6MV) with 30 Gy in 5 weekly fractions. 7-year inclusion, median FU: 48 months	Eligibility criteria based on location, tumour characteristics, immunosuppression and previous treatment	Three recurrences were found
Marriappan <i>et al.</i> <sup>53</sup> (2014), retrospective cohort	N = 25 pts with 37 BCCs. All pts ≥83 years	42 Gy in 7 weekly fractions, no radiation technique mentioned. Median FU: 15 months (range: 1–89)	Unfit for daily treatment	Two recurrences were found
Pampena <i>et al.</i> <sup>38</sup> (2016), retrospective cohort	N = 385 pts with 436 KCs. Elderly disabled pts >60 years (I) vs. other pts (II)	Orthovoltage, 37.75 Gy in 7 weekly fractions (I) or 45 Gy in 15 daily fractions (II). 6-year inclusion, median FU: 31.8 months	Surgery was contraindicated or refused	No difference between treatment groups in OS (multivariable HR: 0.662, 95% CI: 0.387–1.131) DFS (multivariable HR: 0.483, 95% CI: 0.065–3.582), or cosmetic outcome (multivariable RR: 1.048, 95% CI: 0.170–6.473)
Pelissero <i>et al.</i> <sup>54</sup> (2015), retrospective	N = 117 pts with 141 facial BCCs. All pts frail and elderly, median age: 82 years (range: 75–103)	Orthovoltage 55–150 kV or electrons 4–8 MeV with 25–30 Gy in 5–6 weekly fractions. 3-year inclusion, median FU: 61 months (range: 42–85)	Unfit for daily radiation	Complete response in 98.3% of pts and 98.6% of tumours
Russi <i>et al.</i> <sup>55</sup> (2015), retrospective	N = 134 pts with 159 facial BCCs. All pts >75 years	Orthovoltage 55–150 kV or electrons 4–8 MeV with 25–30 Gy in 5–6 weekly fractions. Median FU: 64.5 months (range: 42–88)	Unfit for daily radiation	Complete response in 98.5% of pts and 98.7% of tumours. Recurrence in 3 pts
Terra <i>et al.</i> <sup>39</sup> (2017), retrospective	N = 48 pts with 52 HNCSCCs. Median age: 81 years (range: 50–100)	Photons, electrons or orthovoltage (100–200 kV) with 55, 60 or 70 Gy in fractions of 2 Gy 5×/week. 14-year inclusion, median FU: 23 months (95% CI: 20.9–29.9)	Not applicable, normal protocol	No effect of age on recurrence. Age > 50 univariable HR 0.486 (95% CI: 0.048–4.513), age >70 univariable HR: 0.864 (95% CI: 0.113–6.628)
Valeriani <i>et al.</i> <sup>86</sup> (2017), prospective cohort	N = 21 pts with 26 KCs. All pts >80 years	Electrons (6–12 MeV) or photons (6MV) with 60 Gy in 10 or 12 weekly fractions. 4-year inclusion, 2-year FU	Unfit for surgery	Complete response in 92.4% of tumours. No effect of schedule on response or toxicity

BCC, basal cell carcinoma; CI, confidence interval; DFS, disease-free survival; FU, follow-up; Gy, grey; HNBCC, head and neck basal cell carcinoma; HNCSCC, head and neck cutaneous squamous cell carcinoma; HR, hazard ratio; KC, keratinocyte carcinoma; kV, kilovolt; MeV, megaelectron volt; MV, megavolt; MMS, Mohs' micrographic surgery; OR, odds ratio; OS, overall survival; pts, patients; RR, relative risk; RT, radiotherapy; vs, versus.

sclerosing BCC, reported a complete response rate around 50%.<sup>57</sup> Intralesional treatment with interferon was applied in 16 elderly patients with extensive, recurrent or resistant to other

procedures KC. The treatment was effective in 86.7% of the patients. No severe adverse events related to interferon were reported.<sup>58</sup>

**Table 3** Overview of literature on alternative treatment schedules

Study (year), type	Participants	Intervention and follow-up	Reason for alternative treatment	Primary outcome
<b>Local destructive therapy</b>				
Kuflik <i>et al.</i> <sup>48</sup> (2004), retrospective	<i>N</i> = 2932 pts with 4406 KCs. Age of 3 pts ≤43, other pts 53–95 years	(Curettage) cryosurgery, double freeze–thaw cycle. 30-year inclusion, FU not specified	All tumours amenable for cryosurgery	Complete response in 98.6% of tumours. 62 recurrences
Lubeek <i>et al.</i> <sup>44</sup> (2016), retrospective	<i>N</i> = 102 pts with clinically suspected 109 nBCC. Mean age: 71 years (SD: 13)	C&ED (20 Watt) in at least 2 cycles. 3-year inclusion, median FU: 21 months (range: 1–66)	Every clinically suspected primary nBCC included	No effect of age or high-risk tumour on recurrence risk
Samain <i>et al.</i> <sup>47</sup> (2014), retrospective	<i>N</i> = 138 pts with 144 facial BCCs. Mean age: 76.5 ± 11.1 years	(Curettage) cryosurgery, single freeze–thaw cycle. 7-year inclusion, median FU: 39.5 months (range: 18–74)	Decision made by multidisciplinary panel of experts. Cryosurgery contraindicated in recurrent and morpheiform BCCs	5-year recurrence-free rate 94%
Stewart <i>et al.</i> <sup>49</sup> (2015), retrospective	<i>N</i> = 233 KCs. Average age BCC 78.3 years, cSCC 75.5 years	Shave biopsy. 5-year inclusion, FU not specified	Assessment of cost-effectiveness of excision after shave biopsy	42% of excisions of BCCs no residual tumour, 73% of cSCCs
Yakish <i>et al.</i> <sup>45</sup> (2017), retrospective	<i>N</i> = 80 pts with 89 cSCCs. Mean age 76 years (SD: 10, range: 45–95)	Curettage. 1-year inclusion, median FU: 6 years (range: 0–2502 days)	Assessment of effectiveness of curettage alone in cSCC	Complete response in 97% of tumours
<b>Topical or intralesional therapy</b>				
Anasagasti-Angulo <i>et al.</i> <sup>58</sup> (2009), prospective	<i>N</i> = 16 pts with extensive, recurrent or resistant to other treatments KC. Median age: 70 years (range: 31–89)	IFN formulation peri- and intralesionally, 3×/week for 3 weeks (4 pts also received chemotherapy). 4-year inclusion, FU 1 year	No other therapeutic options after surgery/RT/chemotherapy	Complete response in 46.7% of pts, partial response in 40.0%, 13.3% non-responders
Ohson <i>et al.</i> <sup>57</sup> (2006), prospective	<i>N</i> = 11 pts with 14 BCCs. Age range: 59–92 years	Imiquimod 5% cream, once daily for 5 consecutive days/week for 12 weeks. FU 12 weeks	Unfit for surgery or RT	Complete response in 50% of tumours
Borroni <i>et al.</i> <sup>64</sup> (2013), prospective	<i>N</i> = 36 pts with AK, BD or BCC. Age groups: 61–70, 71–80, 81–90	BP measurement before and after MAL-PDT session. No further FU	Not specified	Highest prevalence of APH (33%) in pts aged 71–80 years
Choi <i>et al.</i> <sup>65</sup> (2017), randomized clinical trial	<i>N</i> = 45 pts with microinvasive cSCC	MAL-PDT or AFL-PDT. FU at 1 week, 3, 12 and 24 months	Unfit for surgery	Complete response rate higher and recurrence rate lower in AFL-PDT group
Fantini <i>et al.</i> <sup>62</sup> (2011), retrospective	<i>N</i> = 135 pts with 194 BCCs. Mean age: 71 ± 12.9 years	MAL-PDT. Median FU: 20 months	Not specified	No effect of age on treatment response
Lindberg-Larsen <i>et al.</i> <sup>61</sup> (2012), retrospective	<i>N</i> = 90 pts with 157 BCCs (sBCC and thin nBCC). Age groups: ≤60, >60	MAL-PDT. 3-year inclusion, FU at 3, 6, 12 and 24 months	Other treatment modalities less favourable and good cosmetic outcome important	Higher recurrence rate in older pts
Nissen <i>et al.</i> <sup>60</sup> (2015), 1: unblinded randomized controlled, 2: retrospective	1: <i>N</i> = 30 healthy volunteers. Age groups: <55, ≥55. 2: <i>N</i> = 67 pts with 100 BCCs. Age groups: 2 of equal size based on median age (61 years)	1: MAL and BF-200 ALA for 24 h, 3-month inclusion. 2: MAL-PDT, minimum FU: 1 year	Not specified	1: declining PpIX formation with age, <i>P</i> < 0.001, <i>F</i> <sup>2</sup> = 0.42. 2: higher treatment efficacy in younger pts
Roozeboom <i>et al.</i> <sup>63</sup> (2014), single-blinded non-inferiority randomized controlled trial	<i>N</i> = 400 pts with sBCC, 385 pts analysed. Age groups: ≤60, >60	MAL-PDT or imiquimod, 2.5-year inclusion, FU at 3 and 12 months	Not specified	Higher probability of treatment success for imiquimod, except for tumours on lower extremities in older pts

AFL-PDT, ablative fractional laser–primed photodynamic therapy; AK, actinic keratosis; APH, acute postoperative hypertension; BCC, basal cell carcinoma; BD, Bowen's disease; BF-200 ALA, BF-200 aminolevulinic acid; BP, blood pressure; C&ED, curettage and electrodesiccation; cSCC, cutaneous squamous cell carcinoma; IFN, interferon; KC, keratinocyte carcinoma; MAL-PDT, methyl aminolevulinic acid photodynamic therapy; nBCC, nodular basal cell carcinoma; PpIX, protoporphyrin IX; RT, radiotherapy; sBCC, superficial basal cell carcinoma; SD, standard deviation.

Topical photodynamic therapy (PDT) with methyl aminolevulinic acid (MAL-PDT) is approved for the treatment of actinic keratosis, Bowen's disease, primary sBCC and thin low-risk nBCC.<sup>59</sup> Studies are contradictory about the effectiveness of PDT in elderly patients. Nissen *et al.*<sup>60</sup> reported that protoporphyrin IX formation decreases with age, leading to a decreased efficacy. Higher recurrence rates in patients older than 60 are also described.<sup>61</sup> Fantini *et al.*<sup>62</sup> did not find age to be predictive for the response rate of BCC. Interestingly, Roozeboom *et al.*<sup>63</sup> found that sBCCs on the lower extremities of elderly patients were more effectively treated with MAL-PDT compared to imiquimod. Acute postoperative hypertension (APH) is mentioned as a possible side-effect of PDT, most prevalent in elderly patients, which could require immediate medical attention in the case of a hypertensive crisis.<sup>64</sup> MAL-PDT could also be combined with laser therapy, as demonstrated by Choi *et al.*<sup>65</sup>, which seemed to increase the response rate and decrease the recurrence rate. A summary of studies regarding topical and intralesional therapy in the elderly population is shown in Table 3.

**Systemic treatment for cSCC** Systemic treatment may be applicable for elderly patients who are not eligible for conventional therapies. However, limited data are available on the effect of age on effectivity and safety. In a study with 14 elderly patients (mean age: 76 years) with aggressive, multiple or recurrent cSCC, treatment with oral 5-fluorouracil (175 mg/m<sup>2</sup> daily

during 3 weeks which on average was repeated 4 times) was evaluated. Measurable improvement was seen in 64% of the patients, and the authors report grade I gastrointestinal symptoms as the only adverse effect.<sup>66</sup>

Recently, the immune checkpoint inhibitor cemiplimab has been approved in the United States of America and Europe for the systemic treatment of advanced cSCC in patients who are not eligible for surgery or radiation.<sup>67</sup> A study by Migden *et al.*<sup>68</sup> showed a response rate of cemiplimab around 50% in patients with advanced cSCC (median age: 73, range: 55–88), with durable disease control in around 65% of the responders. In patients with metastatic cSCC (median age: 71, range: 38–93), the response rate was 47%, with durable disease control in 61% of the patients. However, the effects of age or frailty were not mentioned in this study. Studies on immune checkpoint inhibitors for different indications show that old age is not a contraindication to immune checkpoint inhibition. Nonetheless, possible differences in efficacy between younger and elderly patients are described, but the patient numbers are small and specific clinical trials for elderly patients are needed.<sup>69,70</sup> All reviewed studies concerning systemic therapy are summarized in Table 4.

## Discussion

Reviewing the literature on treatment of KC in elderly patients, we found that surgical treatment is well-tolerated in elderly patients with a similar complication and cure rate as in younger

**Table 4** Overview of literature on systemic therapy

Study (year), type	Participants	Intervention and follow-up	Reason for alternative treatment	Primary outcome
Chang <i>et al.</i> <sup>41</sup> (2016), 1: international multicentre non-comparative phase 2 study, 2: multicentre open-label non-comparative expanded access study	1: N = 104 pts, 71 with laBCC and 33 with mBCC. 2: 119 pts, 62 with laBCC, 57 with mBCC. Age groups: <65, ≥65	Oral vismodegib 150 mg/day. 1: median treatment 10.2 months (<65) and 9.2 months (≥65). 2: median treatment 5.4 months (<65) and 5.5 months (≥65)	Unfit for surgery	No effect of age on treatment outcome or adverse events
Cartei <i>et al.</i> <sup>66</sup> (2000), prospective	N = 14 pts with pretreated cSCC Mean age: 74 years	Mannitol-coated 5-FU tablets 175 mg/m <sup>2</sup> daily for 3 weeks every 5 weeks. FU not specified	Resistant to current standard therapies, pts with high age	Tablets were well-tolerated, response in 64% of pts
Espeli <i>et al.</i> <sup>87</sup> (2016), prospective	N = 26 pts with advanced or metastatic KC. Age groups: pts >80 vs. total group	Carboplatin at area under the curve = 2 or cisplatin 40 mg, bleomycin 15 IU, MTX 40 mg total dose of methotrexate, 5-fluorouracil 500 mg (CMFb) until best response, toxicity or progression of disease	Unfit for surgery	Total group: response in 61.5% of pts, complete response in 26.9%. >80 years: response in 63.6% of pts, complete response in 18.2%

5-FU, 5-fluorouracil; CMFb, cisplatin/carboplatin, methotrexate, fluorouracil, bleomycin; cSCC, cutaneous squamous cell carcinoma; IFN, interferon; KC, keratinocyte carcinoma; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; MTX, methotrexate; nBCC, nodular basal cell carcinoma.



patients. The majority of patients with KC have small tumours, which can be treated with radical excision under local anaesthesia. The burden of such a treatment is relatively low, with little chance of deterioration of the patient and a very good prognosis with a recurrence rate of 5 to 8% and cure rates up to 96% after 5 years.<sup>71</sup> Older patients have larger tumours and consequently larger defect sizes after surgery. Whether this is due to a more aggressive disease in the elderly population or a patient's or doctor's delay is unclear. Although often patients do not report any symptoms from the tumour, it is likely that further growth – in the case of no treatment, or irradical treatment – will cause complaints at some point. Postponing treatment until symptoms arise probably leads to more extensive excision, with a higher risk of irradical resection and complications. Also, it is well known that cSCCs with a larger diameter are more likely to recur and metastasize, with the need for more aggressive treatment. It is also associated with strongly reduced survival rates.<sup>71</sup> Discussion regarding treatment intention is more relevant for patients with locally or locoregionally advanced KCs, especially in cSCCs. As the immune response in ageing is generally worse due to immunosenescence,<sup>72</sup> it could be hypothesized that this is also the case in the anticancer immune response after incomplete excision and that complete resection with adequate margins is even more important in the elderly KC patients.

MMS is the most common form of microscopically controlled surgery. Other forms such as 'slow Mohs' or the 'Breuninger' technique can also be considered, but generally take more time than MMS which can lead to a greater burden of treatment. Cure rates of MMS in BCC and cSCC are superior over conventional surgical excision.<sup>7,8,73</sup> Previous studies report that MMS is well-tolerated in elderly patients.<sup>26,74</sup> However, due to the retrospective nature of these studies, a selection bias is possible. Generally, only fitter octo- and nonagenarians are selected for MMS and their frail counterparts are not. MMS can still be considered in elderly frail patients, especially when the setting can be adjusted to suit the frail patient. Invasive surgery in the right setting could possibly give better outcomes than watchful waiting or radiotherapy, especially in the case of a high-risk tumour. Regional networks where one centre can specialize in the treatment of elderly or frail patients could provide a better treatment setting.

Primary radiotherapy can be a good alternative for surgery, but standard daily irradiations for several weeks is not always feasible for the frail and elderly population. Hypofractionated schedules are applied in clinical practice to reduce the burden of treatment, and seem to achieve promising results. However, more evidence is necessary to determine whether hypofractionated schedules are non-inferior to the daily schedules.

It is still debated whether elderly patients respond differently to treatment with PDT, and attention should be paid to the possibility of acute post-treatment hypertension, especially in patients with hypertension in their medical history.<sup>64</sup> Topical

5-fluorouracil (5-FU) is used on-label in the treatment of actinic keratosis and sBCC, and off-label for cSCC *in situ*. Cure rates between 60 and 90% are mentioned in literature, with higher cure rates in sBCCs. However, the application could be difficult for elderly patients with lesions on hard-to-reach locations.<sup>75,76</sup>

The high number of studies describing adjusted treatment regimens in (frail) elderly patients demonstrates the challenging process of treatment decisions in this patient population. Unfortunately, most of these studies provide little or poor evidence, due to the lack of control groups, short follow-up and poorly defined inclusion criteria. Decision-making in elderly KC patients is very complex and is affected by many factors such as limited life expectancy, frailty, comorbidities and decreased mobility. Especially in older, more vulnerable patients, it is important to consider the potential benefits of a possible curative treatment against 'wait-and-see' or supportive care.<sup>77</sup> Besides patient factors, the burden of treatment and the consequences of withholding (curative) treatment are important variables in the decision-making process on treatment intention. Last but not least, patient preferences also play a role in this process. Preservation of functional independence and quality of life are often mentioned as important priorities for older patients, but their preferences in the treatment of KC are poorly studied and need further exploration in the form of wider use of patient-reported outcome measures.<sup>78,79</sup>

Palliative care or wait-and-see policy should not be confused with terminal care at the end of life. The main goal of palliative care is relief of symptoms caused by the disease, which possibly may but not directly will lead to the death of the patient. Supporting the patient in living life with as less limitations as possible is the main purpose.<sup>80</sup> There is very limited literature focusing on palliative care in dermatology.<sup>81</sup>

If regional metastases are diagnosed, intensive surgical treatment and/or radiation therapy is advised as curative treatment. Pretreatment selection of patients eligible for this intensive treatment is challenging. Despite intensive treatment, 5-year disease-specific survival in these patients does not exceed 54–77%.<sup>82</sup> A careful consideration of (individualized) treatment morbidity on the one hand and potential benefit of the treatment on the other hand should be made together with the patient. Clinical tools, such as frailty measurements and consultation of a geriatrician in elderly and vulnerable patients, could be helpful in the decision-making process for both patient and clinician.<sup>29,83</sup>

A limitation of this literature review is that due to the lack of consensus on the definition of 'elderly', the different statistical methods used in the reviewed studies and the many small sample sizes, treatment outcomes and age groups could not be systematically compared or re-analysed.

## Conclusion

When feasible, surgery is the gold standard for the treatment of elderly patients with KC. However, in elderly patients, tumours

are typically larger at surgery which might lead to a greater defect size. Recurrence rate and disease-specific survival do not differ between elderly and younger patients after surgical treatment. RT is a good alternative for surgery but can be a burden for frail elderly patients because of the frequency of treatments. Hypofractionated RT can be considered as a curative treatment since it was shown to be effective and well-tolerated by most of the elderly patients, although controlled studies with better-defined inclusion criteria and longer follow-up are needed. Several alternative local destructive treatments can be considered in the case of elderly patients with low-risk tumours or patients in which surgery or RT is contraindicated. In elderly patients with aggressive, advanced and/or unresectable KC, systemic treatment options are limited. When deciding on any form of treatment, it is important to consider the potential benefits against 'wait-and-see' or supportive care, especially in elderly or frail patients.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Keywords used in the systematic search performed in MEDLINE