ORIGINAL ARTICLE

Retrospective, Registry-based, Cohort Investigation of Clinical Outcomes in Patients with Cutaneous Squamous Cell Carcinoma and Basal Cell Carcinoma in Finland

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Most cases of keratinocyte cancer can be treated effectively with surgery. However, survival is reduced in patients with advanced disease. This retrospective cohort study evaluated overall survival of patients with invasive keratinocyte cancers, and high-risk features for progression of the disease and mortality in Finnish patients in a real-world setting. A total of 43,143 patients with keratinocyte cancer types of basal cell carcinoma and 10,380 with cutaneous squamous cell carcinoma were identified nationwide. More detailed patient records were available for a subset of patients (basal cell carcinoma *n* = 5,020 and cutaneous squamous cell carcinoma *n* = 1,482) from a regional database. Fifty percent of patients with advanced cutaneous squamous cell carcinoma died approximately 4.5 years after diagnosis. Multivariable models suggested that risk factors for keratinocyte cancer progression were male sex, presence of comorbidities, immunosuppression, and pre-cancerous lesions, while risk factors for disease-specific mortality were advanced disease stage with immunosuppression, other malignancies, and consecutive surgical excisions. These results suggest that identifying patient and tumour factors associated with poor disease outcome could be important when determining appropriate treatment and follow-up; however, further studies are necessary.

Key words: cutaneous squamous cell carcinoma; basal cell carcinoma; skin cancer; real-world evidence; real-world data; cohort study.

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SIGNIFICANCE

Real-world evidence studies of the clinical treatment outcomes of patients with keratinocyte cancer are limited. The current extensive study demonstrated poorer survival in patients with advanced keratinocyte cancer from Finnish registry data. The most common treatment of patients with primary keratinocyte cancer was surgical excision, but patients with advanced stage disease generally had suboptimal outcomes with any subsequent treatment. This study provides new evidence on high-risk features for progression of keratinocyte cancer and mortality, which requires support from further studies, as it may be important for future treatment strategies.

Keratinocyte cancers are the most common cancer types with increasing incidence worldwide (1, 2). Keratinocyte cancer types cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) account for more than 95% of all cases (1–3). In Finland, the incidence of cSCC and BCC in 2019 was 34.3 and 180.4 per 100,000 person-years, respectively, corresponding to a BCC:cSCC ratio of 5:1 (4). Long-term exposure to ultraviolet (UV) radiation is the major risk factor leading to an increased number of individuals with keratinocyte cancer among the ageing population (5–7). In addition, sex, skin type, radiation therapy, prolonged immunosuppression, chronic cutaneous ulceration, human immunodeficiency and papilloma viruses, and certain syndromes or genetic disorders are known risk factors (8–11).

Most keratinocyte cancers occur on highly UV-exposed areas, such as the face and other parts of the head (1, 2). These keratinocyte cancers are also more likely to recur than those occurring on the trunk and extremities (5). Surgical excision is the standard treatment for cSCC and nodular, micronodular, sclerotic or infiltrative BCC. Superficial BCC is primarily treated with cryotherapy, photodynamic therapy (PDT), CO_2 laser or electrodessication (10, 11). Precursor lesions of cSCC (e.g. actinic keratosis (AK) and Morbus Bowen/cutaneous squamous carcinoma *in situ* (cSCCIS)) are treated mainly with non-surgical methods. Less than 1% of BCCs will develop metastases (11), whereas the incidence of metastases ranges from 2% to 46% in cSCC, but generally metastases may remain undetected in clinical practice, especially in locally advanced disease (12). The definition of advanced keratinocyte cancer includes locally advanced or metastatic disease that cannot be treated with a curative intent by surgery or radiotherapy (6, 13, 14). Historically, patient with advanced cSCC have been treated with cisplatin-containing regimens and anti-EGFR-antibody (cetuximab), but other treatment options have been limited. Patients with BCC have benefitted from the recent introduction of hedgehog pathway

inhibitors. Anti-PD-1-antibodies have been shown to be effective in the treatment of advanced keratinocyte cancer (15–19), resulting in recent approvals for indication in the treatment of both cSCC and BCC.

Reports summarizing clinical treatment outcomes are limited, especially those concerning advanced keratinocyte cancer (20–22). Recent updates in international guidelines have underlined the need to identify high-risk features of advanced disease, such as poor histological differentiation, tumour size and depth, location, perineural and lymphovascular invasion and immunosuppression, at an early stage (6, 13, 14).

The aim of this retrospective registry study was to evaluate overall survival (OS), and high-risk features for keratinocyte cancer progression and mortality in real-life clinical setting to facilitate the early-stage identification of patients at risk for keratinocyte cancer progression. In addition, clinical treatment patterns of patients with keratinocyte cancer in Finland were studied.

MATERIALS AND METHODS

Study design and population

This was a retrospective registry study utilizing existing data generated during routine clinical practice and available in the Finnish electronic healthcare registries (see Appendix S1). The study was approved by the ethics committee of the Hospital District of Southwest Finland (HDSF) (study number T72/2020), Statistics Finland (Dnro TK-53-549-20), and the National Institute of Health and Welfare (THL) (Dnro THL/837/5.05.00/2020).

Data sources and inclusion criteria

All adult patients with keratinocyte cancer living in Finland and diagnosed between 2012 and 2019 were included in this study (**Fig. 1**). The cases were identified from the data lake of HDSF, the Finnish Cancer Registry (FCR), and/or the Care Register for Healthcare (specialty care patient register) controlled by THL utilizing topographical (International Classification of Diseases 10th Revision; ICD-10) codes for keratinocyte cancer (C44*; where * indicates any number). In addition to electronic diagnosis-based inclusion of patients to the cohort, a previously described advanced cSCC patient cohort originating from the HDSF, and identified by manual review of the patient records and pathology reports, was included in this study (23). The inclusion of the regional cSCC patients from the cohort described by Knuutila et al. (23) started in 2004. Rest of the regional keratinocyte cancer patients were included starting from 2010. Patients with a first keratinocyte cancer diagnosis before the age of 18 years were excluded from this study. In addition to the HDSF data lake and the FCR, data were collected from the Care Register for Healthcare (specialty and primary care patient registers), and Statistics Finland. The study was divided into nationwide (cases identified from the FCR and the Care Register for Healthcare) and regional (cases originating from HDSF area) analyses based on utilized registries. The nationwide analyses were utilized for reporting overall statistics for the patients and the regional analyses for more detailed results. This was done because the regional data, retrieved from HDSF, contained more detailed information on patients.

Patient subgrouping by keratinocyte cancer type and cancer status

Patients with both cSCC and BCC diagnoses were classified as cSCC patients with BCC as a comorbidity. The results were stratified according to keratinocyte cancer type (BCC/cSCC with or without BCC comorbidity) and the status of cancer defined

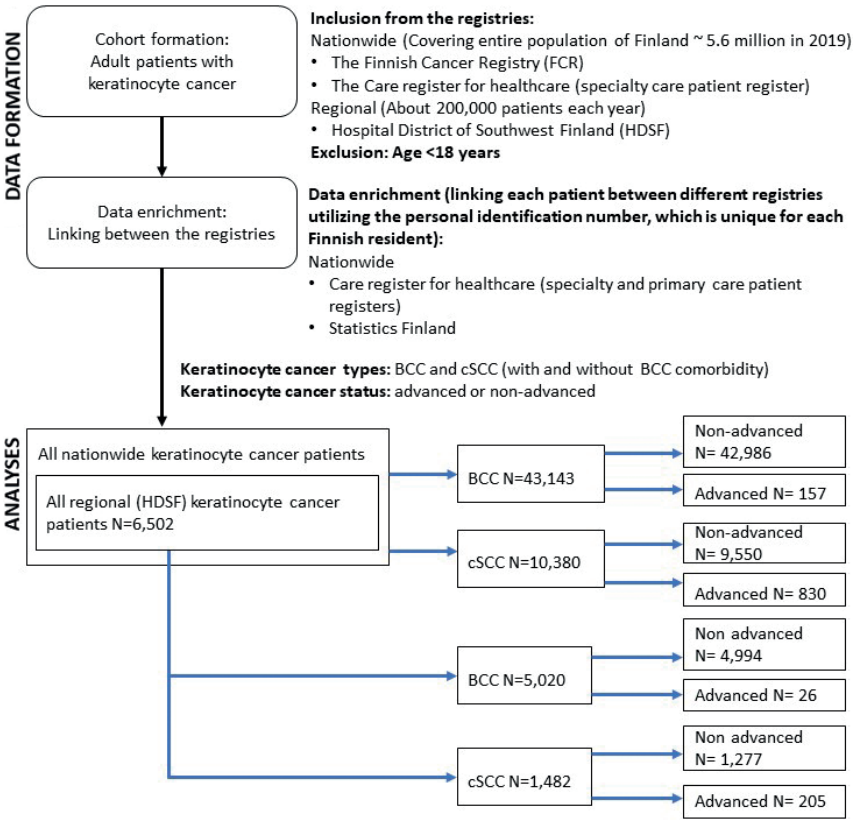

Fig. 1. Flow chart of the data formation and analyses. HDSF: Hospital District of Southwest Finland; BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; Advanced criteria: confirmed presence of keratinocyte cancer associated metastasis, Finnish Cancer Registry (FCR) cancer stage 3 or higher, perineural or lymphovascular invasion, received drug or radiation therapy for cSCC, and/or received 3 or more surgeries for cSCC.

as advanced/non-advanced. The keratinocyte cancer type was inferred based on the structurally recorded ICD-10 diagnosis codes in the HDSF data lake or the Care Register for Healthcare and confirmed status present in the FCR. Inclusion criteria for the advanced-stage cohort were one or several of the following: confirmed presence of keratinocyte cancer-associated metastasis, FCR cancer stage 3 or higher, perineural (PNI) or lymphovascular (LVI) invasion, received drug or radiation therapy for cSCC, and/or received 3 or more surgical excision (treatment-related surgeries, not diagnostic) for cSCC. The criteria were the same for BCC, apart from not including the number of surgeries as an indication of advanced cancer. The criteria for assessing cancer status have been explained in detail in Table SI.

Patient characteristics

Demographic and clinical characteristics were assessed from patient records in structured form or by utilizing text mining. Keratinocyte cancer precursors, namely Bowen's disease, AK, and Charlson's comorbidity index (CCI) (24), were assessed based on the structurally recorded ICD-10 diagnosis codes in the specialty or primary care patient registers. Immunosuppression was inferred when any of the following indicators was detected: a procedure related to organ transplant, an ICD-10 diagnosis code indicating previously performed organ transplant, or administered/prescribed immunosuppressive drug (Table SII). The date of immunosuppression was defined as the date of the earliest record date of the previously described indicators. Other malignancies were defined as any cancer ICD-10 diagnosis code other than C44*, C78* or C79* being recorded (where * indicates any number). The date of the first such recorded diagnosis code was collected. Treatments including surgeries, localized therapy, radiotherapy, and drug therapy were collected. Data on cryotherapy and photodynamic therapy, which are typical treatments for Bowen's disease and AK, were not included here due to changes in recording practices during the study time.

Consecutive surgical excisions were considered to be cSCC-specific based on procedure codes and timing of diagnosis. The number of patients' consecutive surgical excision were reported from 0 to 4 and ≥5 as well as the mean, median, first, and third quartile points of number of surgeries. If there were several surgical excision procedures recorded on the same date, they were counted only once.

The comorbidities for the patients with keratinocyte cancer in the nationwide registry were assessed from structurally recorded ICD-10 diagnosis codes. Both primary and secondary diagnoses were included. The laboratory measures reported for regional data were collected at diagnosis (index).

Outcomes

The primary outcome of this study was overall survival (OS). The secondary outcomes were progression-free survival (PFS), and mortality (keratinocyte cancer-specific and all cause/non-C44). For PFS, disease progression was defined by 1 of the following criteria: third or subsequent related surgery (only used for cSCC), detection of metastasis (censoring the cases with other cancers), drug-based keratinocyte cancer treatment (C44 diagnosis recorded with procedure; Table SIII), or keratinocyte cancer radiation therapy (C44 diagnosis recorded with procedure).

Keratinocyte cancer mortality was defined as having a C44* diagnosis as main or immediate cause of death. The causes of death are recorded at 4-character-level, and thus it was not possible to assess BCC and cSCC mortality separately.

Statistical analyses

Descriptive statistics were used to report the basic and clinical characteristics, including median with standard error (SE), interquartile range, frequencies, and percentages stratified by keratinocyte cancer type (BCC/cSCC) and disease status (advanced/non-advanced). The length of follow-up was defined as time from index until end of follow-up, where index was the first record of C44* diagnosis and the end of follow-up was defined as the end of study (nationwide 31 December 2018 and regional 31 December 2019), or death. The median lengths of follow-up in years were calculated. For patient treatment, the number of operations, therapies received, the number of recurrent events/tumours at the same site or any other distant or local site in patients with keratinocyte cancer were reported.

OS according to treatment type in patients with advanced cSCC, PFS, and mortality were assessed using Kaplan–Meier fits (25). The median survivals, when reached, were reported, as well as the survival estimates with the corresponding confidence intervals (CI). The association of covariates with the keratinocyte cancer mortality, PFS, and OS by treatment type were assessed using multivariable Cox proportional hazards models.

Regional data were utilized in the Cox models for keratinocyte cancer mortality and PFS, while national data were used for the Cox model of OS by treatment type due to a small number of patients receiving radiotherapy or chemotherapy for their keratinocyte cancer. The variables included for PFS were sex, age, CCI, immunosuppression, other malignancies, and precursors (AK and Bowen's disease). The variables included for C44 mortality were sex, age, CCI, immunosuppression, other malignancies, cancer stage (advanced vs non-advanced) and presence of BCC as comorbidity. Precursors were left out of the model for keratinocyte cancer mortality, as there were only a few patients with the precursors who deceased due to keratinocyte cancer. Immunosuppression, other malignancies and cancer stage were included as time-varying covariates, using the corresponding dates. Laboratory measures were log-transformed (base 2) to normalize the distribution for Cox models.

Keratinocyte cancer mortality was assessed using a multi-level Cox model, where the initial state was "alive", and the 2 end states included "keratinocyte cancer death" and "other cause death" to account for the competing risks between C44-mortality and other mortality. The Cox model for OS by treatment type included radiotherapy, chemotherapy, third surgery, age at index, sex, other malignancy and comorbid BCC as covariates. Radiotherapy, chemotherapy, third surgery, and other malignancy were included as time-varying covariates. Note that the same patient may have received more than 1 type of treatment. The hazard ratios (HR), SE, 95% CI and p-values were reported. A significance threshold of $p < 0.05$ was adopted throughout.

Statistical analyses were performed using R version 4.0.2 (26). Only existing data were used, and no imputation of missing values was performed. The proportion of missing values are reported, where applicable.

RESULTS

The number of patients with keratinocyte cancer in the nationwide analyses was 43,143 BCC and 10,380 cSCC, and in the regional analyses 5,020 BCC and 1,482 cSCC. The number of patients categorized with advanced-stage disease was relatively low for both nationwide and regional analyses (of the patients with BCC 0.3% and 0.5%, and of the patients with cSCC 8.0% and 13.8%, respectively) (Fig. 1). No patients were included in the advanced-stage cohort with only LVI or PNI criteria, because all patients with LVI or PNI had also other inclusion criteria in their data (for inclusion criteria see Table SI).

Demographic and clinical characteristics

The median length of follow-up for the nationwide analyses was 3.0 years for both BCC and cSCC, while for the regional analyses the median length of follow-up was 4.1 years for BCC and 3.8 years for cSCC. In total, for nationwide analyses, there were 131,041 BCC patient-years and 30,406 cSCC patient-years, and for regional analyses 20,342 BCC patient-years and 5,699 cSCC patient-years. The median age at diagnosis of the BCC patients was 74.0 and 74.3 years in the nationwide and regional analyses, respectively. Correspondingly, the median age of the patients with cSCC was 79.0 and 79.4 years (nationwide and regional, respectively).

The demographic and clinical characteristics for the regional analyses are shown in **Table I**. Of the studied patients, 74 originated from the cohort described by Knuutila et al. (23) (cSCC advanced) and other patients included were based on a C44 diagnosis (BCC $n=5,020$; cSCC non-advanced $n=1,277$; cSCC advanced $n=131$). Overall, sex distribution of the patients with keratinocyte cancer was equal, except in the cSCC advanced group, in which over 60% of the patients were male. The most common location of BCC and cSCC were other and unspecified parts of face (Table SIV). The American Society of Anesthesiologists (ASA) physical status was missing from 14.8% of the BCC and 8.0% of the patients with cSCC, and majority of patients had a classification of 1–3, with 3 being defined mainly by the oncological state of the patient.

High-risk factors, such as LVI, PNI, and features typical for advanced disease, such as metastasis code or cancer staging, were not frequently recorded, and data were generally missing from the patients' medical records (Table I). Drug therapy was generally rare among patients with BCC, but approximately one-fourth of patients with advanced cSCC received radiotherapy. Surgeries with curative intent were almost exclusively used for treatment at all disease stages. The majority of patients were included into the advanced stage status, based on the criteria of receiving at least 3 subsequent surgeries with curative intent. cSCC patients with BCC as a co-morbidity, as well as all patients with other diagnosed cancers, were not included in the advanced cohort regardless of the number of surgeries.

Pre-cancerous lesions were frequent findings among patients with keratinocyte cancer. AK was found in 23.1% and 39.3%, and Bowen's disease in 5.3% and 16.4% in patients with BCC and cSCC, respectively. There were no differences among incidence between advanced and non-advanced groups. Most of the actual keratinocyte cancer tumours were discovered de-novo, without a previous diagnosis of precancerous lesion, and the lesions were discovered while patients were being treated based on their keratinocyte cancer tumour. Immunosuppression was relatively rare among the patients, with less than 10% receiving any immunosuppressive medication or procedures (Table I).

In BCC and cSCC, 24.4% and 35.2% of patients had been diagnosed with another cancer (Table I). BCC was also a very common finding among cSCC patients, with 49.4% having both cancer types simultaneously. Among the most common other cancer diagnoses were malignant neoplasms of prostate and breast (ICD-10-codes C61 and C50, respectively). Most of the patients had a CCI of 0–2 at index. For the patient group with advanced cSCC, the CCI was from 6 to 8 at advanced stage. Common co-diagnoses (non-cancer) were hypertension, atrial fibrillation and flutter, conductive and sensorineural hearing loss, and skin changes due to chronic exposure to UV radiation. The most common comorbidities recorded at any time-point during follow-up for the nationwide keratinocyte cancer cohort are reported in Table SV.

Overall survival of advanced vs non-advanced status patients with cutaneous squamous cell carcinoma and basal cell carcinoma

The 2-, 3- and 5-year survival probabilities from first BCC diagnosis were 93%, 89% and 80% for non-advanced status, respectively, and for all 3 time-points 71% for advanced status in regional analyses **(Fig. 2**A). In the cSCC patient cohort the 2-, 3- and 5-year OS estimates were 85%, 77% and 66% for non-advanced status, and 71%, 62%, and 47% for advanced status, respectively (Fig. 2A). Of advanced cSCC patients, 50% died during approximately 4.5 years after the diagnosis (Fig. 2).

Concurrent surgical excision

Surgical excision with a curative intent is a common treatment for patients with keratinocyte cancer (**Table II**). Patients with BCC or cSCC with comorbid BCC had surgical excisions more frequently than cSCC patients without BCC. Depending on the subgroup, 4–23% of the patients with keratinocyte cancer had not been operated during the studied period, while approximately half of the patients had at least 1 surgical excision, and 18% had 5 or more surgical excisions. Overall, patients with cSCC and comorbid BCC had more surgical excisions than other patient groups.

The mean number of keratinocyte cancer-related surgical excisions for cSCC patients with comorbid BCC was highest (mean nationwide 2.26/regional 2.98 surgeries), and for BCC patients (mean nationwide 1.24/ regional 1.43 surgeries) slightly higher or at the same level as for cSCC patients without BCC (mean 1.18/1.47 surgeries) (**Table III**). The median number of surgical excisions in cSCC patients with BCC as a comorbidity was 2, while for all other keratinocyte cancer patient groups the median number of surgeries was 1.

Table I. Demographic and clinical characteristics of patients with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) by advanced or non-advanced status of cancer

Variable	Patients with BCC				Patients with cSCC			
	All *n* (%)	Non-advanced *n* (%)	Advanced *n* (%)	*p*-value	All *n* (%)	Non-advanced *n* (%)	Advanced *n* (%)	*p*-value
N	5,020 (100)	4,994 (100)	26 (100)	–	1,482 (100)	1,277 (100)	205 (100)	–
Sex								
Female	2,609 (52.0)	2,596 (52.0)	13 (50.0)	0.996	689 (46.5)	613 (48.0)	76 (37.1)	0.005
Male	2,411 (48.0)	2,398 (48.0)	13 (50.0)		793 (53.5)	664 (52.0)	129 (62.9)	
AK (L57.0 recorded prior to or at index): Yes	695 (13.8)	693 (13.9)	<5 (–)	0.568	321 (21.7)	274 (21.5)	47 (22.9)	0.702
BD/Carcinoma *in situ* on skin (D04 recorded prior to or at index): Yes	131 (2.6)	131 (2.6)	0 (0.0)	–	99 (6.7)	85 (6.7)	14 (6.8)	1.000
AK (L57.0; whole follow-up): Yes	1,158 (23.1)	1,153 (23.1)	5 (19.2)	0.816	582 (39.3)	479 (37.5)	103 (50.2)	0.001
BD/Carcinoma *in situ* on skin (D04; whole follow-up): Yes	265 (5.3)	264 (5.3)	<5 (–)	1.000	243 (16.4)	206 (16.1)	37 (18.0)	0.557
De novo keratinocyte cancer (no records of L57.0 or D04 prior to at index): Yes	4,275 (85.2)	4,251 (85.1)	24 (92.3)	0.414	1,124 (75.8)	971 (76.0)	153 (74.6)	0.728
Lymphovascular invasion (LVI)								
Missing	5,000 (99.6)	4,982 (99.8)	18 (69.2)	–	1,443 (97.4)	1,254 (98.2)	189 (92.2)	–
Yes	8 (0.2)	0 (0.0)	8 (30.8)	–	8 (0.5)	0 (0.0)	8 (3.9)	–
Perineural invasion (PNI)								
Missing	4,991 (99.4)	4,979 (99.7)	12 (46.2)	–	1,436 (96.9)	1,256 (98.4)	180 (87.8)	–
Yes	14 (0.3)	0 (0.0)	14 (53.8)	–	23 (1.6)	0 (0.0)	23 (11.2)	–
BCC as comorbidity: Yes	–	–	–	–	732 (49.4)	678 (53.1)	54 (26.3)	–
Operated at least 3 times: Yes	620 (12.4)	615 (12.3)	5 (19.2)	–	394 (26.6)	266 (20.8)	128 (62.4)	–
Received chemo- or immunotherapy (other cancers exc.): Yes	0 (0.0)	0 (0.0)	0 (0.0)	–	12 (0.8)	0 (0.0)	12 (5.9)	–
Radiotherapy (other cancers exc.): Yes	<5 (–)	0 (0.0)	<5 (–)	–	44 (3.0)	0 (0.0)	44 (21.5)	–
Metastatic (ICD-10 code C78 or C79; other cancers exc.): Yes	<5 (–)	0 (0.0)	<5 (–)	–	<5 (–)	0 (0.0)	<5 (–)	–
Stage at least 3 (Cancer Registry; CSCC)								
Missing	–	–	–	–	435 (29.4)	393 (30.8)	42 (20.5)	–
Yes	–	–	–	–	24 (1.6)	0 (0.0)	24 (11.7)	
Stage at least 3 (Cancer Registry; BCC)								
Missing	782 (15.6)	781 (15.6)	<5 (–)	–	946 (63.8)	776 (60.8)	170 (82.9)	–
Yes	<5 (–)	0 (0.0)	<5 (–)	–	0 (0.0)	0 (0.0)	0 (0.0)	
Other cancer recorded: Yes	1,225 (24.4)	1,212 (24.3)	13 (50.0)	0.005	521 (35.2)	429 (33.6)	92 (44.9)	0.002
Immunosuppressed patients: Yes	333 (6.6)	331 (6.6)	<5 (–)	0.690	125 (8.4)	99 (7.8)	26 (12.7)	0.026
Immunosuppressive medication: Yes	298 (5.9)	296 (5.9)	<5 (–)	0.665	103 (7.0)	82 (6.4)	21 (10.2)	0.064
Transplant diagnosis code recorded: Yes	51 (1.0)	51 (1.0)	0 (0.0)	–	26 (1.8)	17 (1.3)	9 (4.4)	0.005
Transplant procedure code recorded: Yes	31 (0.6)	31 (0.6)	0 (0.0)	–	21 (1.4)	18 (1.4)	<5 (–)	1.000
American Society of Anesthesiologists (ASA) physical status*								
1	428 (10.0)	425 (10.0)	<5 (–)	0.216	66 (4.9)	61 (5.3)	5 (2.5)	0.038
2	1,733 (40.4)	1,720 (40.4)	13 (52.0)		352 (25.8)	305 (26.1)	47 (24.0)	
3	1,891 (44.2)	1,883 (44.2)	8 (32.0)		809 (59.3)	690 (59.1)	119 (60.7)	
4 +	227 (5.4)	226 (5.4)	<5 (–)		136 (10.0)	111 (9.5)	25 (12.8)	
Missing	741 (14.8)	740 (14.8)	<5 (–)	–	119 (8.0)	110 (8.6)	9 (4.4)	
Age at diagnosis (cat.)								
<60 years	661 (13.2)	658 (13.2)	<5 (–)	0.154	93 (6.3)	79 (6.2)	14 (6.8)	0.079
60–64 years	443 (8.8)	440 (8.8)	<5 (–)		66 (4.5)	56 (4.4)	10 (4.9)	
65–69 years	662 (13.2)	655 (13.1)	7 (26.9)		130 (8.8)	109 (8.5)	21 (10.2)	
70–74 years	870 (17.3)	864 (17.3)	6 (23.1)		217 (14.6)	185 (14.5)	32 (15.6)	
75–79 years	878 (17.5)	875 (17.5)	<5 (–)		262 (17.7)	219 (17.1)	43 (21)	
≥80 years	1,506 (30.0)	1,502 (30.1)	<5 (–)		714 (48.2)	629 (49.3)	85 (41.5)	
Charlson Comorbidity Index (CCI)								
0	2,771 (55.2)	2,756 (55.2)	15 (57.7)	0.809	673 (45.4)	572 (44.8)	101 (49.3)	0.272
1	826 (16.5)	821 (16.4)	5 (19.2)		238 (16.1)	210 (16.4)	28 (13.7)	
2	797 (15.9)	795 (15.9)	<5 (–)		277 (18.7)	242 (19)	35 (17.1)	
3	298 (5.9)	296 (5.9)	<5 (–)		141 (9.5)	124 (9.7)	17 (8.3)	
4 +	328 (6.5)	326 (6.5)	<5 (–)		153 (10.3)	129 (10.1)	24 (11.7)	
CCI (at advanced)								
6	17 (0.3)	0 (0)	17 (65.4)		104 (7.0)	0 (0)	104 (50.7)	–
7	7 (0.1)	0 (0)	7 (26.9)		48 (3.2)	0 (0)	48 (23.4)	
8 +	<5 (–)	0 (0)	<5 (–)		53 (3.6)	0 (0)	53 (25.9)	

*Percentages calculated from non-missing values.
p-values are for the difference between advanced and non-advanced status patient groups. *p*-values for variables that are used in the advanced/non-advanced definition are not calculated.
Small patient groups (<5 patients) have not been reported in detail.
Tests used: Wilcoxon signed-rank test: CCI, age, ASA. Fishers' exact test for categorials if number in any cell was 1–4, *t*-test otherwise. If any cell had value 0, *p*-value not calculated.
AK: actinic keratosis; BD: Bowens disease; Advanced disease: confirmed presence of keratinocyte cancer-associated metastasis, Finnish Cancer Registry (FCR) cancer stage 3 or higher, perineural or lymphovascular invasion, received drug or radiation therapy for cSCC, and/or received 3 or more surgeries for cSCC.
exc.: excluded; cat.: category.

Progression-free survival: time until next surgical excision

The likelihood of tumour recurrence was further assessed by Kaplan–Meier regional analysis as the time until the next surgical excision (Fig. S1). The time until next surgery varied according to the number of previous surgeries in all studied patient groups (log-rank-test $p<0.0001$). For all patient groups approximately 50% of the patients had the first surgical excision at the time of diagnosis and a subsequent surgery within 3 months from the previous surgery. Overall, the first surgical excision was common shortly after diagnosis, the second surgery within 3 months from diagnosis, and the third surgery within 3 months after the second. The 4th and 5th surgical excisions were shortly after the third (in less than 3 months).

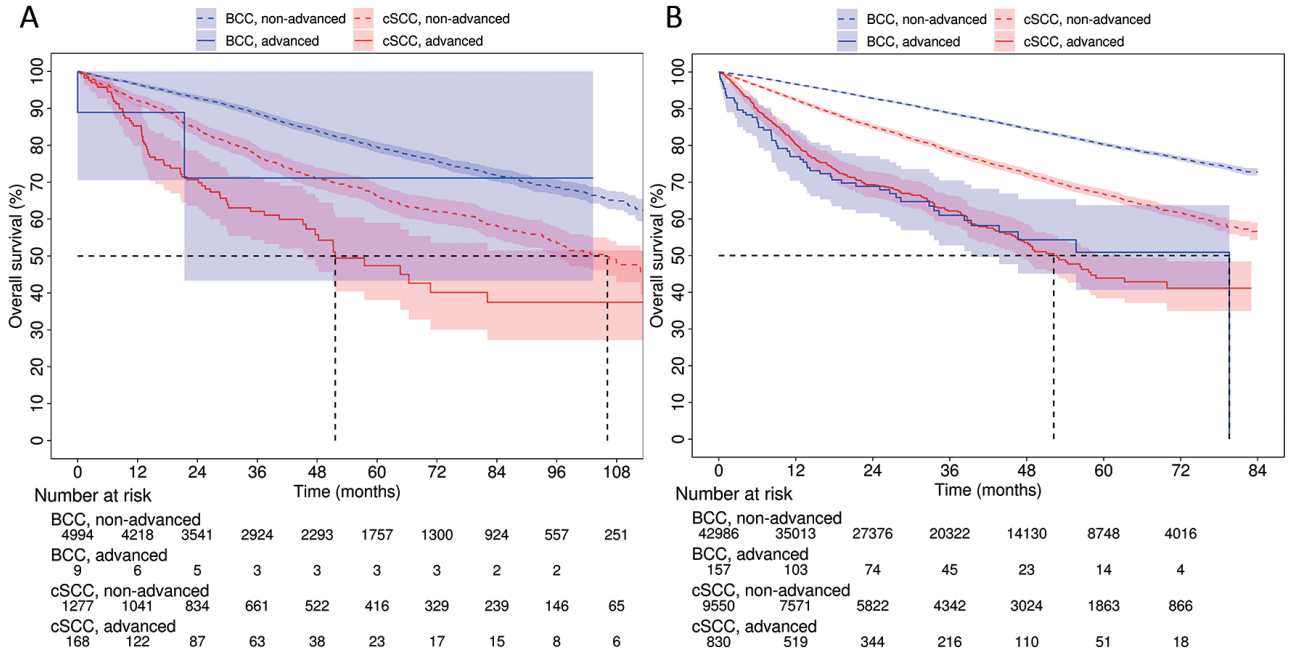

Fig. 2. Kaplan–Meier fit of overall survival in patients with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) by cancer status (non-advanced and advanced). (A) Regional analysis. (B) Nationwide analysis. Overall survival is calculated from first BCC (non-advanced $n = 4,994$ regional/$n = 42,986$ nationwide and advanced $n = 9$ regional/$n = 157$ nationwide) or cSCC (non-advanced $n = 1,277$ regional/$n = 9,550$ nationwide and advanced $n = 168$ regional/$n = 830$ nationwide) diagnosis. *Dashed line* represents median survival. Advanced disease: confirmed presence of keratinocyte cancer associated metastasis, Finnish Cancer Registry (FCR) cancer stage 3 or higher, perineural or lymphovascular invasion, received drug or radiation therapy for cSCC, and/or received 3 or more surgeries for cSCC.

Progression-free survival: keratinocyte cancer-specific and all-cause mortality in patients with cSCC

PFS and mortality were assessed only in patients with confirmed cSCC, as the number of patients with advanced BCC in this study was low and there was no keratinocyte cancer-related mortality present among advanced BCC cases. The keratinocyte cancer-specific and all-cause mortality for the patients with cSCC is illustrated with Kaplan–Meier survival curves (**Fig. 3**A, regional analysis and B nationwide analysis). The 5-year C44-specific mortality was 22% for advanced and 0% in the non-advanced cSCC patients in the regional cohort, which included a more extensive list of criteria for identifying advanced cases. The respective figures were 15% and 0% in the national cohort.

Multivariable analysis of factors associated with keratinocyte cancer progression and patients' survival

The multivariable Cox proportional hazards model showed that, of the covariates, male sex, presence of comorbidities, immunosuppression, and pre-cancerous lesion AK were associated with keratinocyte cancer progression (**Table IV**). Of the covariates, CCI was the strongest predictor for disease progression (19% increase in risk of progression, 95% CI 7.5–32.1%).

Summary statistics of laboratory measures of interest for patients with BCC and cSCC are reported in Table SVI. The multivariable Cox proportional hazards models were fit for mortality and PFS and for each laboratory measure in the patients with cSCC (regional analyses). All Cox models in this study included the same covariates

Table II. Number of keratinocyte cancer patients' surgical excisions

	Nationwide analysis			Regional analysis		
		Patients with cSCC ($n = 10,380$)			Patients with cSCC (n=1,482)	
	Patients with BCC ($n = 43,143$) *n* (%)	cSCC patients with comorbid BCC ($n = 4,426$) *n* (%)	cSCC patients without BCC ($n = 5,954$) *n* (%)	Patients with BCC ($n = 5,020$) *n* (%)	cSCC patients with comorbid BCC ($n = 750$) *n* (%)	cSCC patients without BCC ($n = 732$) *n* (%)
0	9,808 (22.7)	546 (12.3)	1,372 (23.0)	678 (13.5)	32 (4.4)	104 (13.9)
1	21,691 (50.3)	1,580 (35.7)	3,168 (53.2)	2,808 (55.9)	242 (33.1)	398 (53.0)
2	7,292 (16.9)	977 (22.1)	870 (14.6)	914 (18.2)	164 (22.4)	148 (19.7)
3	2,378 (5.5)	522 (11.8)	303 (5.1)	318 (6.3)	106 (14.5)	48 (6.4)
4	1,008 (2.3)	274 (6.2)	124 (2.1)	146 (2.9)	53 (7.2)	26 (3.5)
≥5	966 (2.2)	527 (11.8)	117 (1.9)	156 (3.0)	135 (18.4)	26 (3.5)

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma.

Table III. Mean and median number of surgical excisions in patients with keratinocyte cancer

	Nationwide analysis			Regional analysis		
		cSCC patients ($n=10,380$)			cSCC patients ($n=1,482$)	
	BCC patients ($n=43,143$)	Patients with comorbid BCC ($n=4,426$)	Patients without BCC ($n=5,954$)	BCC patients ($n=5,020$)	Patients with comorbid BCC ($n=750$)	Patients without BCC ($n=732$)
Mean	1.24	2.26	1.18	1.43	2.98	1.47
Median	1	2	1	1	2	1
First quartile	1	1	1	1	1	1
Third quartile	2	3	1	2	4	2

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma.

(see **Tables IV** and **V**). After adjusting for the family-wise error rate with the Benjamin-Hochberg procedure, leukocyte count was the only statistically significant predictor for disease progression (64% increase in the risk of progression per doubling of leukocyte count at index, 95% CI 23–119%, $p<0.001$, $n=925$). No laboratory measurements were associated with the risk of C44 mortality after adjustment. Laboratory measures at diagnosis (index) were missing from 11–91% of the patients, depending on the value measured (Table SVI).

For the multivariable model on keratinocyte cancer (C44)-specific mortality, advanced disease had the highest impact (HR 18.9, CI 9.92–36.04), other malignancies also notably influencing survival (Table V). Age had the highest impact on all-cause mortality (HR 1.11, 95% CI 1.09–1.12), with non-cancerous comorbidities, BCC as comorbidity, and other malignancy being significantly associated with all-cause mortality. However, BCC comorbidity was associated with lower keratinocyte cancer-mortality and all-cause mortality (keratinocyte cancer-specific mortality HR 0.71, CI 0.37–1.39; all-cause mortality (HR 0.59, CI 0.48–0.74).

Overall survival by treatment type among patients with advanced cSCC

Survival was further studied by type(s) of treatment received. The survival of the patients with advanced cSCC by treatment received is illustrated with Kaplan–Meier survival curves (**Fig. 4**). Survival of the patients who had been operated on 3 times was the highest compared with those treated with radiotherapy or chemotherapy. The Cox model showed that compared with other treatments received, the risk of death after diagnosis was higher for patients with advanced cSCC receiving radiotherapy (HR 2.6, 95% CI 2.15–3.11) or chemotherapy (HR 6.3, CI 3.29–12.24) (**Table VI**), whereas having had 3 surgeries was not associated with increased risk of death compared to patients treated with radiotherapy or chemotherapy. Covariate BCC comorbidity reduced HR of OS (HR 0.7, 95% CI 0.65–0.77). It is of note that the group receiving

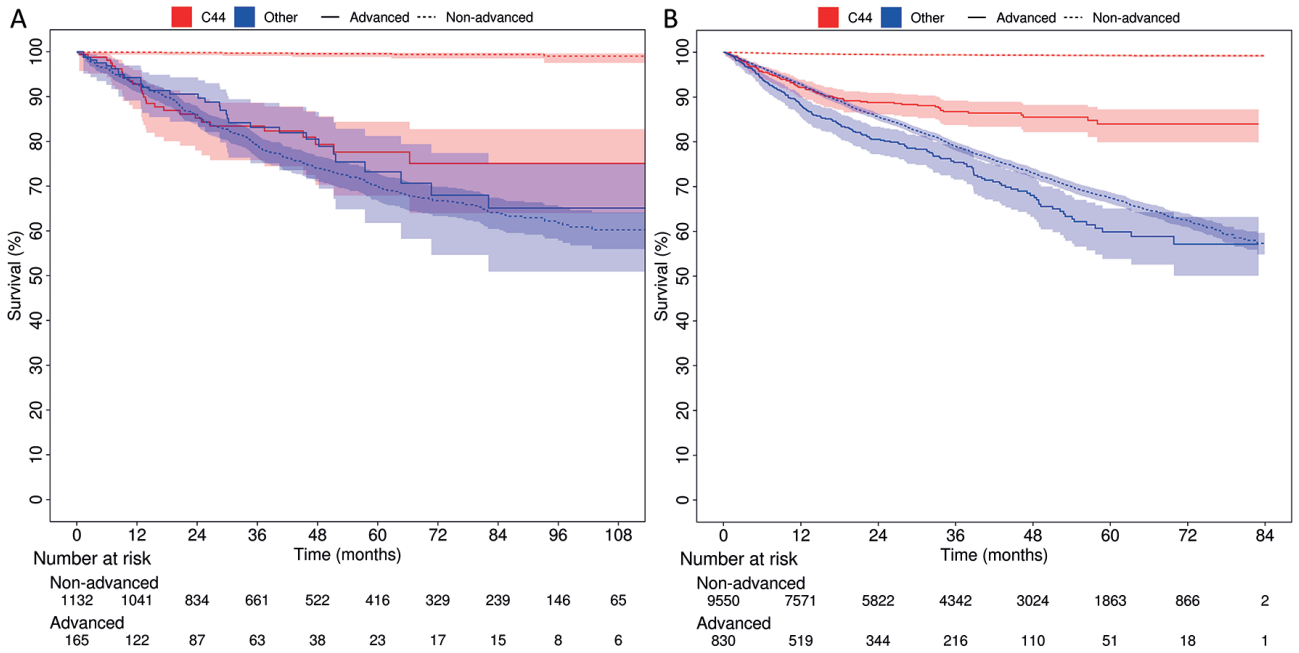

Fig. 3. Kaplan–Meier fit of keratinocyte cancer-specific (C44) and all-cause mortality in patients with cutaneous squamous cell carcinoma (cSCC) by cancer status. (A). Regional analysis. (B) Nationwide analysis. Advanced disease: confirmed presence of keratinocyte cancer associated metastasis, Finnish Cancer Registry (FCR) cancer stage 3 or higher, perineural or lymphovascular invasion, received drug or radiation therapy for cSCC, and/or received 3 or more surgeries for cSCC.

Table IV. Cox multivariable model fit for keratinocyte cancer patients' progression-free survival

Variable	HR	Lower 95% CI	Upper 95% CI	*p*-value
Age, years	1.02	1.01	1.04	<0.001
Sex				
Female (ref.)	1.00	–	–	–
Male	1.56	1.13	2.14	<0.001
Other malignancy				
No (ref.)	1.00	–	–	–
Yes	0.94	0.62	1.44	0.77
Charlson Comorbidity Index (CCI)	1.19	1.08	1.32	<0.001
Immunosuppression				
No (ref.)	1.00	–	–	–
Yes	1.87	0.95	3.69	0.07
Actinic keratosis (L57.0 recorded prior to or at index)				
No (ref.)	1.00	–	–	–
Yes	1.82	1.26	2.63	<0.001
Bowen's disease (D04 recorded prior to or at index)				
No (ref.)	1.00	–	–	–
Yes	1.42	0.71	2.86	0.32

Immunosuppression: a procedure related to organ transplant, an ICD-10 diagnosis code indicating previously performed organ transplant, or administered/ prescribed immunosuppressive drug; HR: hazard ratio; CI: confidence interval; ref.: reference.

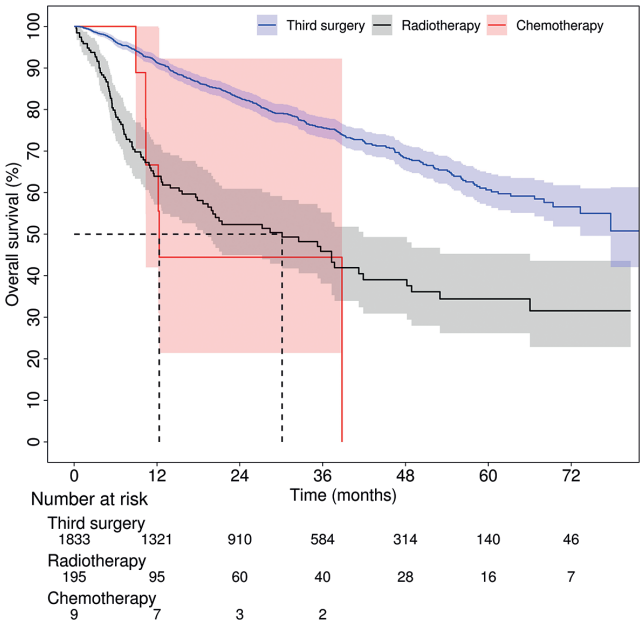

Fig. 4. Kaplan–Meier fit from the beginning of the first administered treatment type until death (event) or end of follow-up (31 December 2019; censoring event) among patients with advanced cutaneous squamous cell carcinoma (cSCC). Note that due to overlap between treatment types, the number of patients at risk at time =0 is lower than those shown in the corresponding Cox fit (Table VI).

chemotherapy treatment was very small ($n=15$), resulting in wide confidence intervals.

DISCUSSION

This study from Finnish real-world data (RWD) demonstrated poorer survival in patients with advanced keratinocyte cancer compared with non-advanced. Fifty percent of patients with advanced cSCC died approximately 4.5 years after the diagnosis. Furthermore, we showed high-risk features for keratinocyte cancer progression and mortality. This study covered approximately 53,500 patients with keratinocyte cancer identified from nationwide registries, with additional data for 6,500 patients with keratinocyte cancer from the regional data lake. The BCC to cSCC ratio in this study was 4:1. As in previous studies (1, 2), the skin of the face was the most common location for keratinocyte cancer in our data.

Recent updates in international guidelines have emphasized the need especially to identify the high-risk features of advanced cSCC at an earlier stage for better prognosis (6, 13, 14). However, in clinical practice high-risk features for cSCC disease progression may remain unnoticed. Thus, guideline updates have included a recommendation for screening patients with keratinocyte cancer (6, 14). A risk feature for keratinocyte cancer progression and mortality observed in this study was advanced status of

Table V. Cox multivariable model fit for keratinocyte cancer-specific and all-cause mortality (non-C44)

	Keratinocyte cancer mortality (C44)				All-cause mortality (non-C44)			
Variable	HR	Lower 95% CI	Upper 95% CI	*p*-value	HR	Lower 95% CI	Upper 95% CI	*p*-value
Age, years	1.05	1.02	1.09	<0.001	1.11	1.09	1.12	<0.001
Sex								
Female (ref.)	1.00	–	–	–		–	–	–
Male	1.04	0.56	1.93	0.91	1.13	0.91	1.41	0.26
BCC as comorbidity								
No (ref.)	1.00	–	–	–		–	–	–
Yes	0.72	0.37	1.39	0.32	0.59	0.48	0.74	<0.001
Charlson Comorbidity Index (CCI)	1.00	0.85	1.19	0.98	1.19	1.12	1.26	<0.001
Immunosuppression								
No (ref.)	1.00	–	–	–		–	–	–
Yes	1.64	0.55	4.90	0.38	0.48	0.23	1.02	0.06
Other malignancy								
No (ref.)	1.00	–	–	–		–	–	–
Yes	2.56	1.30	5.03	0.007	1.52	1.19	1.94	<0.001
Cancer stage								
Non-advanced (ref.)	1.00	–	–	–		–	–	–
Advanced	18.91	9.92	36.04	<0.001	1.15	0.79	1.68	0.47

Immunosuppression: a procedure related to organ transplant, an ICD-10 diagnosis code indicating previously performed organ transplant, or administered/prescribed immunosuppressive drug; Advanced disease: confirmed presence of keratinocyte cancer-associated metastasis, Finnish Cancer Registry (FCR) cancer stage 3 or higher, perineural or lymphovascular invasion, received drug or radiation therapy for cutaneous squamous cell carcinoma (cSCC), and/or received 3 or more surgeries for cSCC; BCC: basal cell carcinoma; HR: hazard ratio; 95% CI: 95% confidence interval; ref: reference.

Table VI. Cox multivariable model results of overall survival (OS) in cutaneous squamous cell carcinoma (cSCC) patients by treatment type (radiotherapy, chemotherapy, or third surgery), nationwide analysis

Variable	HR	Lower 95% CI	Upper 95% CI	*p*-value
Radiotherapy (*n* = 310)	2.59	2.15	3.12	< 0.001
Chemotherapy (*n* = 15)	6.34	3.29	12.23	< 0.001
Third surgery (*n* = 2,064)	1.11	0.99	1.24	0.07
Age at index (years)	1.10	1.10	1.11	< 0.001
Sex (=male; females as ref.)	1.29	1.19	1.40	< 0.001
Other malignancy	1.97	1.82	2.14	< 0.001
BCC as comorbidity	0.71	0.65	0.77	< 0.001

The model was adjusted by age at index, sex, other malignancy, and basal cell carcinoma (BCC) as comorbidity. HR: hazard ratio; CI: confidence interval; ref.: reference.

the disease. Metastases in BCC are relatively rare, but the aggressiveness of distant metastatic cSCC is well established. A previous study by Knuutila et al. (23) showed that metastasis of cSCC usually occurs relatively early, with 84.7% of metastasis detected within 2 years after diagnosis. The current study also found that 51.2% of patients with cSCC progressed within 2 years after diagnosis. Furthermore, advanced status of cSCC increased the risk of keratinocyte cancer mortality in addition to immunosuppression and other malignancies (advanced status HR 18.9, 95% CI 9.92–36.04). Advanced disease also had the largest impact on PFS. In this study, patients were included in the cSCC advanced status cohort, based on, for example, the number of cSCC-specific consecutive surgeries. Pathological data were not systematically collected. Thus, identification of high-risk features remained suboptimal.

Male sex, higher CCI, and AK precursor diagnosis were associated with progression of keratinocyte cancer (≥3 subsequent related surgery/ keratinocyte cancer metastasis/drug-based keratinocyte cancer treatment/ keratinocyte cancer radiation therapy). Of the laboratory measurements, elevated leukocyte count was associated with disease progression (64% increase in the risk of progression per doubling of leukocyte count at index, 95% CI 23–119%). However, data on laboratory measurements were missing from a large proportion of the patients, and thus this result would need further research. In previous studies, risk for metastatic cSCC increased with age, male sex, immunosuppression, higher deprivation quintiles, and location on the ear and lip (6). In the current study, age, other malignancy, and advanced stage were significant factors for keratinocyte cancer-specific mortality, and, age, BCC as comorbidity, higher CCI, and other malignancies were significant factors for all-cause mortality. However, for the patients with BCC as comorbidity, all-cause mortality was lower, which was not explained by younger age of the patients. Furthermore, the cause of death for patients with cSCC was almost equally divided between advanced cSCC and other-cause mortality.

The 5-year C44-specific mortality was higher in the current study for patients with advanced cSCC (22%) than the 5-year C44-specific mortality rate among patients with cSCC according to the FCR in 2017 to 2019 (6%). However, it is of note that statistics obtained from the FCR did not stratify patients by disease type (cSCC and BCC), or disease status (advanced and non-advanced). In the current study, the 5-year mortality for patients with non-advanced cSCC was 0%. OS was higher for patients with BCC compared with cSCC when assessed by Kaplan–Meier fits. However, the likelihood of mortality was increased with age, as shown in Cox multistate model. Overall, the BCC patient group was younger than the cSCC patient group. In the nationwide analysis patients with BCC were 6 years younger at diagnosis than patients with cSCC on average. Thus, age may explain part of the increased survival in BCC. The frequency of other malignant cancers was relatively high; for example, 6% and 8% of the patients with BCC and cSCC had a diagnosis of malignant neoplasm of prostate, and 4% of patients in both groups had a diagnosis of a malignant breast neoplasm. Also, age-related non-cancer co-diagnoses were common in the cohort; for example, hypertension in 40% of patients with BCC and 50% of patients with cSCC.

Non-advanced BCC and cSCC and have typically good prognosis and a low rate of metastases (6, 27). Also, in our results, both BCC and cSCC had good prognosis and could be treated successfully mainly by surgical excision. Consecutive surgeries during a relatively short time-period are typical for patients with cSCC. In this study, approximately 50% of the patients had the first surgical excision at the time of diagnosis and a subsequent surgery within 3 months, while time between each surgery after the third was shorter than 3 months. Survival of the patients with advanced cSCC that had been operated 3 times was the highest compared with those treated with radiotherapy or chemotherapy. Although the advanced cSCC patient population is heterogeneous, the result of the current study on survival of the patients reflects the need for new treatment options (28).

Generalizability and external validity of the results

Finland has equal healthcare, which is primarily funded by taxation. Thus, all permanent Finnish residents are entitled to public healthcare at a uniform level regardless of their financial situation. The findings of the current study can thus be best generalized to countries with similar healthcare systems and access to treatments and diagnostics as in Finland. In addition, as this study is conducted in a single country with a relatively unique genetic heritage, the effect of genetic background on the results cannot be ruled out. Even with these limitations, the study has significant strengths, such as reflection of the Finnish clinical practice for patients with keratinocyte cancer, and inclusion of a real-world patient population and outcomes that are measured in an unbiased

way. The Finnish social and healthcare registries cover all individuals living in Finland, and no patients were excluded from the current study based on their social status or financial capability. In addition, health record data available via data lake technology enable extraction and analysis of large data sets including RWD on disease-related clinical and molecular characteristics and number of medical procedures.

Study limitations

Limitations of this study include its retrospective design. The number of patients with advanced disease was low, and inclusion into the advanced group consisted of criteria derived both from clinical guidelines and by receiving high number of surgeries or radiotherapy/chemotherapy. Advanced disease was identified from the patient records with a set of criteria. Medical records of the patients with advanced cSCC and BCC identified by the criteria from the patient records of HDSF were manually checked by the clinician KM. Furthermore, the patients advanced cSCC, described previously by Knuutila et al. (23), were manually checked. It is possible that we were not able to detect all advanced patients with the criteria, which is especially the case for the nationwide cohort, where data were more limited than in the regional cohort. Furthermore, our surgical procedure data is lacking information regarding whether there was 1 specific lesion or several different lesions. Another limitation is that BCC subtyping was not conducted, due to lack of data. This study utilized radiotherapy, chemotherapy, and surgical excision procedures recorded for keratinocyte cancer treatment (C44 diagnosis recorded with the procedure). In the current data, radiotherapy or chemotherapy treatment was received more often for cSCC than BCC treatment (due to small patient groups numbers are not reported in detail). However, we could not separate whether cSCC patients with BCC comorbidity had received radiotherapy or chemotherapy for cSCC or BCC. Furthermore, in real-world evidence (RWE) studies the content of the information retrieved from various registries might not be the same. For some cases in this study, the keratinocyte cancer diagnosis was not found from all registries that were utilized for inclusion (HDSF, specialty care patient register, and FCR). However, we required here that the keratinocyte cancer diagnosis had to be found from at least one of the registries, and missing diagnosis from others was not an exclusion criterion.

Conclusion

This RWD analysis of Finnish registry data revealed decreased survival in patients with advanced keratinocyte cancer. The most common treatment of primary keratinocyte cancer was surgical excision, but patients with advanced stage disease generally had suboptimal outcomes with any subsequent treatment. The results suggest high-risk factors for disease progression and mortality. Further study on the advantages of identifying keratinocyte cancer patients with high-risk features for disease progression at early-stage is needed, as it may be important for future treatment strategies.

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Conflicts of interest and funding: VMK has served as a consultant for Sanofi, and SV is a former employee of Sanofi and current employee of Janssen. TR, KP and LV are currently employed by Sanofi. PR, JK, KM, ST, LUV, and ML have no conflicts of interest to declare.

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