Real-world Treatment Patterns and Outcomes with Systemic Therapies in Unresectable Locally Advanced and Metastatic Cutaneous Squamous Cell Carcinoma in Germany

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Advanced cutaneous squamous cell carcinoma is a challenge to treat. Conventional systemic treatment options include chemotherapy and epidermal growth factor receptor-inhibitors. The aim of this study was to assess clinical outcomes with systemic treatments in advanced cutaneous squamous cell carcinoma. Patients receiving systemic treatment at the Tübingen Dermato-Oncology centre between 2007 and 2017 were identified ($n = 59$). Median age was 76 years (interquartile range (IQR) 71–80 years), 83.1% of patients were male, 72.9% had metastatic cutaneous squamous cell carcinoma, and 27.1% had unresectable locally advanced cutaneous squamous cell carcinoma. During median follow-up of 52 weeks (IQR 27–97 weeks), overall response rate was 14.3%, and disease control rate was 53.6%. Median progression-free survival was 15 weeks (IQR 8–42 weeks), and median overall survival was 52 weeks (IQR 27–97 weeks). Patients receiving chemoradiation vs chemotherapy alone showed better overall survival (hazard ratio 0.41, $p = 0.014$,) and progression-free survival (hazard ratio 0.42, $p = 0.009$); no differences were observed for metastatic cutaneous squamous cell carcinoma vs locally advanced cutaneous squamous cell carcinoma patients. Although chemotherapy and/or cetuximab showed limited outcomes in advanced cutaneous squamous cell carcinoma, such therapy may still be an option when anti-PD-1 treatment is contraindicated.

Key words: advanced squamous cell carcinoma; chemotherapy; EGFR-inhibition.

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SIGNIFICANCE

This retrospective cohort study described real-world outcomes with conventional systemic treatments in advanced cutaneous squamous cell carcinoma before the approval of anti-PD-1 immunotherapies. In the 59 patients who received systemic treatments, a great variety of chemotherapeutic schemes and EGFR inhibitors was observed. These treatments showed limited effectiveness (response: 14%; median duration to progress: 15 weeks). Outcomes were better for concomitant chemoradiotherapy vs chemotherapy only. These data suggest an unmet need in this patient population and may support the use of newly approved anti-PD-1 immunotherapies. Furthermore, the study provides useful data that can serve as benchmark data to evaluate anti-PD-1 immunotherapies in the real world.

Non-melanoma skin cancer (NMSC) is the most common tumour entity in the fair-skinned world population (1). Cutaneous squamous cell carcinoma (CSCC) is the second most common form of NMSC and accounts for 20% of all epithelial skin cancers (2). The incidence of CSCC is estimated to have quadrupled in Germany over the past 30 years (1, 3).

Especially among patients aged 60 years or older the incidence of CSCC is expected to increase continuously until 2030. Treatment options for these patients are limited due to their comorbidities, which increase with age (2). The main risk factor for developing advanced CSCC (aCSCC) is tumour thickness >6 mm. Immunosuppression and localization at the ear are additional prognostic factors for metastatic CSCC (mCSCC) and desmoplasia for locally advanced CSCC (laCSCC) (4), resulting in an increased risk of local recurrence or metastasis by 20% over 5 years (5).

Before approval of anti-PD-1 agents, therapeutic options in aCSCC were limited, due to the low efficacy of systemic treatments and the reduced general health and comorbidities of elderly patients, making them unsuitable for aggressive systemic treatment (6). As there was low evidence of clinical studies in aCSCC, many approaches were based on protocols developed for malignancies of the head and neck, which has different tumour characteristics. The German S3 guideline for CSCC recommended treatment on an individual basis as no approved systemic therapy was available when the guidelines were developed in 2018 (4, 7).

Clinical outcomes with chemo- or targeted therapy were generally poor, and response rates in the real-world setting often did not reach the levels reported in clinical studies (6, 8–10). Immunotherapeutic agents (i.e. PD-

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L1 inhibitors) were recently approved for unresectable locally advanced and metastatic cSCC, and have shown a high rate of tumour response in clinical studies (11, 12). The current retrospective cohort study describes real-world outcomes with conventional systemic treatments in a population eligible for immunotherapy. These results may be used as benchmark data for evaluation of anti-PD-1 immunotherapies in the real world.

PATIENTS AND METHODS

Patient selection

Patients diagnosed with aCSCC (i.e. laCSCC or mCSCC) from January 2007 to December 2017 were identified from the Interdisciplinary Skin Cancer Board (TUK) of the Department of Dermatology and Comprehensive Cancer Center (CCC) Tuebingen, consisting of dermato-oncologists, dermato-surgeons, medical oncologists, general surgeons, oral and maxillofacial surgeons, head and neck surgeons, radiologists and radio-oncologists.

All patients of this retrospective cohort study were classified into stage III or IV according to the 8th edition of American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 2017 classification at the time of tumour board presentation. The resectability of advanced tumours or metastases and the indication of adjuvant or palliative radiation were discussed according to the current guidelines (13). An adjuvant radiation was recommended if perineural spread or lymphangiosis was seen, or in case of parotideal metastasis, or recurrence in the field of the primary tumour, or if more than 3 lymph node metastases occurred, or if lymph nodes were larger than 3 cm. When resection or radiation was not possible, systemic treatment was recommended, predominantly an inclusion in clinical studies or according to the respective comorbidities. Dependent on renal function, patients received either chemotherapy as cisplatin, carboplatin or paclitaxel, some in combination with cetuximab, or cetuximab monotherapy. A combination of cetuximab and radiation was not applied regularly because the radiation oncologists did not recommend this treatment due to skin toxicity.

Data collection

The data were collected according to a previously developed analysis plan. The inclusion criteria were as follows: diagnosis of an aCSCC in the period from 1 January 2007 to 31 December 2017 and use of systemic treatment in the same period.

Exclusion criteria were immunosuppression, concurrent cancers (except for haematological tumours not requiring systemic treatment, low-grade prostate carcinoma, other primary NMSC), solid organ or bone marrow transplant, infectious disease, such as viral hepatitis, therapy with anti-PD-1, inclusion in a clinical trial and age under 18 years. Immunosuppressed patients were excluded in order to show the outcomes of a collective similar to those analysed in clinical studies. All data were taken from the digital patient's file, containing protocols of the tumour conference, reports from University Hospital Tuebingen as well as reports from external physicians.

Electronic records were used to collect patients' data including: sex, primary tumour characteristics (e.g. primary tumour size, tumour thickness, invasion, desmoplasia, perineural infiltration), immunosuppression, tumour operability, date and age at aCSCC diagnosis, metastases, local and systemic treatments, treatment duration and response, date of last contact or death. All patient and tumour characteristics and treatment data were combined to create an analytic database.

Outcome definitions

The baseline period was defined as time from the primary tumour diagnosis date until start of systemic treatment. The systemic treatment initiation date was defined as index date. Follow-up (FU) period was defined as time from index date of systemic treatment until death, last contact date or end of the observation period (31 December 2018), whichever occurred first.

Overall survival (OS) was calculated from the index date of systemic treatment until death, last contact date or end of the observation period (31 December 2018), whichever occurred first. Patients who died after data cut-off were censored, regardless of the cause of death. Outcomes were assessed separately for mCSCC and unresectable laCSCC patients, according to line of therapy. Response to treatment was assessed by physician evaluation, or imaging as computed tomography (CT) scan, magnetic resonance imaging (MRI) or positron emission tomography-computed tomograhy (PET-CT) and RECIST 1.1 criteria. Physician-based clinical evaluation was performed for laCSCC comparing sizes from photographic reports, as well as interpretation of response for mCSCC and laCSCC from radiological imaging assessments and documented tumour board evaluations. Duration of response (DOR) was assessed for patients achieving complete (CR) or partial response (PR) from the time of first response to the date of first progression or death. Overall response rate (ORR) was defined as the proportion of patients achieving CR or PR to treatment. Disease control rate (DCR) was defined as the proportion of patients achieving CR, PR and stable disease (SD) to treatment. Patients without progression by the end of the observation period or the last contact were censored. Progression-free survival (PFS) was defined as time to first progression or death regardless of cause, whichever occurred first, Overall survival was defined as time to death, regardless of cause. Patients without progression or death before data cut-off were censored at the end of the observation period or at the last contact date, whichever applied first.

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 26.0 (IBM, Chicago, IL, USA) and Stata Version 15 (Stata Corporation, College Station, TX, USA). Numerical variables were reported with mean and standard deviation, median and interquartile ranges, respectively. Median OS and PFS, as well as survival probabilities after 6, 12, and 18 months were estimated by Kaplan–Meier analysis, including 95% CI, and compared with log-rank tests. Throughout all analyses 2-sided $p < 0.05$ was assumed to be statistically significant. All results were summarized for the overall population and by subgroups, as follows: laCSCC vs mCSCC, systemic therapy with/without concomitant radiation and chemotherapy vs cetuximab vs combination of both agents.

RESULTS

Patient characteristics

Altogether, 291 patients with aCSCC were recruited at the CCC and Department of Dermatology Tuebingen (**Fig. 1**). A total of 82 patients underwent systemic treatment in accordance with the decision of the interdisciplinary skin cancer board. Of these, 23 patients were excluded due to immunosuppression, hepatitis, concurrent cancer or concomitant systemic cancer treatment ($n = 12$), mucosal aCSCC ($n = 1$), and receipt of anti-PD-1 ($n = 10$).

The final study sample of 59 patients treated with chemotherapy or epidermal growth factor receptor

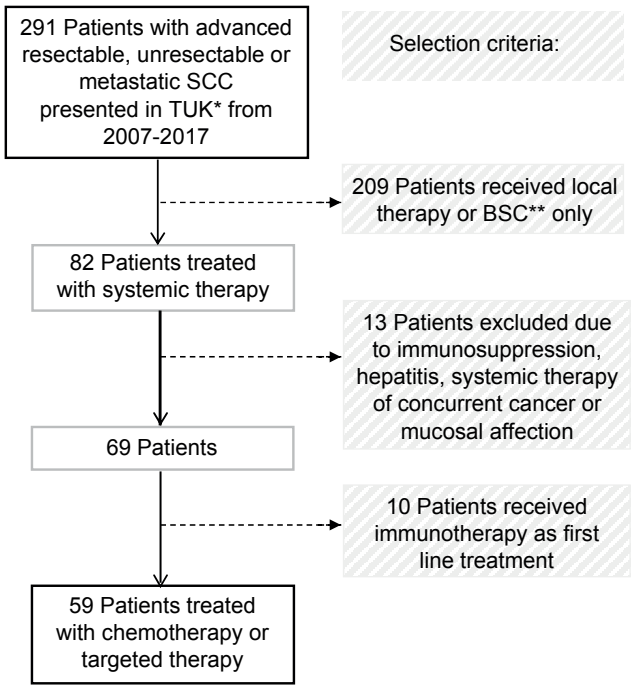

Fig. 1. Schematic presentation of the study flow. *TUK: interdisciplinary skin cancer board **BSC: best supportive care.

(EGFR) therapy consisted of 83.1% men (**Table I**). Median age at diagnosis of aCSCC was 76 years (IQR 71; 80), with 78% older than 70 years. The majority of SCC (78.0%) were located on the head or neck, and 22.0% at the trunk and extremities. Median tumour thickness at primary diagnosis was 6.1 mm (IQR 3.8; 10.0). 27.1% of the primary tumours showed desmoplasia, and 11.9% showed perineural infiltration. Before start of first-line treatment, 96.6% of all patients underwent surgery for primary or aCSCC and 50.8% received radiotherapy.

At aCSCC diagnosis, 22% were stage III and 78% were stage IV according to AJCC/UICC 2017 classification (Table I). Tumours were resectable in 13.6% ($n=8$) of laCSCC and 10.2% ($n=6$) of mCSCC patients (with locoregional metastases ($n=1$) or lymph node metastases ($n=5$). In these patients, surgery was performed with or without radiotherapy. Of 45 patients with unresectable advanced SCC, 30/45 received radiotherapy, 15/45 started with systemic treatment directly.

Systemic treatment in advanced cutaneous squamous cell carcinoma

The median time from aCSCC diagnosis to initiation of systemic treatment was 28 weeks (IQR 14; 65). Twelve patients with locally advanced SCC (laSCC) developed metastases before first-line treatment was started, 4 patients had lymph node metastases, 2 had distant metastases and 6 presented with both distant and lymph node metastases (see Table I).

At start of first-line treatment, 2 (3.4%) patients were stage III and 57 (96.6%) were stage IV; 16 (27.1%) had

Table I. Patient and clinical characteristics of the TUK-SCC 2007–2017 cohort, with systemic treatment other than immunotherapy ($n=59$)

Patient and primary tumour characteristics	
Sex, *n* (%)	
Male	49 (83.1)
Female	10 (16.9)
Age (at advanced SCC diagnosis), mean±SD	74±9.8
Median [IQR]	76 [71; 80]
≤70 years, *n* (%)	13 (22)
71–80 years, *n* (%)	33 (56)
81–90 years, *n* (%)	13 (22)
Localization, *n* (%)	
Upper limb	4 (6.8)
Lower limb	3 (5.1)
Trunk	3 (5.1)
Scalp	13 (22)
Lip	6 (10.2)
Ear	3 (5.1)
Neck	1 (1.7)
Face	23 (39.0)
Anogenital	3 (5.1)
Localization, AJCC, *n* (%)	
Head/neck	46 (78.0)
Trunk/extremities	13 (22.0)
Tumour thickness, median [IQR]	6.1 [3.8; 10.0]
≤6.00 mm, *n* (%)	19 (32.2)
>6.00 mm, *n* (%)	20 (37.3)
Unknown, *n* (%)	20 (33.9)
T stage and tumour size, *n* (%)	
T1 and <2 cm	9 (15.2)
T2 and ≥2 cm	8 (13.6)
T3 and/or ≥4 cm	19 (32.2)
T4 and/or infiltration bones/skull	23 (39.0)
AJCC stage (primary cSCC diagnosis), *n* (%)	
I/II	16 (27.1)
III	28 (47.5)
IV	15 (25.4)
Desmoplasia, *n* (%)	16 (27.1)
Perineural infiltration, *n* (%)	7 (11.9)
Sentinel lymph node biopsy, *n* (%)	3 (5.1)
Positive sentinel lymph node, *n* (%)	1 (1.7)
Advanced SCC characteristics	
AJCC stage, *n* (%)	
III	13 (22)
IV	46 (78)
Group at advanced stage diagnosis	
Locally advanced disease, *n* (%)	
Resectable	8 (13.6)
Unresectable	20 (33.9)
Metastatic disease, *n* (%)	
Resectable	6 (10.2)
Unresectable	25 (42.4)
Kind of metastases, *n* (%)	
Lymph node/locoregional	26 (44.1)
Distant metastases	5 (8.5)
Time from acSCC first-line start, weeks, median [IQR]	28 [14;65]
Treatment prior to first-line start	
Surgery	
Yes	57 (96.6)
No	2 (3.4)
Radiotherapy	
Yes	30 (50.8)
No	29 (49.2)
Characteristics at first-line start	
first-line start AJCC stage	
III	2 (3.4)
IV	57 (96.6)
Group at first-line start	
Locally advanced disease	
Resectable	–
Unresectable	16 (27.1)
Metastatic disease	
Resectable	–
Unresectable	43 (72.9)
Kind of metastases	
Lymph node/locoregionally	26 (44.1)
Distant metastases	17 (28.8)
Visceral	12 (20.3)
Soft tissue	5 (8.5)

SCC: squamous cell carcinoma; SD: standard deviation; TUK: IQR: interquartile range; AJCC: American Joint Committee on Cancer; cSCC: cutaneous squamous cell carcinoma; acSCC: advanced cutaneous squamous cell carcinoma.

unresectable laCSCC and 43 (72.9%) were mCSCC patients. Among mCSCC patients, 26 (44.1%) had lymph-node (LN) or locoregional metastases, and 17 (28.8%) had distant metastases including visceral ($n=12$) and soft-tissue metastases ($n=5$).

Distribution of systemic therapies varied greatly, with 16 different administered treatment regimens (see **Table II**). As no therapeutic regimen was approved until 2019, the type of treatment administered was discussed individually for each patient. The basis for the decision was localization, metastasis, infiltration of deep tissue, performance status, operability and patient's willingness for treatment. Overall, 23 (39%) patients received chemotherapy of various agents, 20 (33.9%) were treated with cetuximab, and 16 (27.1%) underwent therapy with a combination of both. Furthermore, 13 patients, (22.0%) were treated with a combination of systemic treatment with radiotherapy (see Table II).

Table II. Systemic first-line (1L) therapies ($n=59$) and response rates ($n=56$)

	n (%)
Systemic 1L therapies ($n=59$)	
Chemotherapy	23 (39.0)
Epidermal growth factor receptor	20 (33.9)
Chemotherapy + epidermal growth factor receptor	16 (27.1)
Without radiotherapy ($n=46$)	
Cetuximab	19 (32.2)
Bleomycin	3 (5.1)
Capecitabin	4 (6.8)
Carboplatin + gemcitabine	1 (1.7)
Cisplatin + 5-FU	1 (1.7)
Cisplatin + doxorubicin	1 (1.7)
Cisplatin + 5-FU + paclitaxel	1 (1.7)
Paclitaxel	1 (1.7)
Carbo-/cisplatin + cetuximab	9 (15.3)
Cisplatin + 5-FU + cetuximab	2 (3.4)
Paclitaxel + cetuximab	4 (6.8)
With radiotherapy ($n=13$)	
5-FU + mitomycin	2 (3.4)
Cisplatin	8 (13.6)
Cisplatin + 5-FU	1 (1.7)
Cetuximab	1 (1.7)
Carboplatin + cetuximab	1 (1.7)
Response rates ($n=56$)	
In total	
Overall response rate (complete/partial response)	8 (14.3)
Disease control rate (complete/partial response/stable disease)	30 (53.6)
PD (PD)	26 (46.4)
LA disease at 1L start, $n=14$	
Overall response rate	2 (14.3)
Disease control rate	6 (42.9)
PD	8 (57.1)
Metastatic disease at 1L start, $n=42$	
Overall response rate	6 (14.3)
Disease control rate	24 (57.1)
PD	18 (42.9)
Chemotherapy, $n=23$	
Overall response rate	4 (17.4)
Disease control rate	14 (60.9)
PD	9 (39.1)
Epidermal growth factor receptor, $n=19$	
Overall response rate	2 (10.5)
Disease control rate	8 (42.1)
PD	11 (57.9)
Chemotherapy+EGFR, $n=14$	
Overall response rate	2 (14.3)
Disease control rate	8 (57.1)
PD	6 (42.9)
Systemic treatment with radiation, $n=13$	
Overall response rate	1 (7.7)
Disease control rate	10 (76.9)
PD	3 (23.1)
Systemic treatment without radiation, $n=43$	
Overall response rate	7 (16.3)
Disease control rate	20 (46.5)
PD	23 (53.5)

*Patients without documented assessment of response ($n=3$) were excluded.

Outcome analysis

All patients had FU information for at least 3 months, 71.7% for 6 months or more. The median FU time was 52 weeks (IQR 27.0; 97.0). The median duration of treatment (DOT) accounted for 8.0 weeks (IQR 5.0; 16.0).

Response to treatment was assessed primarily using the RECIST1.1 criteria ($n=47$, 83.9%) followed by physician-based response ($n=9$, 16.1%). Three patients were excluded from response analyses due to missing information. In 8/56 (14.3%) patients, CR or PR was reached, 22/56 (39.3%) achieved stable disease.

LaCSCC and mCSCC patients showed similar response rates (see Table II). While the ORR was 14.3% in both groups, the DCR was slightly better in patients with mCSCC (57.1%) than in laCSCC (42.9%). There was no appreciable difference in ORR among patients receiving chemotherapy only, EGFR monotherapy, or combination therapy. However, DCR with chemotherapy only (60.9%) or combination therapy (57.1%), was higher compared with EGFR monotherapy (42.1%). Furthermore, patients who received radiotherapy in combination with chemotherapy vs no radiotherapy, showed better DCR (76.9% vs 46.5%, $p=0.064$).

A total of 47 deaths from any cause were detected. Median OS was 52 weeks (IQR 27.0; 97.0) (see **Fig. 2**a). The OS after 6 months was 71.7% (95% CI 59.9–83.5), 49.4% (95% CI 36.1–62.7) after 12 months and 37.8% (95% CI 24.9–50.7) after 18 months. Median PFS was 15 weeks (IQR 8.0; 42.0) (see Fig. 2b). The probability of PFS after 6 months was 40.6% (95% CI 27.9–53.3), after 12 months was 17.7% (95% CI 7.7–27.7) and 10.6% (95% CI 2.6–18.6) after 18 months.

There was no difference in OS and PFS between laCSCC and mSCCC ($p=0.402$, and $p=0.185$, respectively, Fig. 2c and d), and types of systemic treatment, ($p=0.059$, Fig. 2e and f). However, patients who received additional radiotherapy showed an improved median OS compared with those without radiation (124 weeks (IQR 37;–) vs 49 weeks (IQR 23.0; 87.0), HR 0.41, $p=0.014$, see Fig. 2g). Similar results were found for median PFS (35 weeks (IQR 16.0; 130.0 vs 14 weeks (IQR 14.0; 39.0), $p=0.009$, HR 0.42) (see Fig. 2h).

DISCUSSION

The present study analysed a patient cohort with aCSCC (i.e. laCSCC and mCSCC) receiving treatment with

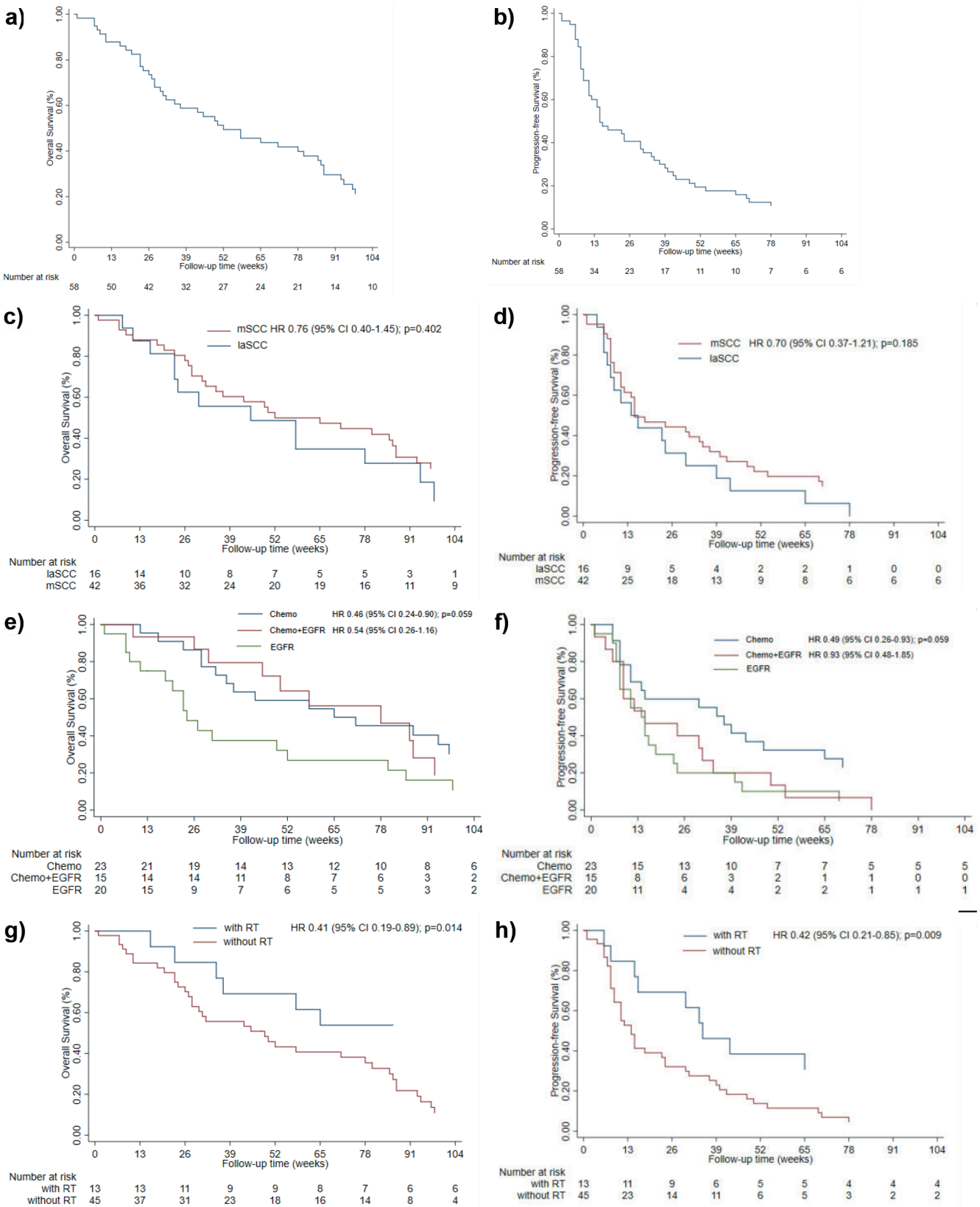

Fig. 2. Analysis of progression-free (PFS) and overall survival (OS) according to the total collective of patients with systemic treatment in advance cutaneous squamous cell carcinoma (aCSCC). (A, B) Locally advanced cutaneous SCC (laCSCC) vs metastatic cutaneous SCC (mCSCC) (C, D), according to the type of systemic treatment (chemotherapy vs epidermal growth factor receptor (EGFR) monotherapy vs a combination of both E, F) and according to systemic therapy with or without radiotherapy (G, H). *p*-values were calculated using the log-rank test.

conventional chemotherapy or targeted therapy. Median age of the study cohort was 76 years, 83% were male and the majority had primary tumour location in the head and neck (67.8%). Our patient population reflects those reported in the current literature. Due to the advanced age patients often have comorbidities, which limit therapeutic options. Until 2019 (i.e. prior to approval of anti-PD-L1 immunotherapies), no standard of care was available for aCSCC (6, 7, 14).

To date, the gold standard in cSCC is surgery, resulting in cure for most patients with early-stage disease (4, 6, 7). As the effectiveness of alternative systemic therapies was limited, especially in the era before anti-PD-1 treatment, surgical treatment was not only performed with curative intention, but also to reduce tumour burden and improve outcome in aCSCC (4, 6, 7). Therefore, patients with aCSCC in the current study mainly underwent surgical (96.6%) or radio-oncological treatment (50.8%) prior to systemic treatment. Hillen et al. (7) showed similar to our results, 92% of the patients were resected before first-line start, and 10% received additional radiotherapy. Amaral et al. (6) reported that 74.4% of patients were regarded to be operable according to the tumour board recommendation.

In the current study, a great variety of systemic therapy strategies were performed, suggesting lack of standard of care treatment approaches in aCSCC, also described in previous studies (6, 7, 14–16). Therefore, only few patients received uniform treatment schemes. Each patient's therapeutic procedure was individually discussed in a tumour board. Due to the lack of randomized clinical trial evidence with systemic treatment in CSCC, some treatment protocols in aCSCC followed those established in head and neck squamous cell carcinoma (HNSCC) guidelines. However, CSCC and oral mucosal HNSCC differ in their respective pathogenesis. While ultraviolet (UV) radiation is the main risk factor for CSCC, enoral tumours arise primarily from toxic agents or chronic infections (17, 18). Furthermore, CSCC patients are older (19–21), due to that fact they show more comorbidities and are often not suitable for aggressive systemic treatments.

Randomized, prospective studies comparing targeted treatment and chemotherapy in aCSCC patients were unfortunately not performed in the past. To date, there is still need for treatment options besides anti-PD-1, especially for patients with contraindications for immunotherapeutic agents or non-responders to anti-PD-1.

As a targeted therapy, the EGFR inhibitor cetuximab was given as a monotherapy in 19 (32.2%) patients, due to its better tolerability vs chemotherapy (8). A combination with radiotherapy was performed in only 1 patient due to high skin toxicity and the concerns by the radiation oncologists (22). In the current study population, differences in clinical outcomes with cetuximab were noted compared with previous studies in aCSCC. ORR to cetuximab accounted for 10.5% and was lower than in most other studies in aCSCC. Hillen et al. (7) detected an ORR of 20% (physician-based or RECIST) and Maubec et al. (8) found an ORR of 28% with cetuximab therapy according to RECIST criteria. Montaudie et al. (23) detected much better response rates with cetuximab than other studies (ORR 53% and DCR: 87%) based on physician assessment or RECIST criteria. In the Maubec study (8), DCR was 69%, which was not attained in our cohort (42.1%). OS and PFS in our patients treated with cetuximab monotherapy (OS: 5.5 months; PFS: 3.2 months) were lower than in the studies of Maubec et al. (8). (OS: 8.1 months; PFS: 4.1 months) and Montaudie et al. (23) (OS: 17.5; PFS: 9.7 months). Patients receiving the EGFR-inhibitor erlotinib showed similar response, but higher DCR (ORR 10% and DCR: 72%, respectively) (24). Based on this, moderate or strong expression of EGFR does not seem to increase the effectiveness of the therapy.

A great variety was also found for treatment approaches using chemotherapy. Platinum-based treatment schemes were used either as monotherapy, or in combination with other chemotherapeutics, cetuximab or radiotherapy (Table II). In the current patient population, ORR of 17.4% with chemotherapy alone was much lower compared with earlier studies in aCSCC evaluating chemotherapy as first-line treatment (ORR 58–100%) (9, 25, 26). Compared with cetuximab, chemotherapy showed to be slightly more effective in terms of response (see Table II), but its use is limited in older patients with higher comorbidities and reduced general health. In other studies, most patients with impaired general condition were not able to receive polychemotherapy (9, 26, 27). Instead, they underwent the more tolerable single chemotherapy or cetuximab treatment.

In aCSCC patients under systemic treatment other than anti-PD-1 agents, clinical outcomes are limited with short median PFS and OS (4, 8–10, 16). This population generally showed poor outcomes under systemic treatment (median PFS 15.0 and OS 52.0 weeks). The 12-month OS was similar to Cowey et al. (14) and Amaral et al. (6) (49.4% vs 51.1% vs 64.7%, respectively). No statistical differences in survival between laCSCC and mCSCC were observed. Comparing different therapeutic regimens, chemotherapy showed the best results for PFS. Furthermore, a combination of chemotherapy and radiotherapy showed better survival rates than chemotherapy alone (see Fig. 2e–g).

Radiotherapy did not lead to complete response, but more patients developed stable tumour disease, which may have led to prolonged median PFS and OS. After 6 months, PFS and OS were much better in patients who underwent radiotherapy compared with those who did not (PFS: 69.2% vs 32.1%, OS: 84.6% vs 70.2%), respectively. It is important to note that the cohort size of patients receiving combined radiotherapy was small ($n = 13$) and sample sizes differed (13 vs 46). Therefore, this result

should be assessed with caution and re-evaluated with larger and equally distributed samples.

Elderly patients with multiple comorbidities often have to endure, with great effort, long journeys and side-effects of therapy, while undergoing chemotherapy or targeted therapy. Newly approved anti-PD-1 treatment should be considered a veritable alternative to systemic therapy. Anti-PD-1 treatment with cemiplimab showed much better response rates (ORR 47–50% and DCR: 61–65%) in clinical studies performed from 2016 onwards (21). This led to an approval of the anti-PD-1 antibody cemiplimab in Germany in 2019. Latest data for laCSCC and mSCC at time of data cut-off showed that median PFS and median OS had not been reached. The ORR was 46.1% (11) for laSCC and 45.2% for mSCC, respectively, and the DCR was 67.8% The Keynote-629 study showed an ORR of 34.3% (95% CI 25.3–44.2) and a DCR of 52.4% (95% CI 42.4–62.2), but 87% had a previous systemic treatment compared with 15–58% in the cemiplimab studies. However, these anti-PD-1 therapies are not recommended in patients receiving immunosuppressive agents as organ transplant receipients. To date, there is still need for treatment options besides anti-PD-1 therapies, especially for patients with contraindications for immunotherapeutic agents or non-responders to anti-PD-1 therapies.

Limitations

Study limitations include the retrospective, single-centre design, which may limit the generalizability of study findings. Due to the various therapeutic schemes, there were treatment groups that were under-represented with very small number of patients (e.g. combination of EGFR and radiotherapy), hence it is difficult to draw conclusions on which scheme works best. No safety analysis could be performed, as information about toxicity was incomplete for patients. Most patients visited our centre in 6-week intervals and for staging procedures; hence toxicity data were not reported regularly by the oncologists. In addition, tumour-specific survival could not be determined exactly for all patients. Data on the individual cause of death was often missing, mostly because patients died outside our centre and the exact causes of death was not revealed. Furthermore, CSCC incidence rates are highest in patients ≥80 years (2), who often have comorbidities, which further complicates the exact determination of the cause of death. Therefore, only OS was calculated. Finally, the data pre-dates approval of anti-PD-1 treatment. Future such real-world studies, comparing outcomes of chemotherapies in general with anti-PD-1 immunotherapies, is needed.

Conclusion

This study demonstrates that systemic treatments with chemotherapy and/or cetuximab show efficacy, but with limited short-term outcome, in aCSCC. Although anti-PD-1 immunotherapy has become the systemic treatment of first-choice, chemotherapy and anti-EGFR-inhibitors are further treatment options for non-responders and for patients with contraindications against immunotherapy. There is still a high medical need for development of alternative treatment regimes for these patients.

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