in vivo *35*: 2283-2288 (2021)
doi:10.21873/invivo.12501

Palliative Radiotherapy for Cutaneous Squamous Cell Carcinoma of the Head-and-Neck Region

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Abstract. *Background/Aim: Cutaneous squamous cell carcinoma (cSCC) is a common type of skin cancer. Options for palliative treatment include systemic agents and radiotherapy. Selection of a radiation regimen should consider the patient's survival prognosis. This study aimed to identify prognostic factors of survival after palliative radiotherapy for cSCC of the head-and-neck. Patients and Methods: Ten factors were analyzed for survival in 12 patients including age, gender, tumor site, histological grade, primary tumor stage, lymph node involvement, distant metastases, upfront surgery, radiation dose and completion of radiotherapy. Results: On univariate analysis, improved survival was significantly associated with lower histological grade (better differentiation) (p=0.022), no distant metastases (p=0.040) and completion of radiotherapy (p=0.014). In the multivariate analysis, lower histological grade (risk ratio=6.05, p=0.100) and completion of radiotherapy (risk ratio=4.87, p=0.115) showed trends. Conclusion: Predictors of survival were identified that can help design individual treatments. Patients require optimal supportive care as completion of radiotherapy was associated with better survival.*

Non-melanoma skin cancer is the most frequently diagnosed malignant disease (1-3). The most common of these tumors are basal cell carcinomas comprising 70-80% of cases (2, 3). Cutaneous squamous cell carcinomas (cSCC) represent the second most common type of non-melanoma skin cancer and account for 20% of these malignancies (2-4). Approximately 70-80% of cSCC occur in the head-and-neck region, and the incidence of these tumors is increasing (4-6).

The vast majority of cSCC can be cured with surgery and/or radiotherapy. Radiotherapy alone is generally used for unresectable lesions or if a patient is unsuitable for surgery due to significant co-morbidities, a poor performance status or very advanced age (2-4, 7). In most cases, radiotherapy alone is administered with curative intent, and longer-course programs are used. For radiotherapy alone (definitive treatment), total doses of 45-50 Gy with doses per fraction of 2.5 to 3.0 Gy are recommended for smaller lesions (<2 cm), and total doses of 60 to 66 Gy (2.0 Gy per fraction) or 50 to 60 Gy (2.5 Gy per fraction) for larger lesions according to the European interdisciplinary guideline on invasive cSCC (7). However, frail or very elderly patients may be unable to tolerate curative treatment and receive a shorter course of radiotherapy with higher doses per fraction (hypo-fractionation). This applies particularly to patients with locally advanced disease and loco-regional or distant metastases, who have worse prognoses than patients with early-stage disease (4, 8). In some patients with locally advanced or metastatic disease, the intent of treatment is palliative with a major focus on relief of symptoms and prevention of complications such as ulceration, bleeding and infiltration of adjacent structures. Several hypo-fractionated radiotherapy programs are available for palliative radiotherapy of cSCC ranging from single large fractions of 12-20 Gy to longer-course irradiation with 50 Gy in 15 fractions over 3 weeks (2, 9-11). Radiotherapy with a higher biologically effective dose (equivalent dose in 2-Gy fractions, EQD2) will likely lead to longer disease control but can be associated with significant acute toxicity.

Moreover, the risk of late radiation-related toxicity increases with the dose per fraction. Therefore, patients with a short survival appear appropriately treated with a short, little stressful treatment regimen. Whereas patients with a longer expected survival likely benefit from a longer-course regimen with a higher EQD2 and a lower dose per fraction (*e.g.* 2.0 Gy).

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Key Words: Cutaneous squamous cell carcinoma, head-and-neck region, palliative radiotherapy, survival, prognostic factors.

Thus, when assigning optimally personalized radiation to a patient requiring palliative radiotherapy for cSCC, it is important to be able to judge the patient's remaining lifetime precisely. Therefore, the major goal of the present study is the identification of prognostic factors for survival in patients receiving palliative radiotherapy for cSCC.

Patients and Methods

The data of 12 patients who received palliative radiotherapy for cSCC of the head-and-neck region between 2009 and 2019 were retrospectively evaluated. The study received approval from the Ethics Committee of the University of Lübeck (18-130A). Eleven patients (92%) were older than 76 years, and 5 patients (42%) were even older than 86 years. In three patients (33%) distant metastases were present at the time of palliative radiotherapy including bone metastases in two patients and lung metastases in one patient. Ten patients (83%) received upfront loco-regional resection, which was microscopically complete (R0) in four patients. Systemic treatment was not given.

Nine patients completed radiotherapy as planned. In these patients, the median total dose was 45 Gy (range=20 to 55 Gy), and the median dose per fraction 3.0 Gy (range=2.5 to 5.0 Gy). In the other three patients, median total dose and dose per fraction were 39 Gy (range=6-40 Gy) and 2.0 Gy (range=2.0 to 3.0 Gy), respectively. In the entire cohort, the equivalent doses in 2 Gy-fractions (EQD2, alpha/beta ratio=10 Gy for tumor control) ranged between 6.0 and 57.3 Gy (median EQD2=42.25 Gy).

A total of 10 potential prognostic factors were analyzed with respect to survival, which was calculated from administration of the first radiation fraction. Investigated factors included age (<80 *vs.* ≥80 years, median age=79.5 years), gender (female *vs.* male), main tumor site (cheek *vs.* ear *vs.* forehead or temple), histological grade (G1-2 *vs.* G3), primary tumor stage (T1-3 *vs.* T4), lymph node involvement (no *vs.* yes), distant metastases (no *vs.* other histology), upfront surgery (no *vs.* yes), EQD2 (≤42.25.0 *vs.* >42.25 Gy) and completion of radiotherapy as planned (no *vs.* yes). The distributions of these factors are shown in Table I.

For univariate analyses, the Kaplan-Meier method and the log-rank test were used. Those factors that were significant on univariate analysis ($p<0.05$) or showed a trend ($p<0.10$) were additionally included in a Cox regression model (multivariate analysis). In the multivariate analysis, p-values <0.05 were considered significant and p-values <0.12 indicating a trend.

Table I. *Potential prognostic factors that were analyzed with respect to survival.*

Factor	N patients	Proportion (%)
Age		
<80 Years	6	50
≥80 Years	6	50
Gender		
Female	6	50
Male	6	50
Tumor site		
Cheek	5	42
Ear	3	25
Forehead/Temple	4	33
Histological grade		
G1-2	10	83
G3	2	17
Primary tumor stage		
T1-3	7	58
T4	5	42
Lymph node involvement		
No	6	50
Yes	6	50
Distant metastases		
No	9	75
Yes	3	25
Upfront resection		
No	2	17
Yes	10	83
RT dose (EQD2)		
≤42.25 Gy	7	58
>42.25 Gy	5	42
Completion of RT		
No	3	25
Yes	9	75

RT: Radiotherapy, EQD2: equivalent dose in 2 Gy-fractions.

Results

In the entire cohort, the median follow-up period was 3.5 months (range=1 to 21 months). In the four patients who were alive at the last contact, median follow-up period was 5.5 months. On univariate analysis, improved survival was significantly associated with a lower histological grade (G1-2) ($p=0.022$), absence of distant metastases ($p=0.040$), and completion of radiotherapy as planned (Figure 1, $p=0.014$). The results of the univariate analyses are summarized in Table II. Of the six patients with lymph node involevement, two patients had extracapsular spread of the lymph node metastasis. The 3-months survival rates were 25% without and 50% with extracapsular spread, respectively ($p=0.78$, log-rank test).

In the multivariate analysis, lower histological grade (risk ratio=6.05, 95% CI=0.68 to 58.84, $p=0.100$) and completion of radiotherapy (risk ratio=4.87, 95% CI=0.65 to 42.55, $p=0.115$) showed trends; absence of distant metastases was not significant (risk ratio=1.36, 95% CI=0.17 to 9.55, $p=0.75$).

Discussion

Non-melanoma skin cancer represents the most common malignancy worldwide (1-3). Approximately 20% of these tumors are cSCC. Most lesions are detected at an early stage and successfully treated with resection plus/minus adjuvant radiotherapy or radiotherapy alone. However, patients with locally advanced or metastatic disease have worse prognoses. Considerable research has been performed in recent years to better understand the pathophysiology of cSCC and improve treatment (12-14).

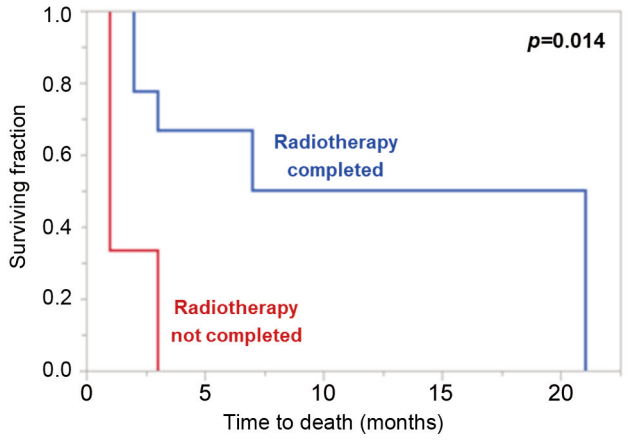

Figure 1. *Kaplan-Meier curves for survival comparing patients in whom radiotherapy was completed as planned ti those patienst in whom radiotherapy was not completed. The p-value was calculated with the log-rank test.*

Table II. *Univariate analyses of survival (p-values from the log-rank test).*

Characteristic	At 3 Months	At 6 Months	At 12 Months	*p*-Value
Age				
<80 Years	33	n.a.	n.a.	0.20
≥80 Years	67	67	50	
Gender				
Female	67	67	50	0.27
Male	33	n.a.	n.a.	
Tumor site				
Cheek	60	60	n.a.	0.92
Ear	33	n.a.	n.a.	
Forehead/Temple	50	50	50	
Histological grade				
G1-2	60	60	45	**0.022**
G3	0	0	0	
Primary tumor stage				
T1-3	57	57	38	0.76
T4	40	40	40	
Lymph node involvement				
No	67	67	50	0.39
Yes	33	n.a.	n.a.	
Distant metastases				
No	67	67	50	**0.040**
Yes	0	0	0	
Upfront resection				
No	100	100	100	0.15
Yes	40	40	27	
RT dose (EQD2)				
≤42.25 Gy	43	43	43	0.95
>42.25 Gy	60	60	30	
Completion of RT				
No	0	0	0	**0.014**
Yes	67	67	50	
Entire cohort	50	50	38	

RT: Radiotherapy, EQD2: Equivalent dose in 2 Gy-fractions, n.a.: Not available. Significant *p*-values are given in bold.

Unresectable lesions are generally treated with curative radiotherapy alone, which includes high total and biologically effective doses and generally takes several weeks. However, some patients, particularly if they are very old or frail, cannot tolerate longer-course radiation programs with high doses and receive shorter-course hypo-fractionated irradiation instead. Moreover, hypo-fractionated regimens are also used to treat patients with locally advanced or metastatic disease. For a considerable number of these patients, the intent is palliative. For palliative radiotherapy of cSCC, several dose-fractionation regimens have been used ranging from single-fraction treatment to multi-fraction regimens lasting three weeks or longer.

When aiming to tailor the radiation treatment to a patient's individual situation, several aspects need to be considered such as the patient's treatment preferences, social situation, travel distance to radiotherapy, age, co-morbidity, and performance status. Another important aspect is the patient's remaining lifespan. If this is very short, the radiation program should be less stressful and time consuming. Considering the limited prognosis, the patients should spend as little as possible of their short remaining lifetime receiving treatment for their cSCC. On the other hand, if the survival prognosis is comparably favorable, longer-term disease control and prevention of late radiation toxicities become more important, and the patients could benefit from a course of radiotherapy with higher total and biologically effective doses but lower dose per fraction. Thus, it is important to accurately estimate an individual patient's survival prognosis prior to assigning a personalized treatment regimen. To facilitate the decision-making process, prognostic factors would be helpful. The present study aimed to identify such factors in a cohort of patients with cSCC treated with definitive or adjuvant palliative radiotherapy.

Until now, very few studies have been performed particularly in patients receiving palliative radiotherapy for locally advanced and metastatic cSCC. In 2003, Veness and Richards stated in their review article that large uncurable lesions often painful and complicated by bleeding and superinfection can be treated with single-fraction radiotherapy using high doses of 12-20 Gy (11). These large fractions were well tolerated and associated with little acute toxicity. For elderly patients with moderate co-morbidity and a good performance status, dose-fractionation regimens of 35 Gy in 5-7 fractions and 40 Gy in 10 fractions were considered appropriate (11). In 2010, Barnes *et al*. presented a retrospective study of 28 patients who received a total of 31 courses of palliative irradiation with 8 Gy for basal cell

carcinoma (five courses) or cSCC (26 courses) (9). After a median follow-up of 17 weeks, the overall response rate was 58.1%, and relief of cSCC-related symptoms was achieved in 61.3% of the cases. Severe late toxicity was not observed. In addition to palliative treatment, short-course hypofractionated radiotherapy was found effective in elderly patients. In 2015, Ferro *et al*. reported a phase II study of 31 patients with early-stage non-melanoma skin cancer, of whom 14 patients were 80 years or older (10). Patients were treated with 30 Gy in 5 fractions over six consecutive days. Thirty patients experienced a complete response after a median follow-up period of 30 months, and the 2-year actuarial local control rate was 93.2%. Late toxicities did not exceed grade 1, and cosmetic outcomes were mainly good or excellent (10). In a systematic review of Gunaratne and Veness, total doses of 30-40 Gy with 1-3 fractions of 5-7 Gy per week resulted in excellent local control and tolerable toxicity (15). In 2018, Fogarty *et al*. presented a split-course regimen, which consisted of 5×5 Gy over one week followed by an 8-week break and another course of 5×5 Gy if complete response was not yet achieved (16). Fourteen patients with a total of 22 lesions (15 cSCC, 5 basal cell carcinomas, 2 melanomas) were treated with this regimen. Overall response at 2 months after completion of the second course of 5×5 Gy was 100%, and toxicity was acceptable.

Considering the range of available regimens of hypofractionated radiotherapy for elderly patients with cSCC or for palliative treatment of advanced cSCC, one challenge for the treating physicians is the selection of the optimal regimen for an individual patient. As mentioned above, personalized treatment concepts should consider the patient's survival prognosis, which can be estimated with the help of pre-treatment prognostic factors. In the present study, lower histological grade (better differentiation of the tumor) and absence of distant metastasis were significantly associated with improved survival on univariate analyses. Moreover, a trend was observed for the histological grade in the multivariate analysis. The predictive value of the differentiation of the tumor for treatment outcomes and the patients' prognoses was previously described in several studies and review articles (5, 6, 8, 17-19). These previous results demonstrate consistency of the findings of the present study. The prognostic role of distant metastases was not explicitly described before, most likely because this is rare in patients with cSCC. However, advanced primary and nodal stage were previously reported to have a negative impact on the patients' prognoses (4, 6, 18, 20-23). Another factor associated with worse prognoses is extracapsular spread of lymph node metastasis, which was reported in several studies and review articles (6, 20, 22-25). In the present study, extracapsular spread showed no significant association with survival. However, this was most likely due to the small numbers of patients with lymph node involvement (n=6) and patients with extracapsular spread of the lymph node metastasis (n=2). Considering the findings of the present study and the data from the literature, patients with risk factors such as high-grade (G3) cSCC, presence of distant metastasis and extracapsular spread of lymph node metastasis have comparably poor prognoses and appear candidates for a short course of radiotherapy. On the contrary, patients with low or intermediate grade (G1-2) tumors without distant metastasis and without extracapsular spread of lymph node metastasis have more favorable prognoses and appear better treated with longer-course radiation programs including higher total and biologically effective doses and lower doses per fraction. However, when considering to follow these recommendations, the small sample size and the retrospective design of the present study, similar to most reported studies, are significant limitations. Moreover, histological grade and distant metastases were not significant in the multivariate analysis and, therefore, not independent predictors of survival. Considering the limitations of this study, there is a risk of misjudgment of a patient's remaining lifespan. This may lead to over- or undertreatment with respect to the patient's well-being or survival. Larger studies, for example pooled analyses, are required to predict a patient's survival prognosis more properly and to provide optimal personalized treatment.

In addition to the two pre-treatment factors, lower histological grade and absence of distant metastasis, completion of the radiotherapy as planned was significantly associated with better survival on univariate analysis and showed a trend in the multivariate analysis. This importance of the completion of the radiotherapy course for survival aspect was previously reported for palliative irradiation of non-cutaneous head-and-neck cancer (26). Thus, close monitoring and optimal supportive care during radiotherapy is important for patients receiving palliative irradiation for advanced cSCC.

In summary, prognostic factors of survival were identified that can help physicians when choosing individual treatment regimens for patients with advanced cSCC who require palliation. For these patients, optimal care during the course of radiotherapy is crucial, since completion of radiotherapy as planned was associated with better survival.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. The data were collected by C.S. and analyzed by S.E.S. and D.R. The article was written and approved by all Authors.

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Received April 9, 2021
Revised April 20, 2021
Accepted April 21, 2021