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# Palliative Local Radiotherapy for Advanced Squamous Cell Carcinoma of the Head-and-Neck: Prognostic Factors of Survival

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**Abstract.** *Background/Aim: A considerable number of patients with advanced head-and-neck cancer (SCCHN) receive palliative radiotherapy. This study aimed to identify prognostic factors for survival to facilitate personalized treatment for these patients. Patients and Methods: Ninety-two patients receiving palliative radiotherapy for SCCHN were retrospectively analyzed. Fourteen characteristics were evaluated for survival including age, gender, performance score, pre-radiotherapy hemoglobin, tumor site and stage, histologic grade, p16-status, equivalent dose in 2 Gy-fractions (EQD2), completion of radiotherapy, upfront surgery and systemic therapy. Results: On univariate analysis, improved survival was significantly associated with pre-radiotherapy hemoglobin ≥12 g/dl (p=0.003), EQD2 >42.3 Gy (p=0.003) and completion of radiotherapy (p<0.001). In the multivariate analysis, hemoglobin levels remained significant (p=0.024). Trends were found for EQD2 (p=0.057) and completion of radiotherapy (p=0.093). Conclusion: Prognostic factors for survival were identified that can facilitate treatment personalization. The fact that higher EQD2 and completion of radiotherapy were associated with improved survival demonstrates the importance of close monitoring and care of these patients during radiotherapy.*

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Squamous cell carcinoma of the head and neck (SCCHN) represents one of the most common cancer types worldwide with an incidence of more than 500,000 new cases per year (1-3). Standard curative treatment for advanced non-metastatic disease consists of surgical resection followed by radiotherapy or radio-chemotherapy. If a resection is not safely possible, the patients are generally treated with curative radio-chemotherapy alone (3-5). Since curative treatment for SCCHN is generally associated with significant toxicity, a considerable number of patients cannot tolerate such aggressive treatment and receives palliative radiotherapy instead (1-7). When distant metastases are present at the time of first diagnosis, local treatment is palliative. Most patients assigned to palliative local radiotherapy require personalized treatment accounting for their remaining lifetime. Many different radiation programs are available for palliative local radiotherapy of SCCHN with total doses ranging from 20 to 60 Gy and overall treatment times ranging from 1 to 6 weeks (1, 2). Additionally, ultra-short programs such as "quad shot" (2×3.5 Gy per day over 2 days, total dose=14 Gy) are employed (8). Similar to other palliative cases in radiation oncology such as brain or bone metastases, patients with a poor estimated survival should ideally receive a radiation program which is short and not cumbersome (9, 10). On the contrary, in patients with better survival prognoses, avoidance of late toxicity and achievement of longer-term local disease control become more important and longer-course radiotherapy programs with lower doses per fraction and higher total doses appear preferable. This study aimed to identify prognostic factors for survival in patients with SCCHN receiving palliative local radiotherapy to facilitate the process of treatment personalization.

## Patients and Methods

Ninety-two patients who received palliative local radiotherapy for advanced SCCHN between 2000 and 2020 with Eastern Cooperative Oncology Group performance scores (ECOG-PS) of 0-3 were included in this retrospective study (11), which was approved by the Ethics Committee of the University of Lübeck (no. 18-130A). Staging was performed in accordance with the 7th edition of the American Joint Committee on Cancer (AJCC) manual, since the human papilloma virus (HPV) status, which is mandatory for oropharynx cancer for classification according to the 8th edition, was not available in 14% of the patients (12-16).

The patients were treated with palliative radiotherapy with planned total doses ranging between 20 and 60 Gy and doses per fraction between 2.0 and 4.0 Gy. Six of the patients in whom radiotherapy was not completed as planned received a total dose of less than 20 Gy. Using both total dose and dose per fraction, the equivalent dose in 2 Gy-fractions (EQD2) was calculated for each patient using an alpha/beta ratio of 10 Gy for tumor control. The median EQD2 delivered was 42.3 Gy (range=2.6-62.5 Gy).

A total of 14 patient and tumor characteristics (Table I) were evaluated for potential associations with survival, which was calculated from the first day of radiotherapy. These characteristics included age (≤68 *vs.* ≥69 years, median age=68 years), gender, ECOG-PS (0-2 *vs.* 3), hemoglobin level prior to radiotherapy (<12 *vs.* ≥12 g/dl), main tumor site (oropharynx *vs.* hypopharynx *vs.* larynx *vs.* oral cavity/floor of mouth), primary tumor stage (T2-3 *vs.* T4), nodal stage (N0-N2b *vs.* N2c-N3), distant metastasis (no=M0 *vs.* yes=M1), histologic grade (G1-2 *vs.* G3), p16-status as surrogate marker for the HPV-status (14) (negative *vs.* positive), EQD2 (≤42.3 *vs.* >42.3 Gy, median=42.3 Gy), completion of radiotherapy as planned (no *vs.* yes), upfront surgery (no *vs.* yes), and additional systemic therapy (no *vs.* incomplete *vs.* completed as planned). Twenty-eight patients received systemic treatment, which included induction chemotherapy with docetaxel, carboplatin and 5-fluorouracil (5-FU) (n=2), paclitaxel, cisplatin and 5-FU (n=2) or docetaxel, cisplatin and 5-FU (n=1). One patient received induction chemotherapy with paclitaxel and cisplatin followed by concurrent paclitaxel. Concurrent systemic therapies in the other 22 patients included paclitaxel with 20-25 mg/m$^2$/twice per week (n=9), cisplatin with 20mg/m$^2$/d1-5 or 25 mg/m$^2$/d1-4 every 4 weeks (n=6), cetuximab (loading dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly, n=3), carboplatin (n=2), paclitaxel followed by cetuximab (n=1) and cisplatin/5-FU (n=1).

Univariate analyses of survival were performed using the Kaplan-Meier method and the log-rank test. *p*-Values <0.12 were considered indicating a trend. Characteristics achieving significance ($p<0.05$) were additionally included in a multivariate analysis performed with the Cox proportional hazards model.

Table I. *Distribution of patient and tumor characteristics.*

| Characteristic | N patients | Proportion (%) |
|---|---|---|
| Age | | |
| ≤68 Years | 48 | 52 |
| ≥69 Years | 44 | 48 |
| Gender | | |
| Female | 20 | 22 |
| Male | 72 | 78 |
| ECOG-PS | | |
| 0-2 | 70 | 76 |
| 3 | 22 | 24 |
| Pre-RT hemoglobin level | | |
| <12 g/dl | 40 | 43 |
| ≥12 g/dl | 31 | 34 |
| Unknown | 21 | 23 |
| Main tumor site | | |
| Oropharynx | 47 | 51 |
| Hypopharynx | 22 | 24 |
| Larynx | 11 | 12 |
| Oral Cavity/FoM | 12 | 13 |
| T-stage | | |
| T2-3 | 32 | 35 |
| T4 | 60 | 65 |
| N-stage | | |
| N0-2b | 41 | 45 |
| N2c-3 | 51 | 55 |
| M-stage | | |
| M0 | 62 | 67 |
| M1 | 28 | 30 |
| Unknown | 2 | 2 |
| Histologic grade | | |
| G1-2 | 50 | 54 |
| G3 | 38 | 41 |
| Unknown | 4 | 4 |
| p16-status | | |
| Negative | 66 | 72 |
| Positive | 13 | 14 |
| Unknown | 13 | 14 |
| RT dose (EQD2) | | |
| ≤42.3 Gy | 50 | 54 |
| >42.3 Gy | 42 | 46 |
| RT completed | | |
| No | 34 | 37 |
| Yes | 58 | 63 |
| Upfront surgery | | |
| No | 75 | 82 |
| Yes | 17 | 18 |
| Systemic therapy | | |
| No | 64 | 70 |
| Incomplete | 16 | 17 |
| Complete | 12 | 13 |

ECOG-PS: Eastern Cooperative Oncology Group performance score, RT: radiotherapy, FoM: floor of mouth, EQD2: equivalent dose in 2 Gy-fractions.

## Results

The median follow-up was 4 months (range=0-36 months) in the entire cohort and 8 months (2-36 months) in the patients who were alive at the last contact. Median survival in the entire cohort was 4 months. On univariate analysis, improved survival was significantly associated with hemoglobin levels prior to radiotherapy ≥12 g/dl (Figure 1, $p=0.003$), an EQD2 >42.3 Gy (Figure 2, $p=0.003$) and completion of radiotherapy as planned (Figure 3, $p<0.001$). In addition, trends were found for an ECOG-PS of 0-2 ($p=0.11$) and tumor site other than hypopharynx ($p=0.11$). The results of the complete univariate analyses are summarized in Table II.

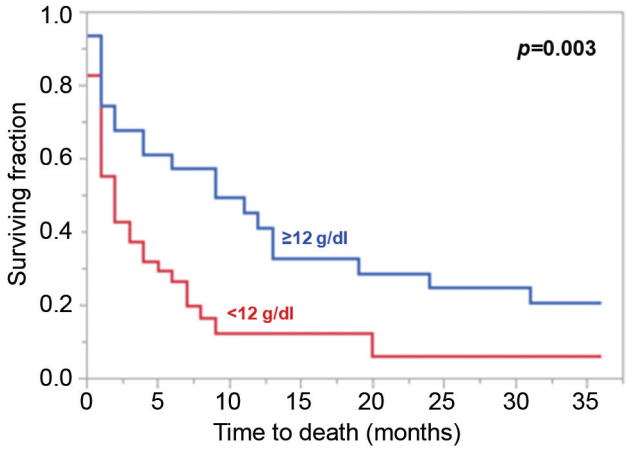


Figure 1. *Kaplan-Meier curves for survival comparing pre-radiotherapy hemoglobin levels of ≥12 g/dl to levels of <12 g/dl.*

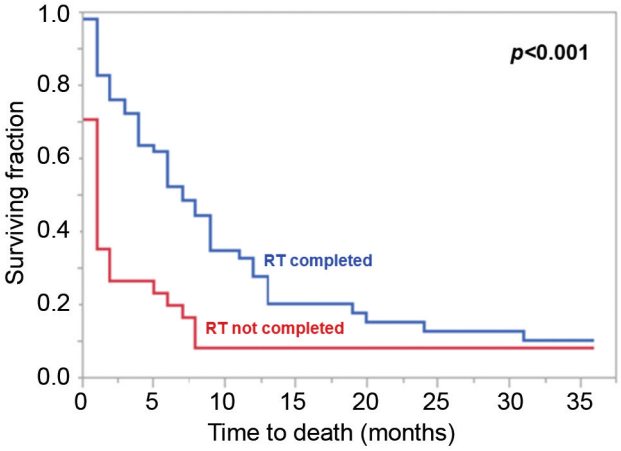


Figure 3. *Kaplan-Meier curves for survival comparing completion of radiotherapy (RT) as planned to non-completion of RT.*

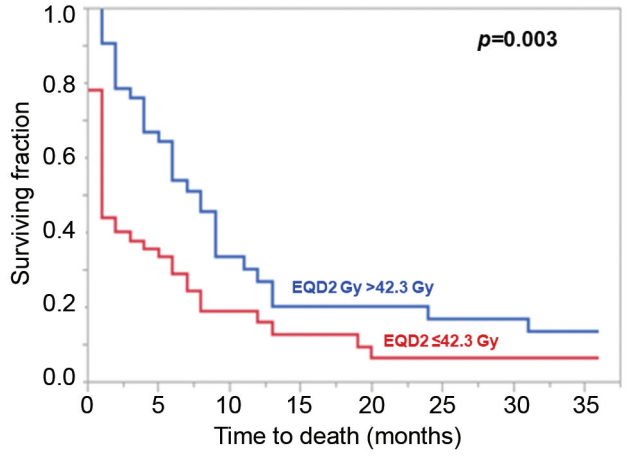


Figure 2. *Kaplan-Meier curves for survival comparing equivalent doses in 2 Gy-fractions (EQD2) of >42.3 Gy to doses ≤42.3 Gy.*

In the subsequent multivariate analysis, pre-radiotherapy hemoglobin levels remained significant [hazard ratio (HR)=1.92, 95% confidence interval (CI)=1.09-3.47, $p$=0.024]. Trends were found for EQD2 (HR=1.70, 95% CI=0.98-2.98, $p$=0.057) and completion of radiotherapy (HR=1.65, 95% CI=0.92-2.91, $p$=0.093).

## Discussion

A considerable number of patients with advanced SCCHN are not candidates for an intensive multi-modality treatment and receive palliative radiotherapy alone. The survival prognoses of these patients vary considerably. In the review articles of Iqbal *et al*. and of Grewal *et al*., median survival times ranged between 3 and 17 months (2, 3). Depending on the patients' remaining lifespan, different radiation programs are considered preferable. For patients with very limited prognoses, the treatment regimen should be short and associated with least possible stress for the patients. Patients with better survival prognoses may benefit from longer-course programs with lower doses per fraction and higher total doses in terms of less late toxicity and improved disease control. Thus, it is important to estimate a patient's expected survival duration as precisely as possible prior to assigning a personalized treatment. The knowledge of prognostic factors facilitates estimation of an individual patient's prognosis.

This study was performed to identify predictors of survival in a cohort of patients treated with palliative radiotherapy for advanced SCCHN. A better survival prognosis was significantly associated with pre-radiotherapy hemoglobin levels ≥12 g/dl, an EQD2 >42.3 Gy, and completion of the radiotherapy course as planned. In addition, trends were found for better a performance score and favorable tumor sites. The importance of pre-radiotherapy hemoglobin was already reported in studies of patients with SCCHN receiving curative treatment. In a retrospective study of 148 patients with SCCHN, pre-radiotherapy hemoglobin levels ≥12 g/dl were significantly associated with treatment outcomes on univariate analyses and with metastases-free survival in the multivariate analysis ($p$<0.001) (17). In another retrospective study of 153 patients receiving radio chemotherapy for stage IV SCCHN, improved loco-regional control (risk ratio=4.12, $p$<0.001) and survival (risk ratio=1.88, $p$=0.048) were significantly associated with pre-radiotherapy hemoglobin levels ≥12 g/dl in the multivariate analyses (6). Similar results were found in two additional retrospective studies of 275 and

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

| Characteristic | At 6 months | At 12 months | *p*-Value |
|---|---|---|---|
| Age | | | |
| ≤68 Years | 41 | 24 | 0.72 |
| ≥69 Years | 39 | 16 | |
| Gender | | | |
| Female | 42 | 17 | 0.83 |
| Male | 40 | 21 | |
| ECOG-PS | | | |
| 0-2 | 43 | 24 | 0.11 |
| 3 | 32 | 11 | |
| Pre-RT hemoglobin level | | | |
| <12 g/dl | 26 | 12 | **0.003** |
| ≥12 g/dl | 57 | 41 | |
| Main tumor site | | | |
| Oropharynx | 48 | 25 | 0.11 |
| Hypopharynx | 23 | 7 | |
| Larynx | 44 | 22 | |
| Oral Cavity/FoM | 42 | 28 | |
| T-stage | | | |
| T2-3 | 46 | 27 | 0.58 |
| T4 | 38 | 18 | |
| N-stage | | | |
| N0-2b | 41 | 18 | 0.65 |
| N2c-3 | 40 | 23 | |
| M-stage | | | |
| M0 | 46 | 25 | 0.20 |
| M1 | 29 | 10 | |
| Histologic grade | | | |
| G1-2 | 43 | 18 | 0.69 |
| G3 | 38 | 26 | |
| p16-status | | | |
| Negative | 37 | 20 | 0.24 |
| Positive | 68 | 23 | |
| RT dose (EQD2) | | | |
| ≤42.3 Gy | 29 | 16 | **0.003** |
| >42.3 Gy | 54 | 27 | |
| RT completed | | | |
| No | 20 | 8 | **<0.001** |
| Yes | 52 | 28 | |
| Upfront surgery | | | |
| No | 41 | 21 | 0.76 |
| Yes | 39 | 24 | |
| Systemic therapy | | | |
| No | 39 | 20 | 0.65 |
| Incomplete | 38 | 13 | |
| Complete | 50 | 40 | |

ECOG-PS: Eastern Cooperative Oncology Group performance score, RT: radiotherapy, FoM: floor of mouth, EQD2: equivalent dose in 2 Gy-fractions. Significant *p*-values are given in bold.

225 patients, respectively, irradiated with curative intention for locally advanced SCCHN (18, 19). One possible explanation for these findings is that a lower hemoglobin level may be a surrogate marker for more advanced disease. A second reason could be the fact that reduced oxygen-carrier capacity in case of lower hemoglobin levels has a negative impact on tumor oxygenation. Oxygen is important for the efficacy of radiation therapy that widely depends on the induction of cytotoxic oxygen free radicals that go on to fragment tumor DNA (20, 21).

The impact of the radiation dose on the prognosis of patients receiving palliative radiotherapy for advanced SCCHN was also previously observed. Stevens *et al.* compared six dose-fractionation regimens in a retrospective cohort of 148 patients with head-and-neck cancer including SCCHN, adenoid-cystic carcinoma and undifferentiated carcinoma of the nasopharynx (22). The longest median survival was achieved with 70 Gy in 35 fractions (13 months) followed by 60 Gy in 25 or 30 fractions (8.9 and 8.5 months, respectively), 30 Gy in 10 fractions (5.9 months), 50 Gy in 20 fractions (5.7 months) and 24 Gy in 3 fractions (3.3 months). In another retrospective study of 110 patients with unresectable SCCHN, radiotherapy was administered with 2.5 Gy-fractions (23). Total doses >40 Gy were associated with significantly ($p$=0.012) better progression-free survival than doses of 40 Gy (EQD2=41.7 Gy). In a recent retrospective study of 106 patients with incurable head-and-neck cancer, median survival was significantly longer in patients receiving 36 Gy in 6 bi-weekly fractions (EQD2=48 Gy) than in patients receiving ≤30 Gy/EQD2≤40 Gy (median survival 26.4 *vs*. 9.5 months, $p$=0.01) (24). Moreover, in a prospective trial that was prematurely closed due to slow accrual after enrollment of 34 patients, 50 Gy in 16 fractions/4 fractions per week (EQD2=54.7 Gy) was associated with longer median survival than 36 Gy in 6 bi-weekly fractions (25). In contrast, a randomized trial of 90 patients did not find a significant difference between the three investigated radiation regimens (26). Patients received either 14.8 Gy in 4 fractions ("quad shot"; EQD2=21.5 Gy if there was no recovery of tumor cells between the two daily fractions), 50 Gy in 16 fractions (EQD2=54.7 Gy) or 20 Gy in 5 fractions (EQD2=23.3 Gy). Median survival times were 11.5, 10.5 and 11.0 months, respectively, and 1-year survival rates 40%, 37% and 33%, respectively. The importance of completion of the planned radiotherapy course for the survival prognosis has also been reported (23, 24, 27). Similar to the current study, completion of radiotherapy was associated with the administered radiation dose, since not completing the treatment results in a lower total dose.

In the present study, better ECOG-PS showed a trend toward improved survival. The data available so far regarding the impact of the performance status on survival of head-and-neck cancer patients receiving palliative radiotherapy are conflicting. In the retrospective study of Laursen *et al.* (n=77), an ECOG-PS of 0-2 (compared to 3-4) was associated with a significantly longer median survival (5.9 vs.1.5 months, $p$=0.007) (28). In addition, Lok *et al.* (n=75) found in their retrospective study that a Karnofsky performance score of ≥70

was an independent predictor of improved survival ($p$=0.001) (29). In contrast, ECOG-PS (0-1 *vs*. 2-3) showed no association with survival ($p$=0.85) in the retrospective study of Garcia-Anaya *et al*. (24). An association between favorable tumor site and improved survival was not reported in studies focusing on palliative radiotherapy of SCCHN but in a study investigating curative treatment for locally advanced tumors (30). Moreover, other studies of patients receiving curative treatment for SCCHN found associations between favorable tumor site and loco-regional control or metastases-free survival (31-33).

Thus, considering the results of the current study and of previous studies, patients with risk factors such as pre-radiotherapy hemoglobin levels of less than 12 g/dl, a poor performance status (ECOG-PS of ≥3) and cancer of the hypopharynx have comparably poor survival prognoses and appear candidates for short-course radiotherapy with higher doses per fraction or even a "quad shot" regimen. Compared to these patients, those patients with pre-radiotherapy hemoglobin levels of ≥12 g/dl, a more favorable performance status (ECOG-PS of 0-2) and cancer mainly located in the oropharynx, larynx or oral cavity/floor of mouth have better survival prognoses can be considered candidates for longer-course radiation with higher total doses and lower doses per fraction. However, the vast majority of the studies performed in patients receiving palliative irradiation for advanced SCCHN including the present study, were retrospective in nature. This aspect including the risk of hidden selection biases needs to be considered when interpreting the results of the available studies. Moreover, existing prospective studies were of limited size resulting in low statistical power.

In conclusion, prognostic factors for survival were identified that can facilitate treatment personalization. Patients with pre-radiotherapy anemia, a poor performance status and hypopharynx cancer appear to have comparably poor survival prognoses and may benefit from short-course radiotherapy, *e.g*. a "quad shot" regimen. Patients with normal pre-radiotherapy hemoglobin levels, a better performance status, and cancer at a favorable site may be candidates for longer-course radiotherapy with a higher EQD2, and lower doses per fraction. Moreover, the fact that a higher EQD2 and completion of radiotherapy were associated with improved survival demonstrates the importance of close monitoring and care of these patients during their treatment so they can complete radiotherapy. Larger prospective trials are required to better define the optimal treatment for patients with advanced SCCHN who are not candidates for curative treatment.

## Conflicts of Interest

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

## Authors' Contributions

The study was designed by all Authors. Data were collected by C.S. and J. R.-I. and analyzed by S.E.S. and D.R. The draft of the article was prepared by D.R. and S.E.S. and the final version approved by all Authors.

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