

Karnofsky Performance Score – An Independent Prognostic Factor of Survival After Palliative Irradiation for Sino-nasal Cancer

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Abstract. *Background/Aim:* Sino-nasal cancer is rare and often diagnosed at advanced stages. Some patients cannot receive curative treatment and are treated with palliative irradiation. We aimed to identify prognostic factors for survival to facilitate treatment personalization for this group. *Patients and Methods:* Twelve patients treated with palliative radiotherapy for locally advanced sino-nasal cancer were retrospectively analyzed for survival. Ten characteristics were evaluated including age, gender, Karnofsky performance score (KPS), pre-radiotherapy hemoglobin, tumor site, lymph node involvement, histology, equivalent dose in 2 Gy-fractions, completion of radiotherapy and concurrent chemotherapy. *Results:* On univariate analysis, KPS ≥ 70 ($p < 0.001$) and completion of radiotherapy ($p < 0.001$) were significantly associated with better survival. Chemotherapy showed a trend ($p = 0.097$). In the multivariate analysis, KPS ≥ 70 was significant ($p = 0.025$), and completion of radiotherapy showed a trend ($p = 0.080$). *Conclusion:* KPS is an independent predictor of survival for palliative irradiation of sino-nasal cancer. Patients require close monitoring and care for side effects, since completion of radiotherapy is important for survival.

Cancers of the nasal cavity and the paranasal sinuses (sino-nasal cancers) are very rare and account for only 3-5% of head-and-neck cancers and less than 0.5% of all types of cancer (1, 2). The most common site involved is the maxillary sinus (60-70%) followed by the nasal cavity (20-30%) and the ethmoid sinus (10-15%) (2). Tumors in the

sphenoid and frontal sinuses account for only 1-2%. The most common type of histology is squamous cell carcinoma (SCC), which represents more than 80% of sino-nasal cancers (2). Sino-nasal cancers can be asymptomatic for a considerable time due to the airspace and the cavities in the corresponding regions (2).

The 5-year survival rates of patients with SCC of the paranasal sinuses were reported to be approximately 50%, 30% and 15% for local, loco-regional and metastatic disease, respectively (2, 3). For adeno-carcinomas, 5-year disease-specific survival rates of 78-95% and a 5-year survival rate of 95% were reported, and for adenoid-cystic carcinomas of the sino-nasal tract 5-year survival rates of 64-86% (4-7).

Locally advanced resectable tumors are generally treated with surgery followed by radiotherapy or (mainly cisplatin-based) chemoradiation (1). Treatment for unresectable tumors generally consists of definitive radiotherapy or chemoradiation. Recommended total radiation doses are 66-70 Gy (doses per fraction of 1.8-2.0 Gy) for definitive treatment and, depending on the extent of resection, 50-66 Gy for adjuvant treatment with at least 60 Gy to the residual tumor and lymph nodes with extracapsular spread (1, 8).

Some patients cannot tolerate high radiation doses, chemoradiation or surgery. This applies particularly to very elderly and frail patients. Moreover, in palliative cases, the major focus of the treatment lies on symptom control and prevention of complications rather than on prolongation of survival. Particularly patients in a palliative situation can benefit from treatment personalization. In patients with a very limited remaining lifespan, the treatment program should not be long or burdensome. These patients likely benefit from hypo-fractionated radiotherapy with doses per fraction mainly ranging between 2.5 and 4.0 Gy. For patients who are in a situation considered palliative but still have a comparably favorable survival prognosis, late radiation-related toxicity and longer-term control of their disease gain importance. Better disease control can be achieved with

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higher total doses, and a reduction of late sequelae with the use of conventional doses per fraction (1-8-2.0 Gy).

These considerations demonstrate that it is important to be able to estimate a patient's survival prognosis prior to treatment. This study was performed to identify independent prognostic factors for survival in patients with locally advanced sino-nasal cancer who require palliative irradiation. These factors can assist physicians during the process of selecting the best personalized treatment for such a patient.

Patients and Methods

Twelve patients treated with palliative radiotherapy for locally advanced cancer of the nasal cavity or paranasal sinus between 2000 and 2019 were retrospectively analyzed for survival. The study was approved by the Ethics Committee of the University of Lübeck (reference 18-130A). Eleven patients had primary tumor stage T4, and one very elderly patient with a poor performance status had a T3-tumor plus lymph node involvement. Surgery was not performed in 10 patients, and two patients received debulking. Histologies included squamous cell carcinoma (SCC, n=7), adenocarcinoma (n=2), solid undifferentiated carcinoma (n=2), and adenoid-cystic carcinoma (n=1).

Nine patients completed their radiotherapy as planned with total doses ranging between 30 and 55 Gy and doses per fraction between 2.0 and 3.0 Gy. All patients who did not complete radiotherapy received total doses <20 Gy. The equivalent doses in 2 Gy-fractions (EQD2) with respect to tumor control (alpha/beta ratio=10 Gy) ranged between 2 Gy and 57.3 Gy. The EQD2 was ≤39.0 Gy in six patients and ≥41.7 Gy in the other six patients. Thus, the median EQD2 was 40.35 Gy. Three patients received concurrent chemotherapy with paclitaxel (20-25 mg/m²/twice per week, n=2) or cisplatin (20 mg/m²/d1-5, n=1).

Ten characteristics were evaluated for associations with survival, which was referenced from the start of palliative irradiation (Table I). Characteristics included age (≤76 vs. ≥79 years, no patient was 77 or 78 years of age), gender, Karnofsky performance score (KPS <70 vs. ≥70), pre-radiotherapy hemoglobin levels (<12 vs. ≥12 g/dl), tumor site (nasal cavity vs. paranasal sinus), lymph node involvement (no vs. yes), type of histology (SCC vs. other histology), EQD2 (≤39.0 vs. ≥41.7 Gy), completion of planned radiotherapy (no vs. yes) and concurrent chemotherapy (no vs. yes).

Univariate analyses were performed with the Kaplan–Meier method and supplemented by the log-rank test. Characteristics that achieved significance in the univariate analysis (*p*<0.05) or showed a trend (*p*<0.10) were additionally analyzed for independence in a multivariate analysis (Cox proportional hazards model).

Results

The median follow-up was 9 months (range=0-36 months) in the whole series and 18 months (range=9-36 months) in those three patients alive at the time of the last follow-up. The median survival time was 10.5 months. On univariate analysis, a KPS ≥70 (Figure 1, *p*<0.001) and completion of the planned radiotherapy (*p*<0.001) were significantly associated with better survival. In addition, concurrent

Table I. Patient and tumor characteristics evaluated for associations with survival.

Characteristic	No. of patients	Proportion (%)
Age		
≤76 Years	6	50
≥79 Years	6	50
Gender		
Female	5	42
Male	7	58
Karnofsky performance score		
<70	5	42
≥70	7	58
Pre-RT hemoglobin level		
<12 g/dl	4	33
≥12 g/dl	4	33
Unknown	4	33
Tumor site		
Nasal cavity	4	33
Paranasal sinus	8	67
Lymph node involvement		
No	7	58
Yes	5	42
Histology		
SCC	7	58
Other	5	42
RT dose (EQD2)		
≤39.0 Gy	6	50
≥41.7 Gy	6	50
Completion of RT		
No	3	25
Yes	9	75
Concurrent chemotherapy		
No	9	75
Yes	3	25

RT: Radiotherapy; SCC: squamous cell carcinoma; EQD2: equivalent dose in 2 Gy-fractions.

chemotherapy showed a trend (*p*=0.097). The results of the entire univariate analyses are shown in Table II.

In the multivariate analysis, KPS ≥70 was significant (*p*=0.025), and completion of radiotherapy showed a trend (*p*=0.080). Administration of concurrent chemotherapy was not significant in the multivariate analyses (*p*=0.39).

Discussion

Some patients with locally advanced sino-nasal cancer cannot withstand multi-modality treatment and receive palliative radiotherapy. Several dose-fractionation regimens are available for palliative irradiation of sino-nasal cancer with overall treatment times ranging between a few days and several weeks. A challenge for the treating radiation oncologists is the selection of the optimal personalized regimen, which should always consider the individual's survival prognosis. If the prognosis is poor, the dose-

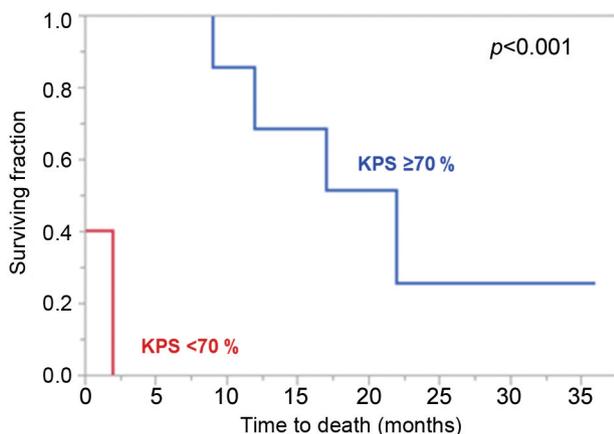


Figure 1. Kaplan–Meier curves for survival comparing patients with a Karnofsky performance score (KPS) of $\geq 70\%$ and patients with a KPS of $< 70\%$. The *p*-Value was obtained using the log-rank test.

fractionation regimen should be short, avoiding patients spending more time than necessary receiving palliative radiotherapy. In contrast, a patient with more favorable survival prognosis (despite a palliative situation) appears better treated with a radiation program including a higher EDD2 and conventional doses per fraction (1.8-2.0 Gy). To provide the best individual radiation treatment, it is important to be able to judge the patient's remaining lifetime. This process can be improved with the availability of significant (ideally independent) prognostic factors. However, very few studies have focused on the palliative treatment of advanced sino-nasal cancers. Farber *et al.* evaluated different palliative treatment approaches in 380 patients with a sino-nasal malignancy from a national cancer database and found that palliative surgery was associated with the best outcomes regarding 1-year and median survival when compared to other treatment modalities (9). However, most of the patients were younger than 70 years and more likely to tolerate surgery compared to the present study, where 67% of the patients were older than 70 years. Jang *et al.* reported a series of 42 patients treated with definitive radiotherapy or chemoradiation for T3-4 N0 SCC of the nasal cavity and maxillary sinus (10). Outcomes were poor for cancer of the maxillary sinus with a 5-year survival rate of 34% and a local control rate of 29%. The corresponding rates for patients with cancer of the nasal cavity were 50% and 52%, respectively. In an earlier study of Hoppe *et al.*, which included 39 patients receiving radiotherapy ($n=4$) or chemoradiation ($n=35$) for unresectable carcinoma of paranasal sinus, the 5-year survival rate was only 15% (11). In both studies, a lower biologically effective radiation dose was the only factor significantly associated with worse survival (10, 11). Since the radiation dose was not a pre-

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

Characteristic	At 6 months	At 12 months	<i>p</i> -Value
Age			
≤ 76 Years	50	33	>0.99
≥ 79 Years	67	44	
Gender			
Female	80	53	0.71
Male	43	29	
Karnofsky performance score			
< 70	0	0	<0.001
≥ 70	100	69	
Pre-RT hemoglobin level			
< 12 g/dl	50	50	0.53
≥ 12 g/dl	100	75	
Tumor site			
Nasal cavity	75	38	0.73
Paranasal sinus	50	38	
Lymph node involvement			
No	57	38	0.69
Yes	60	40	
Histology			
SCC	43	43	0.54
Other	80	30	
RT dose (EQD2)			
≤ 39.0 Gy	50	33	0.20
≥ 41.7 Gy	67	50	
Completion of RT			
No	0	0	<0.001
Yes	78	53	
Concurrent chemotherapy			
No	44	30	0.097
Yes	100	67	
Entire cohort	58	40	

RT: Radiotherapy; SCC: squamous cell carcinoma; EQD2: equivalent dose in 2 Gy-fractions. Significant *p*-Values are given in bold.

treatment factor, it cannot support radiation oncologists when selecting the optimal dose-fractionation regimen for an individual patient. Moreover, the choice of doses given may have reflected the physician's bias to offer higher doses to healthier appearing patients.

The present study was performed to identify additional specific pre-treatment predictors of survival, for patients treated with palliative radiotherapy for advanced sino-nasal cancer. Improved survival was significantly associated with the pre-treatment factor $KPS \geq 70$, and the treatment-related factor completion of the radiotherapy course. In addition, a trend toward better survival was found for concurrent chemotherapy. In the multivariate analysis, KPS maintained significance and is, therefore, an independent predictor of survival. This factor can guide physicians when choosing a personalized radiation regimen. Patients with a $KPS < 70$

appear good candidates for a short-course program with a higher dose per fraction (hypo-fractionation) such as 6×4 Gy or even for best supportive care alone, since all patients died within 2 months. The survival of patients with a KPS ≥ 70 was much better, 67% of the patients survived for 1 year or longer. Therefore, these patients likely benefit from conventionally fractionated radiotherapy with higher total doses (60-70 Gy) in terms of better disease control and less late toxicity. Moreover, patients of the latter group should probably receive concurrent chemotherapy, which showed a trend toward better survival in the present study and led to improved local tumor control in a previous study of Choi *et al.* of 21 patients with locally advanced tumors of the paranasal sinus and the nasopharynx (12).

Another important finding of the present study is the fact that completion of the radiotherapy course is important for the patient's survival prognosis. This aspect has been previously reported for palliative radiotherapy for head-and-neck cancers in general. In the retrospective study of Gamez *et al.* (n=21), patients were planned to receive three cycles of an ultra-short regimen called "quad shot" that consisted of 2×3.7 Gy per day for 2 days, given every three weeks to a total of three cycles supplemented by carboplatin or cetuximab (13). A greater number of completed cycles was significantly associated with better survival ($p=0.03$). Moreover, in the retrospective study of Garcia-Anaya *et al.* (n=106), palliative radiotherapy was planned to be 30-36 Gy, given in 5-6 bi-weekly fractions of 6 Gy (14). Patients who received 30 Gy or less had a significantly worse median survival than patients who received more than 30 Gy (9.5 vs. 26.4 months, $p=0.01$). These data demonstrate that it is very important to provide close monitoring and supportive care for patients receiving palliative irradiation for malignant tumors in the head-and-neck region including sino-nasal cancers. This affords them a better opportunity of completing radiotherapy, which appears to improve survival.

When interpreting the findings of the present study (and of previous studies), one should be aware of the retrospective design, which always bears the risk of hidden selection biases. Prospective trials are needed. However, regarding the rarity of patients with sino-nasal cancers, in particular patients assigned to palliative irradiation, such trials are difficult to perform and not expected soon.

In conclusion, KPS proved to be an independent predictor of survival for patients who received palliative irradiation for sino-nasal cancer. Patients with a KPS < 70 appear suitable candidates for a short course of radiotherapy or best supportive care alone, and patients with a KPS ≥ 70 appear to benefit from dose-fractionation regimens similar to those used for curative treatment probably combined with concurrent chemotherapy. Patients receiving palliative irradiation for sino-nasal cancer need close monitoring and optimal supportive care, since survival depends on the completion of the radiotherapy course as planned.

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 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 was approved by all three Authors.

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